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Cure of multiresistant *Acinetobacter baumannii* central nervous system infections with intraventricular or intrathecal colistin: case series and literature review

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***Objectives*: CNS infections due to multiresistant *Acinetobacter baumannii* (MRAB) are an emerging problem in neurosurgical patients. Colistin remains one of the few remaining treatment options for MRAB but has poor CNS penetration. We describe our experience with intraventricular or intrathecal colistin for this infection.**

***Methods*: Cases known to have received intraventricular or intrathecal colistin for CNS infections due to MRAB were retrospectively reviewed regarding colistin treatment, colistin efficacy and adverse events.**

***Results*: Five patients were identified. All were admissions to the neurosurgical ICU and all were cured of their CNS infections. Three cases were complicated by drug-induced aseptic meningitis or ventriculitis.**

***Conclusions*: This largest case series to date shows that direct instillation of colistin into the CNS may cause chemical meningitis or ventriculitis but it is an effective treatment option for MRAB CNS infection. Further study of dosing regimens is needed.**

Keywords: *A. baumannii*, CNS infections, polymyxin E, injections, ventriculitis, meningitis

Introduction

Multidrug-resistant *Acinetobacter baumannii* (MRAB) is increasingly common,[1] and CNS MRAB infections are now seen.[2–9] MRAB isolates at our hospitals are resistant to all available parenteral antibiotics other than amikacin, severely limiting therapeutics. Amikacin has poor CNS penetration and when formulated with the preservative sodium metabisulphite is not recommended for intraventricular or intrathecal use. The new glycylcycline tigecycline, active *in vitro* against MRAB, is bacteriostatic and its role in CNS infection is undefined. Colistin (polymyxin E) has good activity against Gram-negative bacilli including ~98% of MRAB isolates in recent studies.[1] CNS penetration of colistin is poor, but recent case reports suggesting efficacy of this drug administered directly into the CNS for MRAB ventriculitis/meningitis prompted its use in our cases.

Materials and methods

Cases were identified from the authors' personal experience and were defined as having (i) clinical evidence of CNS infection, (ii) isolation of MRAB from CSF and (iii) receiving colistin via intraventricular or intrathecal routes.

Retrospective chart review was performed. Risk factors for MRAB infection (prior colonization, admission to ICU and preceding use of broad-spectrum antibiotics) were recorded. Survival or death, response to treatment and adverse drug reactions were recorded. Cure was defined as absence of clinical and laboratory evidence for ongoing infection at the last day of original admission.

Colistimethate sodium (colistin methane sulphonate; colistin methylsulphonate) ['Coly-Mycin M Parenteral (Injection)', Parke-Davis, supplied by Link Medical Products Pty Ltd, Sydney, Australia] was used for all cases and all administration routes. Intravenous dosing was 5 mg/kg/day (maximum 300 mg) in divided doses. Intraventricular or intrathecal dosing was 5–10 mg in 1–2 mL of

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sterile normal saline, given after removal of a greater or equal volume of CSF. The intraventricular colistin was given via an external ventricular drain (EVD), which was then clamped for 1 h and released. Intrathecal colistin was given via lumbar puncture.

Clinical isolates of *A. baumannii* were identified by morphology, Gram stain and reactions with the Vitek 2 GNI card (bioMérieux-Vitek, Australia, Pty Ltd). Susceptibility to colistin was determined by disc diffusion (10 μg disc, Oxoid Australia Pty Ltd) at John Hunter Hospital and Etest (AB Biodisk, Solna, Sweden) at South Western Area Pathology Service.

Results

Five patients were identified, as summarized in Table 1. Two were male and three female, aged 4–74 years. Three infections were associated with an EVD and one with a CSF leak. One patient had prior MRAB colonization, four patients received broad-spectrum antibiotics prior to their MRAB infections, and all were resident in the ICU before infection developed. Three received intraventricular colistin and two received intrathecal colistin. All five were cured of their infections.

No nephrotoxicity, neurotoxicity or neuromuscular blockade was noted with systemic colistin use. One patient died (case 1) but this was unrelated to the infection or treatment. Chemical meningitis or ventriculitis was noted in cases 3, 4 and 5.

All MRAB isolates were susceptible to colistin and amikacin but resistant to all other antimicrobials tested.

Case synopses

Case 1. A 74-year-old woman admitted for bowel perforation and myocardial infarction. Subarachnoid haemorrhage (SAH) with obstructive hydrocephalus occurred, and an EVD was inserted on day 3. On day 8, the EVD was removed; the tip and CSF grew *Staphylococcus epidermidis* and MRAB. Intravenous vancomycin and amikacin were commenced. Her condition worsened. Recurrent hydrocephalus was detected, another EVD was inserted on day 12, CSF grew MRAB, and intraventricular colistin was commenced, 5 mg then 10 mg daily for 18 days. CSF samples from day 15 to 31 were culture negative and clinically the infection resolved. On day 32 another myocardial infarction resulted in death.

Case 2. A 56-year-old woman presenting with SAH and obstructive hydrocephalus. An EVD was inserted and was replaced three times (days 4, 5 and 11). CSF and the EVD tip from day 11 grew MRAB. Intravenous amikacin and colistin 150 mg 12 hourly were commenced but the CSF remained culture positive for MRAB. On day 17, intraventricular colistin was commenced at 5 mg initially then 10 mg daily for 3 days. CSF cultures were negative from day 19 and sepsis resolved, but treatment was truncated due to poor neurological outcome. The patient survived and was transferred to a nursing home.

Case 3. A 38-year-old woman presented with a closed head injury. An EVD was inserted on day 1 and removed on day 10. Culture-negative ventriculitis was treated with intravenous vancomycin, meropenem and amikacin from days 21 to 41. CSF from a newly inserted EVD on day 40 yielded MRAB. Intraventricular colistin was administered from days 42 to 53, initially 5 mg then 10 mg daily. She also received intravenous colistin and amikacin from days 50 to 63. CSF became culture negative from day 46. On day 53 despite clinical improvement the CSF white cell count rose to 210×10^6/L, so colistin was ceased and the CSF leucocytosis resolved. Clinical recovery occurred and the patient underwent rehabilitation.

Table 1. Summary of cases

	Case				
	1	2	3	4	5
Age (years)	74	56	38	26	4
Gender	Female	female	female	male	male
Infection site	ventriculitis	ventriculitis	ventriculitis	ventriculitis	meningitis
Colistin treatment	intraventricular 19 days	intraventricular 3 days intravenous 21 days	intraventricular 12 days intravenous 14 days	intrathecal 5 days intravenous 21 days	intrathecal 24 days intravenous 15 days
Other antibiotics	intravenous amikacin, vancomycin	intravenous amikacin	intravenous amikacin	intravenous amikacin	intravenous amikacin
EVD	Yes	yes	no[a]	yes	no
Colonization with MRAB	No	no	no	yes	no
ICU admission	Yes	yes	yes	yes	yes
Prior antibiotics	Yes	yes	yes	no	yes
Outcome	Cure	cure	cure	cure	cure
Toxicity	None	none	chemical ventriculitis	chemical meningitis	chemical meningitis

MRAB, multiresistant *Acinetobacter baumannii*; EVD, external ventricular drain.
[a]Originally an EVD was inserted and then removed, but there was no EVD *in situ* for 30 days prior to placement of the second EVD; CSF obtained when new EVD inserted grew MRAB.

Case 4. A 26-year-old man presenting with lower limb injury and intracerebral haemorrhages requiring EVD insertion. The leg wound became infected with MRAB and intravenous amikacin was commenced on day 8. Blood, CVC tip, CSF and EVD tips submitted on days 13 and 14 grew MRAB. Intravenous and intrathecal colistin (initially 5 mg then 10 mg daily) were commenced on day 14. CSF cultures were negative on days 15 and 19. Despite clinical recovery, on day 19 the CSF white cell count rose to 588×10^6/L, falling when intrathecal colistin was ceased. Intravenous colistin and amikacin ceased on day 35. The patient was discharged to rehabilitation.

Case 5. A 4-year-old boy presenting with medulloblastoma requiring craniotomy. On day 10 focal seizures occurred, CT showed leptomeningeal enhancement, and MRAB was isolated from CSF and blood. Intravenous amikacin and colistin 2.5 mg/kg 12 hourly were commenced. CSF remained culture positive, so intrathecal colistin was administered, initially 1 mg, then two doses of 2 mg, then 4 mg daily for 13 days. A CSF leucocytosis of 165×10^6/L developed and the intrathecal colistin dose was reduced to 2 mg, with reduction in the leucocytosis. CSF cultures became negative on day 3 of intrathecal colistin. The meningitis resolved but functional recovery was poor despite rehabilitation.

Discussion

Administration of colistin directly into the CNS appears to be successful and well tolerated apart from a high incidence of chemical ventriculitis. All 5 patients were cured, as were all 11 previously reported episodes of MRAB treated with intraventricular or intrathecal colistin (Table 2).[2–9] This is superior to 70% (9/13 cases) survival from *Acinetobacter* spp. meningitis treated with intravenous β-lactams and aminoglycosides.[10]

In cases 2 and 5, the CSF remained culture positive despite intravenous colistin, with subsequent cure only after administering colistin directly into the CNS. Of the 10 reviewed cases (total 11 episodes) given intraventricular or intrathecal colistin for MRAB CNS infection,[2–9] 3 failed to respond to initial intravenous colistin.[3,5,6]

Cases 1, 2 and 5 failed to respond to treatment including amikacin and cases 3 and 4 developed infection while on amikacin, showing that this drug fails despite *in vitro* susceptibility.

Intraventricular colistin alone can be adequate therapy for MRAB CNS infection. Case 1 was effectively treated by intraventricular colistin without intravenous colistin and in case 3 the CSF was sterilized using intraventricular colistin before intravenous colistin was initiated. There is one other reported case cured using only intrathecal colistin,[7] and two cases where CSF continued to grow MRAB despite intravenous colistin and cure was achieved with intraventricular colistin.[5,6]

Treating MRAB CNS infection with intraventricular or intrathecal colistin alone will avoid the significant renal toxicity associated with the intravenous route of administration. Although adverse reactions to intravenous colistin were not observed in our series, direct CNS instillation of colistin produced CSF inflammatory changes in cases 3, 4 and 5. In cases 3 and 4, the

Table 2. Published cases of MRAB CNS infections treated with direct instillation of colistin into the CNS

Ref	Age	Sex	Infection	Colistin		Other antibiotics[a]	Outcome
				route	dosage		
2	16	M	Ventriculitis	intraventricular	5 mg bd 20 days	tobramycin	cure
2	34	F	Ventriculitis	intraventricular	5 mg bd 5 days; 10 mg bd 13 days	tobramycin	cure
3[b]	28	M	meningitis and ventriculitis	intraventricular	1.6 mg[c] daily 21 days[d]	colistin and amikacin	cure
3[b]	28	M	meningitis and ventriculitis	intraventricular	3.2 mg[c] daily 42 days[d]	colistin and amikacin	cure
4	4	NS	Meningitis	intraventricular	20 unspecified doses	cefotaxime and unknown aminoglycoside	cure
5	23	F	meningitis and ventriculitis	intraventricular	5 mg bd 21 days	nil[e]	cure
6	38	F	Ventriculitis	intraventricular[f]	4 mg daily to 6 mg bd[c] (total 2 weeks)	nil[e]	cure
7	41	F	Meningitis	unknown[g]	5 mg daily 1 day; 10 mg daily 21 days	Nil	cure
8	NS	NS	Meningitis	intraventricular[f]	10 mg bd 8 days	Colistin	cure
8	NS	NS	Meningitis	intraventricular[f]	20 mg daily 10 days	Colistin	cure
9	49	F	meningitis and ventriculitis	intraventricular[f]	3.2 mg[c] daily 17 days	ampicillin and sulbactam	cure

Ref, reference; bd, twice daily; NS, not specified.
[a]Intravenous route of administration in all cases.
[b]Two separate episodes of MRAB CNS infection in one patient.
[c]Dose converted from international units (IU) to milligrams (mg) for comparative purposes (conversion 1 mg = 12 500 IU).
[d]Concurrent intraventricular amikacin.
[e]Prior systemic antibiotics (including intravenous colistin) ceased when IT colistin commenced.
[f]Although the report uses the term 'intrathecal', according to our definition, the route of administration was actually intraventricular.
[g]Although the report uses the term 'intrathecal', the exact route of administration in the text is unspecified.

chemically induced CSF leucocytosis led to the discontinuation of colistin by this route, while in case 5 a dose reduction in intrathecal colistin allowed it to be continued. This has not been reported previously.[2–9] One case of a seizure secondary to an intraventricular colistin dose of 8 mg was also reported.[6]

An intraventricular or intrathecal dose of 5 mg initially then 10 mg once daily was used for the adult patients in this series. Reported dosages range from 1.6 to 20 mg/day as single or divided doses.[2–9] Notably, the lowest reported doses of 1.6–3.2 mg were combined with intrathecal amikacin.[3] The twice daily regimens are only practical if an EVD or ventricular shunt is *in situ*, and a higher frequency of administration might increase the risk of inadvertently introducing another pathogen into the CNS.

The intrathecal or intraventricular colistin regimen used was selected based on dosages used in the literature and the fact it worked on the initial patients. CSF volumes of distribution of neurosurgical patients vary considerably thus varying the therapeutic dose. EVD drainage rates are widely variable—in those with excess drainage, intraventricular antibiotics will be diluted more, and conversely if drainage is minimal, higher levels and possibly greater toxicity may result. We clamped the EVDs for 1 h to deal with the problem of excessive drainage. Further study of these parameters is required.

Intraventricular or intrathecal colistin is effective and well tolerated apart from reversible chemical meningitis/ventriculitis and should be considered for MRAB CNS infection.

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Transparency declarations

None declared.

References

1. Henwood CJ, Gatward T, Warner M *et al*. Antibiotic resistance among clinical isolates of *Acinetobacter* in the UK, and *in vitro* evaluation of tigecycline (GAR-936). *J Antimicrob Chemother* 2002; **49**: 479–87.

2. Fernandez-Viladrich P, Corbella X, Corral L *et al*. Successful treatment of ventriculitis due to carbapenem-resistant *Acinetobacter baumannii* with intraventricular colistin sulfomethate sodium. *Clin Infect Dis* 1999; **28**: 916–7.

3. Kasiakou SK, Rafailidis PI, Liaropoulos K *et al*. Cure of post-traumatic recurrent multiresistant gram-negative rod meningitis with intraventricular colistin. *J Infect* 2005; **50**: 348–52.

4. Kaplan SL, Patrick CC. Cefotaxime and aminoglycoside treatment of meningitis caused by gram-negative enteric organisms. *Pediatr Infect Dis J* 1990; **9**: 810–4.

5. Bukhary Z, Mahmood W, Al-Khani A *et al*. Treatment of nosocomial meningitis due to a multi-drug resistant *Acinetobacter baumannii* with intraventricular colistin. *Saudi Med J* 2005; **26**: 656–8.

6. Sueke H, Marsh H, Dhital A. Using intrathecal colistin for multidrug resistant shunt infection. *Br J Neurosurg* 2005; **19**: 51–2.

7. Vasen W, Desmery P, Ilutovich S *et al*. Intrathecal use of colistin. *J Clin Microbiol* 2000; **38**: 3523.

8. Berlana D, Llop JM, Fort E *et al*. Use of colistin in the treatment of multiple-drug-resistant gram-negative infections. *Am J Health Syst Pharm* 2005; **62**: 39–47.

9. Benifla M, Zucker G, Cohen A *et al*. Successful treatment of *Acinetobacter* meningitis with intrathecal polymyxin E. *J Antimicrob Chemother* 2004; **54**: 290–2.

10. Chen SF, Chang WN, Lu CH *et al*. Adult *Acinetobacter* meningitis and its comparison with non-*Acinetobacter* gram-negative bacterial meningitis. *Acta Neurol Taiwan* 2005; **14**: 131–7.