Intraventricular polymyxin B for the treatment of neonatal meningo-ventriculitis caused by multi- resistant *Acinetobacter baumannii* – case report and review of literature

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SUMMARY: Piparsania S, Rajput N, Bhatambare G. Intraventricular polymyxin B for the treatment of neonatal meningo-ventriculitis caused by multi-resistant *Acinetobacter baumannii*– case report and review of literature. Turk J Pediatr 2012; 54: 548-554.

Central nervous system infections due to multi- and pan-drug resistant *Acinetobacter baumannii* are an emerging problem in intensive care patients. A high mortality rate is seen in neonatal and central nervous system infections. Treatment can be prolonged and challenging. Polypeptide antibiotics remain one of the options but have poor cerebrospinal fluid (CSF) penetration. We present our experience of successfully treating pan-drug resistant *A. baumannii* neonatal meningitis and ventriculitis with intraventricular polymyxin B. This was administered by repeated ventricular punctures due to lack of consent for insertion of a ventricular reservoir.

Key words: neonatal ventriculitis, pan-drug resistance, Acinetobacter baumannii, polymyxin B.

Acinetobacter baumannii is a gram-negative coccobacillus that is saprophytic and ubiquitous in both the natural and hospital environment[1,2]. This organism forms part of normal skin flora in about 25% of the population[3].

Acinetobacters have several virulence factors that enhance their virulence in immune-compromised or debilitated individuals[4]. Acinetobacter infections are uncommon and usually involve organ systems with a high fluid content, such as the respiratory tract, cerebrospinal fluid (CSF), peritoneal fluid, and urinary tract[5]. *A. baumannii* can cause severe central nervous system (CNS) infections such as meningitis and ventriculitis, especially in postoperative neurosurgical patients or immunologically compromised patients in the intensive care setting[6].

In recent years, multi-drug resistant and pan-drug resistant *A. baumannii* (MDRAB, PDRAB) have become important nosocomial pathogens, posing significant treatment issues[7-16]. MDRAB is resistant to almost all antibiotic groups, although anecdotal success in treatment has been reported with aminoglycosides, carbapenems, β-lactamase inhibitors, tigecycline, rifampicin, and colistin[7-15]. PDRAB remain resistant to most antibiotic groups (see discussion)[17].

Polymyxins (A to E; only B and E used clinically) are polypeptide bactericidal antibiotics used in the treatment of urinary tract, blood stream and meningeal infections caused by gram-negative organisms[18,19]. These antimicrobials have always been reserved drugs for resistant infections because of the potential life-threatening side effects including nephrotoxicity, neurotoxicity and neuromuscular blockade. In more recent years, these antimicrobials have re-emerged with an important place in the global epidemic of multi-drug resistant gram-negative nosocomial infections, especially with Pseudomonas aeruginosa and Acinetobacter spp[12,18].

Treatment of MDRAB or PDRAB meningitis and ventriculitis is prolonged, complex and challenging. Adjunctive treatment with intrathecal (IT) or intraventricular (IVT) polymyxins along with prolonged intravenous (IV) treatment with high-dose carbapenems or aminoglycosides remains the most effective option described in the literature[20-22].

There are isolated case reports of successful treatment with IV colistin therapy alone[23-27]. Some of these reports suggest that peak CSF levels of colistin approximate the minimum inhibitory concentration (MIC) for most multi-drug resistant *P. aeruginosa* and *A. baumannii* strains[23,25]. Most other literature suggests poor CSF penetration for polymyxins, which remains unenhanced in the presence of meningeal inflammation[18,23,28,29]. There are several reports indicating failure with systemic therapy alone[21,30-34], with successful outcomes more likely to be achieved with IVT or IT instillation of colistin or polymyxin B in children[3,27,32-44] and adults[21,22,30-32,34,39,45-57] with or without concurrent systemic (IV or intramuscular) therapy. Hence, there should be a low threshold for administration by IT or IVT, especially if prompt improvement does not occur with IV treatment[18].

Neonatal data on PDRAB ventriculitis remains limited, with only one case report published to date of IVT colistin (polymyxin E) in a neonate with *A. baumannii* infection[58]. This is a French article, for which no abstract was available as of 10 April 2012.

We present here a case report of a preterm out-born male infant affected by PDRAB meningo-ventriculitis and his successful treatment with IVT polymyxin B in combination with IV netilmicin and polymyxin B. This is followed by a review of controversies in the literature and a discussion of the problems we faced during the treatment.

Case Report

Baby PR was delivered vaginally in a district hospital of central India at 32 weeks of gestation following the premature rupture of membranes for more than 72 hours and spontaneous onset of labor. His mother received two doses of betamethasone as well as antibiotics before delivery. He had an Apgar score of 6 at the 1st minute and 9 at the 5th minute and weighed 1.5 kilograms at birth. His initial neonatal course was relatively straightforward with administration of one dose of surfactant, ventilation for 12 hours and subsequent continuous positive airway pressure (CPAP) for one week, and IV amoxicillin and gentamicin for 48 hours, which were stopped as blood cultures were negative. The baby did not require total parenteral nutrition or umbilical catheterizations. His initial head scan on day 2 was normal. Beyond the first week of life, the baby was stable with full enteral feeding and no respiratory support.

The baby had a septic deterioration at the end of the second week with recurrent apneas requiring ventilation. Blood tests revealed an increase in C-reactive protein (CRP: 80 mg/L; normal: <5 mg/L) and white blood cell count (23,000/mm^3; normal: 4000–11000/mm^3). All of the sepsis screening was performed and treatment was commenced with IV cefotaxime and gentamicin for late-onset sepsis. Blood culture obtained on that day showed the growth of MDRAB. The organism was sensitive to ceftazidime, polymyxin B, trimethoprim, colistin, netilmicin, and amikacin, but was resistant to all other 3rd and 4th generation cephalosporins, other aminoglycosides, quinolones, carbapenems, modified and enhanced penicillins (also with sulbactam), aztreonam, and chloramphenicol. Lumbar CSF examination revealed severe pyogenic meningitis. There was elevated CSF protein level - 1014 mg/dl (normal: 65-150 mg/dl), low CSF glucose – 20 mg/dl (normal: 24-63 mg/dl), and high white blood cell count - 500 cells/mm^3 with 100% polymorphs (normal: 0-29 lymphocytes/mm^3)[59]. However, CSF obtained was insufficient for culture. The patient was referred to our tertiary neonatal unit on the 18th day of life because of a further increase in CRP (220 mg/L) and the positive blood culture results.

Antibiotic treatment was changed to IV ceftazidime and amikacin as per the blood culture results. The patient showed a clinical improvement over the next 48 hours with successful extubation and decline in his CRP.

Unfortunately, there was further deterioration on the 22nd day of life with bulging anterior fontanel and increasing head circumference. Cranial ultrasonography was suggestive of hydrocephalus and ventriculitis. Ventricular CSF examination on that day showed elevated proteins - 863 mg/dl, low sugar - 13 mg/dl, and a high white cell count - 2,360/mm^3 with 90% polymorphs. CSF culture showed the growth of PDRAB that was sensitive only to polymyxin B and netilmicin, but resistant to all other antibiotics as listed above.

Further advice was sought at this point from

the microbiology and neurosurgical teams. IV netilmicin (5 mg/kg 12 hourly for 6 weeks) and polymyxin B (20,000 units 12 hourly for 6 weeks) were started on day 26 of life. IVT polymyxin B (40,000 units per dose) was given by alternate day ventricular puncture for four weeks (14 doses) as the family did not consent to the insertion of a ventricular reservoir.

Ventricular CSF examination after four weeks of therapy showed improvement: protein – 124 mg/dl, sugar – 35 mg/dl, and cell counts – 48/ mm^3 (mainly lymphocytes). CSF culture was negative. IV therapy was continued for another two weeks.

Computed tomography of the brain performed after the treatment showed massive communicating hydrocephalus but no evidence of ventriculitis. Ventriculoperitoneal shunting was performed four weeks after stopping treatment, and the baby was discharged at the chronologic age of 4.5 months.

On subsequent follow-up at the corrected (for prematurity) age of two years, his head was growing consistently along the 25th percentile on the World Health Organization (WHO) growth chart[60] and weight and height were just below the 10th percentile. His automated brain evoked audiometry was normal. He had a Bayley's Motor Development Index (MDI) of 80 and a Pervasive Development Index (PDI) of 65[61]. Bayley Scales of Infant Development-II (1993) assess the attainment of key developmental milestones in children from 1 to 42 months in two main domains: MDI and PDI as above. It is a tester-observed score only and although parental reports can be recorded, they do not contribute to the final scores. Raw scores are adjusted for the chronological age and index scores are obtained. Despite a lack of standardization in premature babies, this test is widely accepted as a reliable measure of development[62].

A diagrammatic representation of the clinical course of this patient is shown in Figure 1.

Discussion

Neonatal acinetobacter infections are not uncommon in neonatal units in developing countries. A recent five-year retrospective chart review from Karachi, Pakistan reported 122 positive cultures for acinetobacter in 78 neonates[17]. The most common sites reported for the positive cultures were blood (n=57), trachea (n=55), tissue/wound/body fluids (n=4), eye (n=4), urine (n=1), and CSF (n=1). Pan-drug resistance was very high (71% of isolates), and there was a very high mortality rate of 47%. A similarly high mortality of 14.5% (68/469) was observed in a systematic review of all published pediatric case series and reports up to 2008[42].

Management of neonatal PDRAB sepsis, meningitis and ventriculitis in our patient was fraught with several difficulties, namely:

A. Relative rarity of neonatal PDRAB meningo-ventriculitis and hence the lack of literature;

B. Poor CSF penetration of the relevant antibiotics in adults and children with limited neonatal data[18,63];

C. Refusal by the family for insertion of a ventricular reservoir for IVT antibiotics and the risk of repeated ventricular punctures; and

D. Evidence in the literature that IVT in neonatal ventriculitis is associated with increased mortality.

Resistance to common antibiotics is a major problem in treating acinetobacter infections[2,6,7,10,11,13,64]. The presence of carbapenem-resistant *A. baumanii* was reported in the United States in 1991[15]. A PDRAB was first reported in Taiwan in 1998[65].

Acinetobacter spp. isolates are divided into the following three drug resistance categories:

(a) Pan-resistant Acinetobacter is defined as isolates resistant to all five classes of antimicrobial agents considered first-line therapy for Acinetobacter infections. These include – (i) anti-pseudomonal cephalosporins (ceftazidime or cefepime), (ii) anti-pseudomonal carbapenems (imipenem or meropenem), (iii) ampicillin–sulbactam, (iv) fluoroquinolones (ciprofloxacin or levofloxacin), and (v) aminoglycosides (gentamicin, tobramycin or amikacin)[6,17].

(b) Multidrug-resistant Acinetobacter is defined as strains resistant to more than two of the above five drug classes[6,17].

(c) Susceptible acinetobacter (SA) is defined as susceptible to all first-line drug classes[6,17].

Polymyxins B and E (colistin) are valuable

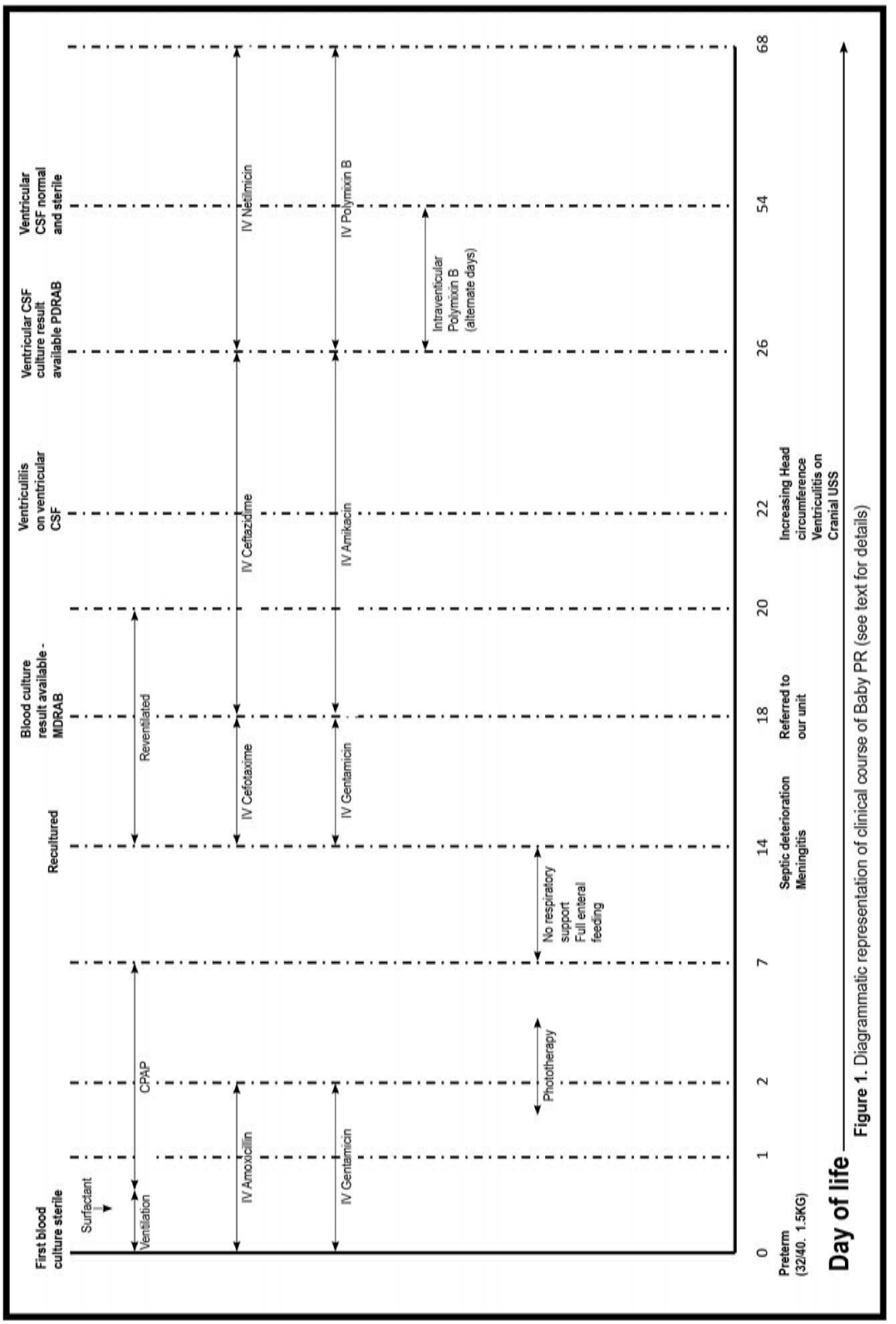

Figure 1. Diagrammatic representation of clinical course of Baby PR (see text for details)

antimicrobials for the treatment of PDRAB infections[18,26,66]. In a systematic review of patients with meningitis or ventriculitis treated with IV or IVT polymyxins published in 2007[29], a total of 64 patients were identified over 56 years (1950-2006). Monotherapy with polymyxins via IT or IVT route was used in 11/64 patients, combination of systemic and local polymyxins was used in 25/64 patients, and various combinations of local polymyxins with systematic and/or local antibiotics were used in the remaining 28/64 patients. Treatment was successful in 51/64 episodes (80%): in 26/30 episodes (87%) due to P. aeruginosa and in 10/11 episodes (91%) due to Acinetobacter spp. Toxicity related to local administration of polymyxins was noted in 17/60 (28%) patients. The most common toxicity was meningeal irritation (12 cases). Discontinuation of treatment was necessary in four episodes and dose reduction in four episodes; irreversible toxicity was not reported. No toxicity was observed in our patient.

Polymyxins B sulfate for injection (Aerosporin; 500,000 units/vial; Glaxo-SmithKline, India) is supplied in powder form suitable for preparation of sterile solutions for intramuscular, intravenous, intrathecal, or ophthalmic use. The prepared solution needs to be refrigerated and needs to be discarded after 72 hours. For IV use, 500,000 polymyxin B units are dissolved in 300 to 500 ml of 5% dextrose injection and given by continuous infusion. For IT administration, 500,000 polymyxin B units are diluted in 10 ml sodium chloride for injection.

Intraventricular (IVT) administration by itself in neonatal ventriculitis remains controversial. A recent Cochrane review shows that IVT for neonatal ventriculitis is associated with a three-fold increase in mortality as compared to patients receiving IV antibiotics alone, thus advocating the avoidance of this modality of treatment[67]. Unfortunately, given the poor CNS penetration of both polymyxin B and netilmicin, the therapeutic options available in our patient were limited.

Intraventricular (IVT) administration should be through a ventricular reservoir, and multiple ventricular punctures are generally not recommended due to the risk of trauma to the brain and secondary infection[67]. Therefore, we were cautious and only administered the IVT on alternate days. However, the successful outcome in our patient without any complications calls for further evaluation of this modality of treatment.

In conclusion, our experience suggests the safety and efficacy of IVT polymyxin B in conjunction with an effective systemic agent as a potential life-saving antimicrobial therapy for pan-drug resistant, gram-negative neonatal meningo-ventricular itis. At the same time, we have been able to show the safety and efficacy of alternate-day ventricular punctures for IVT administration as an alternative to a ventricular reservoir, without development of any complications.

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