Intrathecal colistin for treatment of multidrug resistant (MDR) Pseudomonas aeruginosa after neurosurgical ventriculitis

**Colistina intratecale nel trattamento di un caso di ventricolite post-chirurgica da Pseudomonas aeruginosa multi resistente**

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**INTRODUCTION**

Cerebrospinal fluid (CSF) shunts significantly improve the quality of life in patients with acute hydrocephalus. However, CSF infection associated with shunts is a severe complication with high morbidity and mortality [1]. The incidence of shunt-associated infection has a range of 1%-18%, and several independent risk factors have been identified [2-5]. Organisms causing shunt-associated infections typically adhere to the device surface and form biofilms, which makes clinical and laboratory diagnosis difficult and treatment challenging. Clinical symptoms are often non-specific, especially when shunt-associated infections are caused by low-virulence organisms. Often, only signs of intracranial hypertension attributable to shunt malfunction are present, but these are difficult to evaluate in patients with a poor Glasgow Coma Scale (GCS) [6].

It is therefore crucial to diagnose shunt-associated infection both early on and accurately so as to be able to plan appropriate medical and/or surgical intervention. The fluid is usually colonized by Gram-positive bacteria, but long stays in Intensive Care Units (ICU) permit colonization by Gram-negative bacteria. Gram-negative infections are normally treated with carbapenems which are usually considered the treatment of choice for severe infection due to their high penetration through the cerebral blood barrier [7]. However, the increasing resistance of carbapenems worldwide has led to the revival of old antibiotics: polymyxin E (or colistin) and B which are active against Gram-negative bacteria like Acinetobacter spp, Pseudomonas aeruginosa, Klebsiella spp and Enterobacter spp. The antibacterial action of these drugs targets the cell membrane.

**CASE REPORT**

G.P., a 57-year-old male, was admitted to our Anaesthesia and Emergency Department (A&E) for spontaneous cerebral trunk haemorrhage; his GCS was 5. He was then intubated, stabilized and underwent a Computed Tomography (CT) scan. He was then transferred to a neurosurgery department within another hospital where the CSF shunt was positioned. After 4 days he returned to our hospital, continuing intracranial and clinical monitoring and awaiting stabilization of his neurological clinical status. Upon admission to the ICU he commenced treatment using intravenous ampicillin-sulbactam (12 g/die) which was then continued for 14 days following a tracheotomy which showed poor neurological status (GCS 8). After 3 days, the patient’s recovery was complicated by...
pneumonia, fever (39°C) and hypoxia with a positive bronchial culture for susceptible *Staphylococcus aureus* and *Klebsiella pneumoniae* susceptible to the third-generation cephalosporin that we started.

At that time the fluid was still haematic without infection and white blood cells (WBCs) were 12x10^3/ml. Despite the patient’s unchanged clinical status, after a few days his WBCs were 10x10^3/ml and the fever had decreased to 38°C. However, after 7 days, the liquor was positive to *Pseudomonas aeruginosa* susceptible to amikacin (MIC <1 µg/ml), colistin (MIC <0.5 µg/ml), meropenem (MIC <1 µg/ml) and to methicillin-resistant *Staphylococcus aureus* but sensitive to vancomycin and teicoplanin (MIC <1 µg/ml); therefore we commenced a therapy with meropenem 1 g every 8 hours and vancomycin 2.5 g/die by continuous intravenous infusion.

After seven days the liquor and tracheal aspirate were still positive to *Pseudomonas aeruginosa*: susceptible to amikacin (MIC <8 µg/ml) and colistin (MIC = 1 µg/ml), intermediate to meropenem (MIC = 8 µg/ml) and resistant to imipenem (MIC >8 µg/ml). The haemodynamic was unstable and the pulmonary exchange was severely compromised (P.O_2_/Fi.O_2_ <100), as confirmed by the thoracic X-ray.

The liquor was still haematic, and the cerebral CT scan showed dilatation in the ventricle and also the presence of blood inside the fourth ventricle; however, the patient was not transportable to a neurosurgical department in order to change the shunt.

The fever was still around 38°C and WBCs were 12x10^3/ml. For this reason we decided that an appropriate treatment for the patient would be intravenous aztreonam 2 g every 8 hours plus amikacin (1 g/d) and intrathecal colistin (125,000 IU/d) diluted in 5 ml of normosaline solution in a single shot, closing the catheter for at least three hours.

After 4 days the liquor was sterile and the tracheal aspirate continued to react positively to *Pseudomonas aeruginosa*, susceptible to amikacin (MIC <8 µg/ml) and colistin (MIC = 1 µg/ml), and resistant to meropenem (MIC >8 µg/ml) and imipenem (MIC >8 µg/ml); the WBC count was 8x10^3/ml and the temperature was 37.3°C, the haemodynamic parameters were satisfactory and the respiratory exchange had improved. After 5 days and, in all, 9 days of treatment, the WBC count was 7.5x10^3/ml; the aspirate became negative and the patient’s temperature was 36.8°C.

After continued routine monitoring of the liquor, monitoring of intracranial pressure and the CT scan, the patient was then transferred to the Neurosurgical Department 50 days later for definitive intraoperative drainage. He returned the same day and was discharged to a normal ward following a week without fever and stable neurological condition (CGS 10).

### DISCUSSION

Colistin is a cationic cyclic decapeptide, which is linked to a fatty acid through an α-amide linkage with molecular weight of 1750 Da. Two forms of colistin are commercially available: colistin sulphate and colistimethate sodium which is less potent and toxic. Antibacterial action targets the cell membrane of Gram-negative bacteria and initial association of drug and bacterial membrane occurs through electrostatic interaction between the cationic polypeptide and anionic lipopolysaccharide (LPS) molecules in the outer membrane of the bacteria. Colistin displaces magnesium and calcium which normally stabilize the LPS molecule and increase the permeability of the cell envelope, leakage of cell contents and cell death. In addition to direct antibacterial activity, colistin also has potent anti-endotoxic activity; it neutralizes the lipid A portion of the LPS molecule: the endotoxin of Gram-negative bacteria (8).

The Gram-negative bacteria can develop resistance to colistin.

Colistin exhibits its bactericidal activity in a concentration-dependent manner and proves extremely rapid at killing in a concentration-dependent manner. However, re-growth was observed at concentrations up to 32x MIC for some isolates. Colistin exhibited modest post-antibiotic effect (PAE) for *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and other Gram-negative microorganisms. Surprisingly, negative PAE (range: -0.8 min to -8.15 h) was observed.

These findings suggest that monotherapy using colistin methanesulphonate, the parenteral form of colistin, and long dosage intervals (e.g., 24 h) may be problematic when treating infections caused by colistin heteroresistant Gram negative and is poorly distributed to pleural cavity, lung, bones, and cerebrospinal fluid (CSF) [9, 10]. However, a recently published case-study of meningitis due to *Acinetobacter baumannii*...
showed that 1,000,000 IU of colistin intravenously every 6 hours resulted in sufficient penetration of the central nervous system (CNS): the concentration of colistin in CSF was 25% of the serum concentration [1].

*Pseudomonas aeruginosa* remains an organism with high intrinsic resistance and also a high ability to acquire adaptive resistance during therapy [12, 13, 23]. Until the year 2000, no published data concerning intrathecal colistin treatment were available.

In a letter to the Editor, Vasen and coll. report a case of meningitis caused by MDR Gram-negative bacteria, which was treated successfully by the use of intrathecal colistin [14]. These authors further conclude that in such cases of meningitis which are caused by multiresistant Gram-negative bacteria, intrathecal administration of colistin could be considered an effective alternative treatment.

Quinn reports two cases of MDR *Pseudomonas aeruginosa* meningitis after neurosurgery, and goes on to conclude that once again, the use of intrathecal colistin is a safe and effective treatment option for MDR *Pseudomonas aeruginosa* [15]. Yagmur and Esen report one case of treatment with intrathecal colistin for MDR *Pseudomonas aeruginosa* which provided a successful outcome when treating a 16-year-old boy suffering from an infected ventriculo-peritoneal shunt, where colistin was administered (5 mg/day for 21 days) [16].

In the Guidelines for the Management of Bacterial Meningitis, among the recommended antimicrobial agents is colistin at the dosage of 10 mg/die [17]. However, direct instillation into the ventricles of the antimicrobial agents through an external ventriculostomy or shunt reservoir is occasionally necessary in patients suffering shunt infections and/or those unable to undergo surgery to remove the device. The USA Food and Drugs Administration does not approve antimicrobial agents for intraventricular use and their indications are not clearly defined.

A report of two cases of MDR *Pseudomonas aeruginosa* meningitis and ventriculo-peritoneal shunt (VPS) infection which were both successfully sterilized through use of intrathecal colistin (10 mg/day), after the development of nephrotoxicity associated with previous intravenous administration, shows that the use of intrathecal colistin is a potentially safe, effective, and viable treatment option for MDR *Pseudomonas aeruginosa* CNS infections when intravenous administration is not a feasible option due to renal toxicity of colistin (18). Suarez Fernandez et al. [19] showed that in seven cases, all with documented nosocomial CNS infection due to MDR Gram-negative, the combined treatment of intrathecal and intravenous colistin seems safe and effective. When administered by local route to patients with continuous CSF drainage, they suggest a base dosage of colistin of 10 mg every 12 hours with temporary interruptions of the drainage. Gump and coll. report a case of ventriculitis of *Pseudomonas aeruginosa* which demonstrated intermediate sensitivity to amikacin and resistance to all other antibiotics tested [20]. After failing to respond to intravenous imipenem as well as intravenous and intrathecal amikacin, the patient was successfully treated with intravenous and intrathecal colistin.

Enfanto reports the case of a 24-year-old man, hospitalized two weeks prior, suffering emergent craniotomy and craniectomy after a high-speed motor vehicle accident and then readmitted to hospital with high fevers of unknown origin, hydrocephalus, and a change in mental status [21]. The patient did not improve after empirical antibiotic therapy and cerebrospinal fluid revealed a MDR extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*. Following the completion of a seven-day course of intrathecal colistin, repeated cerebrospinal fluid surveillance cultures were obtained and documented to be sterile.

Ng and coll. report in a case series that although direct instillation of colistin into the CNS may cause chemical meningitis or ventriculitis, it is an effective treatment option for MDR Gram-negative CNS infection [22].

**CONCLUSION**

Direct instillation of colistin in the CNS is safe, effective and suitable for treating infections sustained by MDR Gram-negative bacteria especially when the patient’s condition does not permit transport in order to remove the shunt. Although there is still a risk of chemical meningitis, it remains one of the few treatment options for bacteria resistant to carbapenems and aminoglycosides. However, further study of the required dosage is still required.

**Key words**: cerebrospinal fluid, colistin, intrathecal.
Cerebrospinal fluid (CSF) shunts significantly improve the quality of life in patients with acute hydrocephalus. However, infections associated with a CSF shunt constitute a severe complication with high morbidity and mortality. We describe a case of CSF shunt infection cured with intrathecal colistin.

SUMMARY

Il posizionamento della derivazione liquorale esterna migliora in modo significativo la qualità di vita dei pazienti affetti da idrocefalo. Tuttavia, le infezioni associate a shunt sono serie e gravate da morbilità e mortalità elevate. Si descrive un caso di infezione associata a derivazione liquorale esterna trattata con colistina intratecale, con esito favorevole.

REFERENCES


