Colistin-resistant *Acinetobacter baumannii* as a cause of neonatal ventriculitis

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Acinetobacter baumannii causes invasive paediatric infections, including bacteraemia and meningitis, but neonatal meningitis and ventriculitis is uncommon. The treatment of multidrug resistant (MDR) *Acinetobacter* infections often relies on colistin, a polymyxin antibiotic, as a last resort. Increased use of this drug has led to the emergence of colistin resistance. An unusual case of colistin-resistant *Acinetobacter baumannii* ventriculitis in a premature neonate managed with intraventricular colistin is described.

Keywords: *Acinetobacter baumanii*, colistin, neonatal, ventriculitis

Introduction

Acinetobacter baumannii causes invasive paediatric infections, including bacteraemia and meningitis.[1] Neonatal meningitis and ventriculitis caused by *Acinetobacter* species is uncommon.[1] Colistin, a polymyxin antibiotic, is used in the treatment of multidrug resistant (MDR) *Acinetobacter* infections—often as a last resort.[1] The increasing use of colistin in the treatment of resistant Gram-negative infections has been associated with emergence of colistin resistance.[1] We describe an unusual case of colistin-resistant *Acinetobacter baumannii* ventriculitis in a premature neonate managed with intraventricular colistin.

Case presentation

Following an uneventful pregnancy, a 28-week preterm male infant, weighing 1.02 kg, was delivered via normal vertex delivery at a tertiary hospital in Durban, KwaZulu-Natal. Syphilis and human immunodeficiency virus (HIV) serology testing on the mother were negative. The infant's Apgar scores were 1 and 3 at 1 and 5 minutes respectively. He received benzyl-penicillin due to the unexplained preterm labour.

On day four of life, he developed respiratory distress with an increase in respiratory rate, blood-stained nasal secretions and his chest X-ray had features suggestive of pneumonia. He was ventilated and his antibiotics were changed to piperacillin-tazobactam and amikacin for suspected nosocomial pneumonia. An endotracheal aspirate (ETA) obtained on intubation cultured an extended spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* and multi-drug resistant (MDR) *Acinetobacter baumannii*. The identification and susceptibility of the organisms were performed using the Vitek 2 (bioMérieuxSA, France) automated system. The MDR *A. baumannii* was resistant to most available antibiotics, including carbapenems, cephalosporins, fluoroquinolones, aminoglycosides and aztreonam. It was susceptible to colistin with a minimal inhibitory concentration (MIC) of 2 µg/ml and tigecycline (2 µg/ml). The *Klebsiella pneumoniae* was susceptible to carbapenems and colistin. Colistin was commenced intravenously at a dose of 40 000 iu/kg/dose 8 hourly and continued for 10 days. General infection prevention and control measures including hand hygiene and contact barrier precautions were strictly adhered to.

On day 14 of life, he developed seizures and a cranial ultrasound done for the first time showed dilated ventricles with bilateral resolving grade 3 intra-ventricular haemorrhages. Post-haemorrhagic hydrocephalus was diagnosed (Figure 1). He was commenced on phenobarbitone. He was successfully extubated the following day and remained stable and seizure free for the next three weeks.

On Day 44 of life, he developed vomiting and feed intolerance. On examination, he was ill-looking with a full fontanel. Septic markers were elevated with a white cell count of 27.35×10^9/l and C-reactive protein of 55 mg/l. Cerebrospinal fluid (CSF) microscopy revealed 10 neutrophils, 36 lymphocytes and 20 erythrocytes. CSF glucose was 0.2 mmol/l, protein 14.6 g/l and chloride 88 mmol/l. MDR *A. baumannii*, susceptible only to colistin (MIC: 2 µg/ml) and tigecycline (MIC: 2 µg/ml), was cultured from CSF. Intravenous colistin was restarted.

Repeat CSF evaluation after 12 days of intravenous colistin remained culture positive for *Acinetobacter* spp. The colistin MIC of this isolate was 4 µg/ml. The isolate from the initial ETA specimen and the two CSF isolates were sent to a reference laboratory and antimicrobial susceptibility was confirmed using Sensititre broth microdilution method (Trek Diagnostic Systems, UK) as recommended by the joint Clinical Laboratory Standards Institute (CLSI)-European Committee on Antimicrobial Susceptibility Testing (EUCAST) Polymyxin Breakpoints Working Group.[2]

With no alternative therapeutic options available, intraventricular colistin was administered and meropenem (MIC: 2 µg/ml) commenced intravenously. Strict cohorting was instituted until the neonate could be isolated. Contact precautions were reinforced and appropriate equipment cleaning and decontamination of the environment was implemented.

Insertion of an external ventricular device (EVD) was requested from the paediatric neurosurgical team. The procedure was
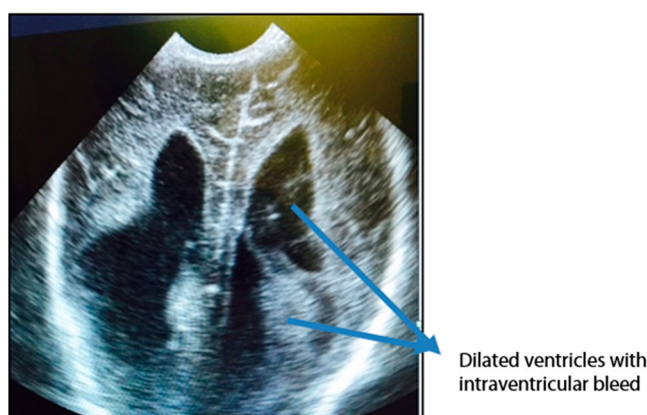
Figure 1: Cranial ultrasound scan: coronal view showing dilated ventricles with intraventricular haemorrhage.

not done due to a shortage of intensive care beds at the facility at that time.

The parenteral colistin formulation at 40 000 iu/kg/dose was administered daily via ventricular puncture, alternating sides each day. CSF was sent daily for chemistry, microscopy and culture prior to the colistin dose to assess treatment response. Cell counts as well as the organism colony counts progressively decreased. After eight days of intraventricular colistin and intravenous meropenem, CSF culture was negative with 22 neutrophils, 0 lymphocytes, and 0 red blood cells per mm^3 on microscopy.

On day 10 of dual therapy, he developed features on the CSF microscopy suggestive of chemical ventriculitis (312 neutrophils, 94 lymphocytes, 160 red blood cells per mm^3). Colistin was deferred for a day and then restarted with a 48-hourly dosing interval. CSF cultures remained negative. A total of 14 days' intraventricular therapy and 21 days' intravenous therapy with colistin was administered. Intravenous meropenem was given for 14 days. The CSF cultures remained negative. He improved clinically and was discharged for further outpatient management. He was reviewed at neonatal clinic a week later and subsequently lost to follow-up.

The isolate from the initial ETA and the two CSF isolates that were resistant to colistin underwent genotyping. The two resistant isolates tested negative for the presence of the plasmid-mediated mcr-1 gene. Pulsed-field gel electrophoresis (PFGE) was performed and clustering was done according to Tenover criteria.[3] A cluster is defined as PFGE patterns differing by three or fewer bands. The three *A. baumannii* isolates produced identical banding patterns, suggesting genetic relatedness (Figure 2).

Discussion

Colistin is one of few therapeutic options for treating multi-drug and pan-drug resistant Gram-negative infections.[1] Central nervous system (CNS) penetration of colistin is reportedly poor, owing to its high molecular weight and polycationic structure.[4] Intraventricular (IVT) or intrathecal (ITH) administration of colistin has been advocated but data regarding its usage in the neonatal period are very limited.[4]

Karaiskos *et al.* discussed the use of IVT or ITH colistin for resistant *A. baumannii* ventriculitis and meningitis.[4] They reported 83 episodes in 81 patients, 71 adults and 10 children and neonates. Colistin was administered via the IVT and ITH route in 52 and 22
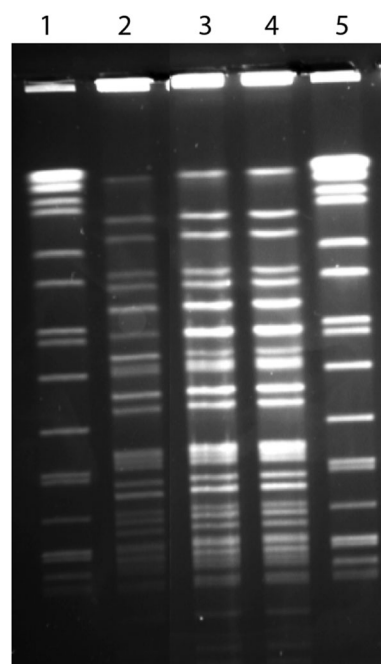
Figure 2: Pulsed-field gel electrophoresis of the three *Acinetobacter baumannii* isolates. Lane 1: Control strain; Lane 2: Isolate (collection date: June 25, 2015); Lane 3: Isolate (collection date: August 17, 2015); Lane 4: Isolate (collection date: August 24, 2015); Lane 5: Control strain.

cases, respectively. In total, 89% had successful outcomes although toxicity in the form of chemical ventriculitis was noted in nine cases (11%) and was the most common adverse event.[4] Although reversible, it can present with signs and symptoms of bacterial meningitis, with a raised CSF cell count and low glucose concentration.[4] The possibility of relapse or reinfection needs to be considered. However, CSF cultures remained sterile as in our patient.

Katragkou *et al.* reviewed the use of ITH or IVT colistin alone or in combination with systemic antibiotics for treating MDR *A. baumannii* CNS infections.[5] Sterilisation of CSF occurred within a median of 4.5 days.[5] It was well tolerated and may be effective salvage therapy. Alternative therapeutic options including tigecycline, sulbactam, aminoglycosides and rifampicin have also been used successfully.[4] None of these alternatives were considered appropriate in our case as tigecycline is contraindicated under eight years of age; the risk of using rifampicin in our endemic TB environment and sulbactam is unavailable. Further, tigecycline and sulbactam use achieve low CSF levels in the absence of active meningeal inflammation and aminoglycosides do not penetrate the blood–brain barrier.[4] Treatment with a combination of colistin, a carbapenem and ampicillin-sulbactam has been associated with the lowest mortality rate.[4]

Colistin resistance is increasingly reported but to our knowledge this is the first case of colistin-resistant *Acinetobacter baumannii* ventriculitis in South Africa. Mehar *et al.* reported a case of neonatal septicaemia with meningitis and ventriculitis caused by carbapenem resistant *A. baumannii* in a preterm male baby. However, this organism was colistin susceptible and was successfully treated with intraventricular colistin and intravenous netilmicin.[1]

Colistin resistance is thought to occur in patients who have received colistin therapy or to be acquired through nosocomial transmission. Qureshi *et al.* reported the molecular

epidemiology of colistin-resistant *A. baumanii* in 20 patients to elucidate the mechanism underlying this resistance.[6] Genetic relatedness determined by PFGE showed that colistin-susceptible and resistant isolates from the same patients were highly related, but isolates from different patients were not.[6] This suggests that resistance evolves during therapy as it occurred almost exclusively among patients that had received colistin. In our case, PFGE results were indistinguishable. The isolates were genetically related and likely the same strain that acquired resistance upon exposure to colistin. The plasmid-mediated *mcr-1* gene was not detected; however, we cannot exclude horizontal mechanisms of transmission as the *mcr-2* gene was not screened for and this would require further investigation. Colistin resistance may also be due to chromosomally mediated resistance with loss of lipopolysaccharide (LPS) production caused by mutations in any of the lipid A biosynthesis genes.[7,8]

Neonatal ventriculitis caused by Gram-negative bacteria is difficult to manage. Conventional therapy with intravenous antibiotics may not be sufficient to eradicate bacteria. Our case was further complicated in that the neonate had a highly resistant organism. Intraventricular colistin was successfully used as a last resort. Of concern is the rapid development of colistin resistance exposure and the potential for spread within overcrowded neonatal facilities.

Implementation of IPC measures to prevent spread of MDR organisms in under-resourced settings is challenging. Limiting patient transfer is difficult with the poor availability of high-care and specialised units. Screening cultures for carriage of MDR organisms may help with early detection of colonised patients.[9] These patients serve as a reservoir and transmission via the hands of healthcare workers to patients and surfaces can be overcome by implementation and regular monitoring of hand hygiene programmes.[9] Source isolation of colonised and infected patients in single rooms can prevent spread of MDR organisms but this is limited in overcrowded settings.[9] Cohorting patients who are positive for the same MDR organisms is recommended.

Conclusion
Neonatal meningitis and ventriculitis due to multi-drug resistant organisms are emerging and therapy with currently available

intravenous antibiotics may not be sufficient. The use of intraventricular antibiotics, although challenging, may be used successfully. Sustaining simple IPC interventions can be beneficial in reducing spread of multi-drug resistant organisms.

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References
1. Mehar V, Zade P, Joshi M, et al. Neonatal ventriculitis with multi drug resistant Acinetobactor baumanii: a case report and review of literature. Pediat Therapeut. 2012;2:131. doi:10.4172/2161-0665.1000131
2. EUCAST Guidance documents: recommendations for MIC determination of colistin (polymyxin E) As recommended by the joint CLSI-EUCAST Polymyxin Breakpoints Working Group. (22 March 2016).
3. Tenover FC., Arbeit RD, Goering RV, et al. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. J Clin Microbiol. 1995;33(9):2233–9.
4. Karaiskos I, Galani L, Baziaka F, et al. Intraventricular and intrathecal colistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant Acinetobacter baumannii ventriculitis and meningitis: a literature review. Int J Antimicrob Agents. 2013;41:499–508.
5. Katragkou A, Roilides E. Successful treatment of multidrug-resistant Acinetobacter baumannii central nervous system infections with colistin. J Clin Microbiol. 2005;43(9):4916–7.
6. Qureshi ZA, Hittle LE, O'Hara JA, et al. Colistin-resistant Acinetobacter baumannii: beyond carbapenem resistance. Clin Infect Dis. 2015;60 (9):1295–303.
7. Ahmed SS, Alp E, Hopman J, et al. Global epidemiology on colistin resistant Acinetobacter baumannii. J Infect Dis Ther. 2016;4:287.
8. Olaitan AO, Morand S, Rolain J-M. Mechanisms of polymyxin resistance: acquired and intrinsic resistance in bacteria. Front. Microbiol. 2014;5:643.
9. Tacconelli E, Cataldo MA, Dancer SJ, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 2014 Jan;20(Suppl. 1):1–55.