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# INTRATHECAL USE OF POLYMYXIN B FOR TREATMENT OF MULTI-RESISTANT MENINGITIS

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## ABSTRACT

Multi-resistant gram-negative nosocomial meningitis is a serious life-threatening infection presenting a therapeutic dilemma. We report a neurosurgical patient who developed a post-operative brain abscess due to multi-resistant *Acinetobacter lwoffii*, sensitive only to polymyxin B. Successful management was accomplished by administration of intravenous and intrathecal polymyxin B. Rapid CSF sterilization occurred with excellent clinical recovery and without any serious side-effects related to polymyxin B. To our knowledge this is the first reported case of intrathecal use of polymyxin B from Pakistan.

Meningitis is a serious complication that may occur after any neurosurgical procedure. Management becomes especially challenging when the organism responsible is multi-drug resistant. Multi-resistant *Acinetobacter* has become one of the more common nosocomial pathogens in hospitals.<sup>1</sup>

*Acinetobacter* species are non-motile, oxidase-negative, gram-negative coccobacilli found commonly in soil and water, but they can be part of normal flora. They are opportunistic pathogens that readily colonize patients who have compromised host defenses. A variety of human infections caused by *Acinetobacter* species have been documented, including nosocomial pneumonia (most often related to endotracheal tubes or tracheostomies), endocarditis, meningitis, skin and wound infections, peritonitis (in patients receiving peritoneal dialysis), and urinary tract infections. Sporadic cases of conjunctivitis, osteomyelitis, and synovitis have also been reported.<sup>2</sup> Multi-drug resistant pathogens are becoming common in ICU settings and are very difficult to treat with commonly available antibiotics.<sup>1</sup> In many situations involving post-neurosurgical meningitis, intrathecal use of antibiotics is necessary to clear the infection. There is very limited published experience with intrathecal use of Polymyxin B in South Asia. In this report, we share our experience of successful intrathecal use of polymyxin B for the treatment of multi-resistant *Acinetobacter* meningitis.

## CASE REPORT

A 25-year-old gentleman sustained head injury after a road traffic accident and presented to the emergency room with post-traumatic recurrent seizures. On examination, his Glasgow Coma Score (GCS) was 7/15 (localizing pain but no eye/verbal response). Endotracheal intubation was performed due to poor neurological status.

A CT scan showed bi-frontal contusions with compound frontal sinus and base of skull fractures. Craniotomy for frontal reconstruction and debridement was performed. The patient was weaned off the ventilator in 3 days and discharged on day 14 with no focal neurological deficit. One day after discharge he presented to the emergency room with fever, drowsiness and a generalized tonic-clonic seizure. Examination showed GCS 11/15 (E4, M5, V2) and a repeat CT scan showed a ring-enhancing lesion in right basal ganglia, at the location of previous intracerebral hemorrhage. Radiologic appearance of the lesion was suggestive of an abscess with development of hydrocephalus and acute cerebral edema.

An urgent ventriculostomy drain was inserted and frank pus was drained. Gram stain revealed gram-negative diplococci and culture grew *Acinetobacter lwoffii*, sensitive only to polymyxin B and resistant to imipenem, ceftazidime, cefepime, piperacillin-tazobactam,

ampicillin-sulbactam, quinolones, and amikacin. The patient remained ventilated and was started on intravenous polymyxin 750,000 units twice daily along with intrathecal polymyxin B 50,000 units (5 mg) once daily. Total treatment duration was two weeks of intrathecal and 4 weeks of intravenous polymyxin B.

Remarkable recovery was noted over the next two weeks and the patient was extubated on day 28 with GCS 14/15 (E4, M5, V5). CSF culture became negative 48 hours after starting intrathecal polymyxin B. A ventriculo-peritoneal shunt was inserted on day 41 and he was discharged home on day 50 of admission. Outpatient follow-up three months post-discharge confirmed he was doing well.

## DISCUSSION

Approximately 60 - 70% cases of meningitis caused by gram-negative bacilli occur following neurosurgical procedures.<sup>3</sup> Multiple antibiotic resistance threatens successful treatment of *Acinetobacter* infection worldwide. Overuse of ultra-broad spectrum antibiotics such as imipenem has been associated with reports of several outbreaks caused by carbapenem-resistant strains, often leaving polymyxins and ampicillin-sulbactam as the only antibiotics with in-vitro activity against these organisms, rendering therapy of these cases as a serious challenge.<sup>4,5</sup> Experience with nosocomial meningitis and ventriculitis following neurosurgical procedures indicates that the most favorable outcome results from removal of infected shunts, creation of an external ventriculostomy opening, and daily administration of systemic and intraventricular bactericidal antibiotics capable of crossing the blood-brain barrier easily.<sup>3</sup>

The case presented here posed a challenging problem since the organism showed resistance to all antibiotics including ceftazidime, cefepime, imipenem, ampicillin-sulbactam and aminoglycosides, and was sensitive to polymyxin B alone. Multi-resistant pathogens are becoming more common in ICU settings, especially in patients who have been treated with multiple broad spectrum antibiotic agents, had invasive devices implanted or procedures performed in the hospital, and had prolonged stay in an intensive care unit.<sup>4,6</sup> Recent experience with the use of intravenous polymyxin B is mainly limited to these settings.

Polymyxin B is one of the earliest agents employed in the treatment of gram-negative bacillary meningitis, particularly that due to *Pseudomonas aeruginosa*.<sup>7,8,9</sup> Only

**Table 1** Serial CSF Analysis

CSF Analysis	Day 1	Day 7	Day 14	Day 24
Glucose(mg/dl)	23	55	70	55
Chloride(mEq/L)	120	115	118	110
Protein(mg/dl)	114	715	398	96.1
TLC(per cu mm)	2800	304	40	05
Polymorphs(%)	90	60	70	*
Lymphocytes(%)	10	40	30	*
RBC(per u mm)	120	1346	40	*
Pus cells	Numerous	Few	Few	Rare
Gram stain	+++	Nil	Nil	Nil
Culture¶	positive	negative	negative	Negative

\*Cells insufficient for differential count

¶ CSF cultures negative 48 hours after starting intrathecal polymyxin B

two polymyxins, B and E (colistin), have been produced commercially; polymyxin B has been in clinical use more commonly. Polymyxin B demonstrates potent bactericidal activity against most strains of *P. aeruginosa*, *Escherichia coli*, *Enterobacter* species, and *Klebsiella* species, damaging the plasma membrane in a manner similar to that of cationic detergents. It penetrates poorly into CSF, and the presence of meningeal inflammation does not enhance absorption.<sup>10</sup> Beneficial reduction in cerebral edema and endotoxin production has been demonstrated in experimental studies in rabbits when high-dose intravenous polymyxin is administered concurrently with another antibiotic.<sup>11</sup>

Use of polymyxin alone has been successful in therapy for more than forty three patients with meningitis and ventriculitis caused by a number of gram-negative bacteria.<sup>4</sup> Although several authors advocate the separate use of polymyxin B intramuscularly, intravenously, or intrathecally, cure rate seem to be more frequent among patients receiving combination systemic and local therapy (intrathecal or intraventricular) or local polymyxin B as an adjunct to other systemic therapy.<sup>7,12</sup> Sterilization of CSF occurs promptly (within 24-48 hours) when therapy is given in conjunction with surgical repair and/or foreign-body removal.<sup>13</sup>

The majority of reported patients received prolonged intrathecal or intraventricular therapy with polymyxin B (3-38 days; 13-205 mg). Most patients received 10-14 days of therapy with a total dose of 30-50 mg (3-5 mg daily). Our patient received a 14-day course with a total of 70 mg (5 mg intrathecally daily of pure polymyxin B base, which is equivalent to 50, 000 units of polymyxin B).

**Table 2** Clinical Response

Clinical Status	Day 1	Day 7	Day 14	Day 24
Seizures	Generalized	Generalized	Generalized	None
Fever	High-grade Persistent	High-grade Persistent	Intermittent Spike	None
GCS	11/15	5/15	14/15	15/15
Pupils	BERL*	Mid-dilated but reactive to light	BERL	BERL

\*BERL Bilaterally equal and reactive to light

CSF levels range from 1.2-112 U / ml in children receiving 10,000-40,000 U of polymyxin intrathecally.<sup>10</sup> Bactericidal activity in CSF was assayed in one patient who received intrathecal polymyxin B and was cured. The CSF trough was bacteriostatic at a 1:8 dilution and bactericidal at a 1:4 dilution.<sup>14</sup> In vitro synergy of polymyxin B with imipenem and other antimicrobial agents against Acinetobacter, Klebsiella, and Pseudomonas species have been documented.<sup>15</sup>

Polymyxin B is nephrotoxic and neurotoxic and has been associated with renal insufficiency, giddiness, neuromuscular blockade, and hyponatremia when used parenterally; and with pain, numbness, paresthesia, confusion, coma and convulsions when used intrathecally. The chemical arachnoiditis seen with polymyxin B is dose-dependent.<sup>9,13,16,17</sup> The parenteral dose ranges from 2.5-3 mg / kg per day in two divided doses. The intrathecal dosage is 5 mg once daily for adults, 2 mg daily for children <2 years of age, and 3-4 mg daily for older children. Neurotoxicity is seen when the dosage exceeds 5 mg or 50,000 U per day.<sup>10</sup>

Our patient did not develop any nephrotoxicity due to polymyxin. He had prolonged seizures, which started prior to administration of polymyxin B and may have been related to the development of brain abscess and late post-traumatic meningitis. The seizures were probably not related to the use of polymyxin B as they subsided while the patient continued to receive intrathecal polymyxin B.

## CONCLUSION

This report and our experience suggest the benefit of reinstating polymyxin B as a potential life-saving antimicrobial therapy for multi-resistant, gram-negative meningitis. Intrathecal polymyxin B appears to be safe and should be combined with an effective systemic agent to improve efficacy of therapy and minimize emergence of resistance.

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