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Case Report

Extended-spectrum beta-lactamase-producing and carbapenemase-producing *Enterobacter cloacae* ventriculitis successfully treated with intraventricular colistin☆

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SUMMARY

We present a case of post-neurosurgical ventriculitis caused by carbapenemase-producing *Enterobacter cloacae* successfully treated with intraventricular colistin. *Enterobacter spp* are intrinsically resistant to aminopenicillins, cefazolin, and cefoxitin due to the production of constitutive chromosomal AmpC beta-lactamases. Moreover, extended-spectrum beta-lactamase-producing *Enterobacter spp* have been identified in the USA and Europe, and carbapenems are considered the drug of choice in these cases. Our isolate was sensitive only to fosfomycin, tigecycline, and colistin, and 6 days of intravenous colistin had failed to eradicate the infection. This case provides clinical evidence to support the administration of intraventricular colistin in such patients.

1. Introduction

Enterobacter spp are significant causes of nosocomial infections and are intrinsically resistant to aminopenicillins, cefazolin, and cefoxitin due to the production of constitutive chromosomal AmpC beta-lactamases. Moreover, extended-spectrum beta-lactamase (ESBL)-producing *Enterobacter spp*, particularly *Enterobacter cloacae*, have been identified in the USA and Europe, and carbapenems are considered the drug of choice in these cases.[1] We describe here a case of post-neurosurgical ventriculitis caused by carbapenemase-producing *E. cloacae* successfully treated with intraventricular colistin.

2. Case report

A 5-year-old boy (weighing 20 kg), successfully operated for astrocytoma, was brought to hospital 4 days after the intervention because of a cerebrospinal fluid (CSF) leak from the surgical wound and fever. On admission, physical examination revealed a temperature of 40 °C, a pulse of 104 beats per min, a respiratory rate of 22 breaths per min, and a blood pressure of 94/52 mmHg. He was alert and oriented to time and place. Neither clinical signs of meningeal irritation nor focal neurological signs were present. Laboratory examinations revealed a white blood cell count of 13.15×10^9/l with 69% neutrophils and 19% lymphocytes. C-reactive protein (CRP) was 5.16 mg/dl (normal values <0.5 mg/dl) and procalcitonin 0.88 μg/l (normal values <0.5 μg/l). Results of

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urinalysis were unremarkable. Cultures of blood and urine were drawn and results were subsequently negative. The wound was revised and a sample of CSF was drawn from the cerebral ventricles. CSF was turbid with a glucose concentration of 10 mg/dl, a protein level of 180 mg/dl (normal values 15–45 mg/dl), and a white cell count of 2.24×10^9/l with 95% neutrophils. Gram staining of CSF revealed no organisms. Pending the culture results the patient was empirically treated with intravenous ceftazidime (500 mg/6 h) and teicoplanin (200 mg/day). Culture of CSF yielded *E. cloacae* subsp. *cloacae*, which was identified using the Vitek-2 system (bioMérieux Inc.). The isolate was sensitive to fosfomycin (minimum inhibitory concentration (MIC) ≤16 mg/l), tigecycline (MIC ≤1 mg/l), and colistin (MIC ≤0.5 mg/l); it exhibited intermediate sensitivity to amikacin (MIC 16 mg/l) and was resistant to amoxicillin–clavulanate (MIC ≥32 mg/l), piperacillin–tazobactam (MIC ≥128 mg/l), cefotaxime (MIC ≥64 mg/l), cefepime (MIC ≥64 mg/l), ertapenem (MIC ≥8 mg/l), meropenem (MIC ≥16 mg/l), gentamicin (MIC ≥16 mg/l), ciprofloxacin (MIC ≥4 mg/l), and trimethoprim–sulfamethoxazole (MIC ≥320 mg/l). Analysis of beta-lactamase genes by PCR and sequencing revealed the presence of bla_{VIM-1}, bla_{TEM-1}, and bla_{SHV-12}.[1]

Once the organism was identified and antimicrobial susceptibility testing obtained (4 days later), ceftazidime and teicoplanin were substituted with a combination of intravenous colistin methanesulfonate (2 000 000 IU/12 h) and intravenous rifampin (400 mg/day). Due to the persistence of the CSF leak, the surgical wound underwent surgical revision two times and then an external ventricular derivation catheter was positioned. At 10 days after the first surgical revision (and 6 days of intravenous colistin) the patient continued to be febrile and the CSF culture was still positive for *E. cloacae* subsp. *cloacae*. Parenteral therapy was then discontinued and intraventricular colistin methanesulfonate 125 000 IU (10 mg)/day was started. The colistin dose was diluted in 5 ml of sterile normal saline and given through the ventricular drainage after removal of an equal volume of CSF. After each dose, the ventricular drainage was clamped for 1 h and released. The patient became afebrile 48 h after beginning intraventricular colistin. CSF cultures performed daily became negative after 2 days. After a further 5 days, the CSF culture was still sterile, with a CSF white cell count of 6×10^6/l. Hence the ventricular drainage was closed and the therapy stopped. At that time laboratory examinations revealed a white blood cell count of 6.15×10^9/l with 41% neutrophils, a CRP of 0.18 mg/dl, and procalcitonin of <0.05 μg/l. After another 5 days, the ventricular drainage was removed. No complications or side effects or major changes in laboratory data were observed during the treatment. The patient was then discharged from the hospital with moderate neurological consequences (he walks awkwardly on the right side requiring a small amount of support for balance disorders and has a horizontal nystagmus), and has been followed-up for 6 months, with no evidence of relapse or CSF leak.

3. Discussion

Carbapenem-resistant *Enterobacteriaceae* have been reported worldwide, largely as a consequence of the acquisition of carbapenemase genes. However, to the best of our knowledge, no other cases of carbapenemase-producing *E. cloacae* ventriculitis or meningitis have been reported in the international literature.

Our strain was susceptible only to colistin, fosfomycin, and tigecycline. Intraventricular colistin has been used successfully to treat multidrug-resistant *Acinetobacter baumannii* meningitis and ventriculitis.[2] In our patient, 6 days of intravenous colistin failed to cure the ventriculitis, while CSF culture became negative after only 2 days of intraventricular colistin. The penetration of colistin into CSF is poor, both in patients with non-inflamed meninges and in those with inflamed meninges.

Recent pharmacokinetic studies have demonstrated that the intravenous administration of colistin in critically ill patients with external ventricular drainage- associated ventriculitis caused by Gram-negative bacteria provides a maximum concentration of colistin in the CSF of 11% that present in serum.[3] Probably, as suggested by Ziaka et al., it would be best to administer a combined intravenous–intraventricular treatment. In fact, higher levels in CSF throughout the dosing interval are obtained with this approach, and a high level of colistin may be crucial in controlling multidrug-resistant infections.[3] A further advantage of the use of combined intravenous–intraventricular treatment would be the possibility of curing other possible undiagnosed infectious foci.[2]

Fosfomycin crosses maximally into CSF in the presence of inflamed meninges. However, its activity seems to be reduced in human CSF.[4] Moreover, fosfomycin was not available in our hospital. Tigecycline is currently not recommended in cases of meningeal infections, based on data showing modest penetration into the CSF in healthy volunteers.[5] Even though recent data suggest a higher penetration of tigecycline into the CSF in cases of inflamed meninges than in non-inflamed meninges, drug levels may remain too low for efficient treatment of meningitis at the studied dose level of 50 mg twice daily.[5]

In conclusion, our case report, in addition to documenting the occurrence of carbapenemase-producing *E. cloacae* ventriculitis for the first time, provides clinical evidence to support the administration of intraventricular colistin in such patients.

Conflict of interest: All authors declare no financial or personal relationships with other people or organizations that could inappropriately influence the manuscript content.

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