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CLINICAL ARTICLE - VASCULAR

Outcomes in meningitis/ventriculitis treated with intravenous or intraventricular plus intravenous colistin

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Abstract
Background The aim of this work is to evaluate the outcome of patients treated with intrathecal colistin for meningitis/ventriculitis.
Methods This retrospective case series study included patients presenting with nosocomial meningitis/ventriculitis following neurosurgical interventions and having intravenous (IVC group) or intravenous and intrathecal/intraventricular colistin (ITC group) treatment between 2006 and 2014.
Results Thirty-four patients presented nosocomial meningitis/ventriculitis; 11 (32.5 %) were included in the IVC group and 23 (67.6 %) in the ITC group. The most frequent isolated bacteria were *Acinetobacter baumannii*. The mean dose was 170,000 (±400) IU and the duration of intraventricular treatment was 16.0 (±8.3) days. The duration of intravenous treatment was 16.0 (±8.3) days in the ITC group and 15.3 ± 7.6 days in IVC group. Hospital mortality was significantly lower in the ITC group compared with the IVC group (13 vs. 72.7 %, $p = 0.001$).
Conclusions The combination of intravenous plus intraventricular (IV-IVT) colistin therapy may improve outcomes in patients attending with meningitis/ventriculitis due to multidrug resistance infections.

Keywords Nosocomial meningitis/ventriculitis · Intrathecal/intraventricular colistin treatment · CNS infections

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Introduction

The treatment of acute hydrocephalus with external ventricular drainage (EVD) is a lifesaving procedure, but it is associated with complications such as EVD-related infections (EVD-M), which may range between 1 and 18 % [5–7, 9, 25–27, 33]. EVD-M may be caused by Gram-negative (-) or Gram-positive (+) bacteria; however, Gram-negative infections predominate [18, 35, 38] during the last years and Gram-negative multi-drug resistance (MDR) bacteria is a notable problem [15]. Notably, in a previous study [15], *Acinetobacter baumannii* and *Pseudomonas aeruginosa* MDR were the most frequent isolates (98 %) of Gram-negative bacilli in post-neurosurgical treatment of meningitis and ventriculitis. These MDR bacteria present resistance in antibiotic families, which are considered as selective agents for central nervous system infections such carbapenems. On this basis, older antibiotics such as colistin have once again attracted interest [13].

Nevertheless, colistin penetration in the CNS (central nervous system), even when meninges are inflamed, is poor, and its concentration in cerebrospinal fluid (CSF) reaches approximately 10 % of its concentration in serum [2, 24, 40]. On this basis, alternative therapeutic strategies may be necessary and the intrathecal use of colistin has been suggested as an adjacent therapy to intravenous administration for infection

control [12]. Previous studies have reported that treatment with intravenous and intrathecal colistin with a wide dosing range from 1.6 to 40 mg (20,000–500,000 IU) may be associated with excellent cure rates [29, 32]; however, deaths [31, 39] and complications [29] such as chemical meningitis have been reported as well, in small series. In the largest and most recent study, Debonis et al. [8] reported no antibiotic-therapy-related side effects or deaths in nine patients who received 10–20 mg of colistimethate whereby all patients were cured. Nevertheless, more data are needed to draw firm conclusions of the role of intrathecal antibiotic therapy.

In the present study, we therefore aimed to add further evidence in the literature using our experience in the management of meningitis/ventriculitis with intrathecal colistimethate sodium. We compared two different therapeutic strategies, intravenous (IV) or IV plus intraventricular (IVT) colistimethate sodium treatment, and we assessed with respect to hospital mortality and length of hospital stay.

Materials and methods

This was a retrospective case series study that was performed in a tertiary care academic neurosurgical center at the University Hospital of Larissa. The study included all patients hospitalized in the neurosurgical department (26 beds) provided they were > 18 years and had been receiving therapy with IV or IV-IVT colistin (in the form of colistimethate sodium, which is the standard compound used in this center) for meningitis/ventriculitis, between 2006 and 2014. Cases that presented positive culture or Gram stain CSF but normal levels of glucose, protein, and cytology were considered as contamination but not infection and were excluded from the study. Data was retrieved from the electronic database of the department after careful reviewing of all records of patients (electronic and hard copies) hospitalized between 2006 and 2014. Data collection was performed by two qualified research nurses (MC and ET) and the data was reviewed and analyzed by two physicians (GF and DM) on the basis of a structured form that included questions related to protocol. The protocol included points (listed and defined statistically) related to a list of variables (items, "database fields") that were essential for the study to be completed; such as the characteristics of the population (i.e., age, gender, medical history), type of treatment, microbiology—including bacterial susceptibility to antibiotics—, hospital-related infections, and the main end points (overall survival, adverse effects related to treatment). The study was approved by the ethics committee of the University Hospital of Larissa.

After inclusion, patients were classified into two groups: patients who received with IV-IVT colistimethate sodium treatment (the ITC group), and patients who had received only IV colistimethate sodium treatment (the IVC group).

Endpoints

The primary outcome was hospital mortality. Secondarily, we examined the length of hospital stay (in survivors) and the duration of fever attributed to EVD-M.

Clinical data and definitions

Demographic and clinical data, information on underlying diseases, the average residence time before neurosurgery interventions, history of colonization and antibiotic treatment, earlier appearance of meningitis, computed tomography (CT) scan findings, Glasgow Coma Scale (GCS) at intubation time, type of neurosurgical intervention and the severity of clinical condition according to the Acute Physiological and Chronic Health Evaluation II (APACHE II) scoring system were retrieved from patients' records and documented; APACHE II score is a severity-of-disease classification system that is applied within 24 h of a patient's admission: an integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death [34]. CT brain scan findings were used to describe brain injury (damage at one or both cerebral hemispheres, presence or not subarachnoid hemorrhage (SAH) at the basal cisterns and intraventricular involvement), SAH, intracerebral or/and intraventricular hemorrhage (ICH/IVH), and benign brain tumors.

Nosocomial meningitis/ventriculitis was defined according to Centers for Disease Control (CDC) definition [23]. CNS infections should require at least one of the following two criteria: the presence of a microorganism isolated in CSF and fever > 38 °C in the absence of other recognized cause and any of the following: increased leukocytes (>10 per mm^3 with > 50 % polymorphonuclear leukocytes), increased protein (>45 mg/dl), and/or decreased levels of glucose (<40 mg/dl) in CSF. Patients were considered to have mixed bacterial infection when two or more microorganisms were isolated from the CSF cultures. A positive culture or Gram stain CSF with normal levels of glucose, protein, and the number of cells in the absence of symptoms was not considered as an infection. According to institutions, therapeutic protocol patients were considered as cured if they presented no fever in the last 10 days and no isolated microorganisms in last two CNS cultures [32]. CSF samples were obtained via intraventricular catheter or lumbar puncture at rest. MDR bacteria were defined as Gram-negative multi-drug resistant as previously reported [30]; Gram-positive MDR bacteria were methicillin resistant *Staphylococcus aureus* and *Enterococcus faecium*. Colistin-resistant bacteria were considered isolates with minimal inhibitory concentration >2 μg/ml by both broth microdilution and E-test methods.

Intrathecal infusion of colistimethate sodium was administered in a standard way in this center through an EVD system,

which was then closed for 1 h. Microbial clinical isolates were identified by morphology, Gram stain, and the reactions with the card Vitek 2 GNI card (bioMerieuxVitek, Australia, Pty Ltd, Generic Network Interface). Sensitivity to colistin was determined by disk diffusion (10-μg disc) (Oxoid, Basingstoke, Hants, England), and isolates were considered susceptible if the inhibition zone was ≥11 mm, as previous antibiotic therapy was defined as a treatment for at least 48 h during the 10 days prior to the diagnosis of meningitis.

Statistical analysis

Data are expressed as mean (±SD). Data were assessed for normality using the Shapiro–Wilk test. Nominal data were analyzed using the Fisher's exact test. Continuous data were analyzed using Student's *t* test or the Mann–Whitney *U* test as appropriate. A p value < 0.05 was considered as statistically significant. Statistical analyses were performed with the use of Statistical Product and Service Solutions (SPSS) software, version 15 (SPSS Inc., Chicago, IL, USA).

Results

A total of 2300 patients were hospitalized during the studied period (Fig. 1). Nine-hundred-twenty (40 %) underwent surgery and 586 of them (63.6 %) were treated with EVD. Thirty-four patients (5.6 %) presented meningitis/ventriculitis due to bacteria—MDR in 26 (76.4 %) cases, which were all sensitive to colistin. Of these 34 patients, 11 (32.5 %) received IV colistimethate sodium treatment (IVC group) and 23 (67.6 %) received IV and intraventricular colistimethate sodium treatment (ITC group) via EVD catheters. Their baseline characteristics are shown in Tables 1 and 2. The mean dose of colistimethate sodium therapy used was 170,000 (±400) [or 13.6 (0.03) mg]. Three different dosing schemes of administration, corresponding in three different time-periods: 150,000 IU of colistin once daily [seven (30.4 %) cases], 180,000 IU once daily [seven (30.4 %) cases] and 200,000 IU once daily [nine (39.1 %) cases]. The daily dose of intravenous colistimethate sodium was 9 × 106 IU divided in three doses (this was the standard scheme, used in 94.1 % of cases); the dose was reduced in cases with renal impairment. In 24 out of 34 (70.5 %) of patients, the isolated microorganism in the CSF was *Acinetobacter baumannii* - (15 or 65.2 % of the ITC group and 9 or 81.8 % of the IVC group) (Table 2). No significant risk factor for different Gram-negative bacterial species or MDR susceptibility was identified (see online resource).

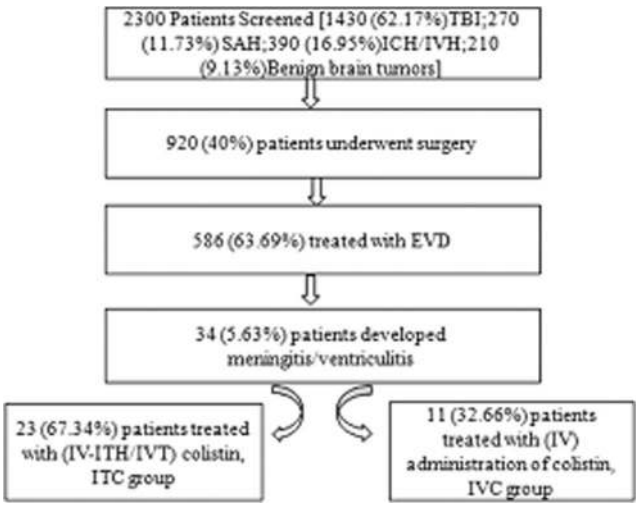

Fig. 1 A total of number of patients were hospitalized during the study period and were screened for eligibility. *TBI* traumatic brain injury, *SAH* subarachnoid hemorrhage, *ICH/IVH* intracerebral hemorrhage/intraventricular hemorrhage, *EVD* external ventricular drainage, *IV-ITH/IVT* intravenous-intrathecal/intraventricular, *IV* intravenous

Patients who presented ventriculitis and other infections in the same period had GOS median (range) 3 (4) and mortality 33.3 % and patient without other infections in the same period had GOS median (range) 3.5 (4) and mortality 35.6 %.

Outcomes

Clinical outcomes are shown in Table 3. Hospital mortality was significantly lower in the ITC group (three deaths, 13.0 %) compared to the IVC group (eight deaths, 72.7 %) (log rank, Mantel–Cox, $p = 0.001$). Characteristics of survivors and non-survivors are shown in Table 4. In survivors, the mean daily dose of colistin treatment was significantly higher while EVD-related fever duration (days) was significantly shorter in survivors compared to non-survivors (5.4 ± 0.4 vs. 8.4 ± 0.5, $p = 0.001$).

Notably, receiver operator characteristic (ROC) analysis showed that fever duration with a cut-off of 6.5 days could predict poor outcome (death) with a sensitivity of 70 % and specificity of 91 % (Fig. 2, AUC 0.8, $p = 0.001$). Among *Acinetobacter baumannii* cases, which consisted of the largest group of patients, 13 out of 15 (86.6 %) patients in the ITC group survived, whereas only one out of nine (11.1 %) patients in the IVC group.

Cure rates were significantly higher in the ITC group compared to the IVC group: 20 out of 23 (86.9 %) vs. three (28.2 %) ($p = 0.001$). Length of hospital stay in patients who were discharged alive were 87.9 ± 11.0 and 68.0 ± 22.1 days, respectively ($p = 0.60$).

Discussion

The present study suggests that intravenous/intrathecal treatment was associated with increased survival compared with patients who were treated with intravenous antibiotics only. In

Table 1 Baseline characteristics of patients with external ventricular drainage-related infections according to the treatment used

	Group ITC ($n = 23$)	Group IVC ($n = 11$)	p value
Age, years	53.5 ± 2.9	44.5 ± 5.2	0.03
Sex (male), *n* (%)	8 (34.7)	5 (45.4)	0.54
APACHE II score	15.9 ± 0.6	15.5 ± 1.5	0.20
GCS intubation, median (range)	8 (7)	7 (5)	0.40
Cause of admission			
-TSAH, *n* (%)	6 (26.0)	5 (45.4)	0.25
-TBI, *n* (%)	3 (13.0)	1 (9.0)	0.73
-ICHor/+IVH, *n* (%)	12 (52.1)	4 (36.3)	0.17
-Benign brain tumors, *n* (%)	2 (8.6)	1 (9.0)	0.97
Postneurosurgical complications			
-Cerebral edema, *n* (%)	9 (39.1)	4 (36.3)	0.87
-Hydrocephalus, *n* (%)	3 (13.0)	–	0.21
-Abscess/sepsis, *n* (%)	2 (8.6)	–	0.31
-Thromboembolism, *n* (%)	–	2 (18.1)	0.03
-CSF leak, *n* (%)	2 (8.6)	1 (9.0)	0.97
Intraventricular daily dose of colistin, IU × 10^3	170 ± 0.4	0.0 ± 0.0	–
Duration of intraventricular treatment, days	16.0 ± 8.3	–	–
Intravenous daily dose of colistin, IU × 10^6	8.8 ± 0.1	8.2 ± 0.8	0.56
Duration of intravenous treatment, days	16.0 ± 8.3	15.3 ± 7.6	0.77
Fever duration, days	6.1 ± 0.5	7.0 ± 0.7	0.36

Data are presented as mean ± SD, or otherwise indicated

Group ITC patients with intravenous-intraventricular colistimethate sodium treatment, *Group IVC* patients with intravenous colistimethate sodium treatment, *GCS* Glasgow Coma Scale. *APACHE* Acute Physiological and Chronic Health Evaluation scoring system, *TSAH* traumatic subarachnoid hemorrhage, *TBI* traumatic brain injury, *ICH* intracerebral hemorrhage, *IVH* intraventricular hemorrhage, *CSF* cerebrospinal fluid

p value for the difference between groups

addition, we found that EVD-related fever duration could predict poor outcome (death) in these patients. These findings of the present retrospective study points out that this treatment may provide an advantage in the management of Gram-negative MDR CNS infections and offers a basis for a large future trial.

Meningitis/ventriculitis is one of the most noteworthy complications in patients undergoing craniotomy, mainly at those who show again excision for recurrent glioma [34]. The incidence in patients with EVD can be a lot higher and can reach 8 % [23]. In our study, 586 patients were treated with EVD, and 34 patients (5.6 %) developed meningitis/ventriculitis, with multi-drug resistant bacteria such as *Acinetobacter baumannii* in their majority. Previous studies reported that the frequency of nosocomial meningitis/ventriculitis caused by *Acinetobacter baumannii* was between 3.6 [20] and 11 %

Table 2 Isolated microorganisms in CSF of patients with external ventricular drainage-related infections according to the treatment used

	Group ITC ($n = 23$)	Group IVC ($n = 11$)
Acinetobacter baumannii, *n* (%)	15 (65.2)	9 (81.8)
Pseudomonas aeruginosa, *n* (%)	8 (34.7)	2 (18.1)
Klebsiella pneumonia, *n* (%)	2 (8.6)	4 (36.3)
Enterobacter cloacae, *n* (%)	1 (4.3)	2 (18.1)
Staphylococcus Epiderm.-Heamol., *n* (%)	–	2(18.1)

Polymicrobial cases: four cases with *Acinetobacter baumannii* and *Klebsiella pneumonia*, two cases with *Acinetobacter baumannii* and *Enterobacter cloacae*, one case with *Pseudomonas aeruginosa* and *Enterobacter cloacae*, one case with *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, and one case with *Acinetobacter baumannii* and *Klebsiella pneumonia* and *Staphylococcus epidermidis*

Group ITC patients with intravenous-intraventricular colistimethate sodium treatment, *Group IVC* patients with intravenous colistimethate sodium treatment, *CSF* cerebrospinal fluid

p value for the difference between groups

Table 3 Outcomes of patients with external ventricular drainage-related infections according to the treatment used

	Group ITC ($n = 23$)	Group IVC ($n = 11$)	p value
Mortality, *n* (%)	3 (13.0)	8 (72.7)	0.001
Length of hospital stay, days	87.9 ± 11.0	68.0 ± 22.1	0.60
ICU stay, days	51.7 ± 5.9	33.8 ± 4.1	0.07
Fever duration, days	6.1 ± 0.5	7.0 ± 0.7	0.36
Cured, *n* (%)	20 (86.9)	3 (28.2)	0.001

Data are presented as mean ± SD, or otherwise indicated

Group ITC patients with intravenous-intraventricular colistimethate sodium treatment, *Group IVC* patients with intravenous colistimethate sodium treatment, *ICU* intensive care unit

[17] of cases and patients at risk for post-neurosurgical bacterial meningitis included those with cerebrospinal leakage, concomitant incision infection, prolonged duration of surgery, surgery that enters a sinus, increased severity of illness, prolonged external ventricular drainage, and need for repeat surgery [20].

Table 4 Clinical characteristics of survivors and non-survivors

	Survivors ($n = 23$)	Non-survivors ($n = 11$)	p value
Age, years	52.7 ± 2.9	44.0 ± 4.9	0.82
Sex (Male), *n* (%)	10 (43.4)	3 (27.2)	0.36
APACHE II score	16.4 ± 0.9	14.5 ± 1.4	0.16
GCS intubation, median (range)	8 (7)	7 (5)	0.14
Cause of admission			
TSAH, *n* (%)	8 (34.8)	3 (27.3)	
TBI, *n* (%)	3(13.0)	1 (9.1)	
ICHor/+IVH, *n* (%)	9 (39.1)	6 (54.5)	
Benign brain tumors, *n* (%)	3 (13.0)	–	
Other in-hospital infections			
Bloodstream, *n* (%)	10 (43.4)	5 (45.5)	
VAP, *n* (%)	12 (52.2)	7 (63.6)	
UTI, *n* (%)	5 (21.7)	2 (20.0)	
A. baumannii in CSF, *n* (%)	13 (56.5)	3 (27.3)	
Group ITC, *n*(%)	20 (86.9)	3 (27.2)	0.001
Intraventricular daily dose 150,000, *n* (%)	5 (21.7)	2 (18.1)	
Intraventricular daily dose 180,000, *n* (%)	7 (30.4)	–	
Intraventricular daily dose 200,000, *n* (%)	8 (34.7)	1 (9.0)	
Intraventricular daily dose > 180,000, *n* (%)	15 (65.2)	1 (9.0)	
Duration of intraventricular therapy, days	19.3 ± 8.1	15.6 ± 8.5	0.457
*< 12 days, n (%)**	9 (39.1)	8 (72.7)	
> 12 days, n (%)	14 (60.9)	3 (27.3)	
Group IVC, *n* (%)	3 (13.0)	8 (72.7)	0.001
Intravenous daily colistin dose, IU × 10^6	8.8 ± 0.1	9.0 ± 0.0	0.56
Duration of intravenous treatment, days	18.0 ± 7.5	14.7 ± 8.2	0.214
Fever duration, days	5.4 ± 0.4	8.4 ± 0.5	0.001

Data are presented as mean(SD), or otherwise indicated

Group ITC patients with intravenous-intraventricular colistimethate sodium treatment, *Group IVC* patients with intravenous colistimethate sodium treatment, *GCS* Glasgow Coma Scale. *APACHE* Acute Physiological and Chronic Health Evaluation scoring system, *tSAH* traumatic subarachnoid hemorrhage, *TBI* traumatic brain injury, *ICH* intracerebral hemorrhage, *IVH* intraventricular hemorrhage, *CSF* cerebrospinal fluid, *ITH* intrathecal, *IV* intravenous, *VAP* ventilator-associated pneumonia, *UTI* urinary tract infections

*12 days was the median duration of intraventricular therapy

p value for the difference between groups

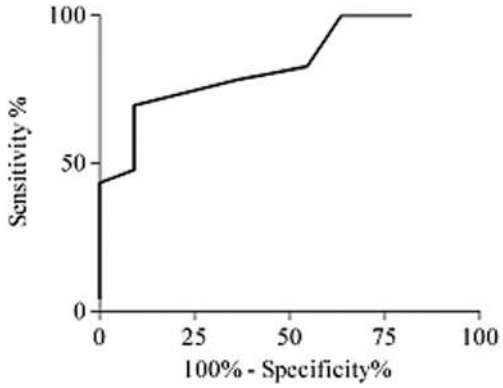

Fig. 2 Receiver operator characteristic (ROC) analysis

In our series, the frequency of infections due to *Acinetobacter baumannii* was a lot higher: 15 patients (65.2 %) of ITC group and nine patients (81.8 %) of IVC group with meningitis/ventriculitis were caused by *Acinetobacter baumannii* (Table 2). The increased frequency of MDR infections may explain the remarkably increased mortality that was found in IVC group (72.7 %). In contrast, mortality in ITC group was significantly lower (13.0 %) and similar with aforementioned reported rates [17, 20]. This difference between ITC and IVC suggests that intrathecal treatment may be efficient in the treatment of difficult MDR infections.

Intrathecal treatment with colistin is used because colistin's spectrum of activity includes Gram-negative bacilli [14, 16] and especially because it is effective against MDR bacteria such as *Acinetobacter baumannii*, which have emerged during the last years in the nosocomial setting. However, it has been mentioned by previous studies that colistin has poor penetration through the blood–brain barrier even during inflammation [3, 4, 40]; thus, using intravenous monotherapy in patients with bacterial meningitis, the CSF colistin levels are 5–10 % of those in blood. The use of intrathecal administration can increase the levels of the drug in CSF achieving the necessary concentration for efficient bacterial killing [40]. Previous studies reported improved clinical outcome in cases with CNS infection by A*cinetobacter baumannii* or *Pseudomonas aeruginosa* using combined IV-IVT antibiotics therapy [1], and this is crucial, especially in cases with MDR infections.

Intrathecal treatment with colistin is an accepted treatment modality but its background is not solid, and there is some reluctance in its use. There are concerns regarding its efficacy, the risk of chemical meningitis/ventriculitis or of secondary infections due to the amount of manipulations concerning the EVD, the dosage regimen, the duration of treatment. The Infectious Diseases Society of America (IDSA) in 2004 proposed a daily dosage of colistin administered via the intrathecal/intraventricular (ITH/IVT) route, equal to 10 mg (125,000 IU) [36], but in practice there is a wide range from 1.6 to 40 mg (20,000–500,000 IU) [11, 28] and the dose is selected empirically. In many studies proposed as measures for the therapeutic colistin levels the terms of milligrams (mg) while others use the international units (IU) [11, 28]. One million IU (mIU) of colistin is equivalent to approximately 80 mg [10]. In our data, the daily dose used was based on institutions policies and were 150,000 IU of colistin once daily, in seven (30.4 %) cases patients received 180,000 IU and 9 (39.1 %) cases received 200,000 IU. The mean intraventricular daily colistin dose in survival patients was higher compared to non-survival and a dose > 180,000 IU was significantly associated with survival (Table 4). The latter may indicate that non-survivors might have been under-treated. This question cannot be excluded with certainty based on our data since colistin levels have not been determined and this is a limitation of this retrospective study. However, these findings merit further investigation because the optimal dose for intrathecal treatment has not yet been established and our results may be used to form the basis of a future study.

In our study, fever duration between survivors and non-survivors was different; fever duration was associated with lower mortality indicating most likely infection control in survivors. Notably, ROC analysis showed that fever duration with a cut-off of 6.5 days could predict poor outcome (death) with a sensitivity of 70 % and specificity of 91 %.

Previous clinical studies have suggested that there is increased risk of nephrotoxicity associated with colistin [19, 21, 22] and mainly with intravenous administration [37]. In our data, the IV mean daily colistin dose was not different between survivors and non-survivors (Table 4). The mean dose of intravenous therapy was standard based on actual institutions policies (9×10^6 IU of colistin daily, divided into three doses) while in some cases with renal impairment the dose was decreased. Furthermore, no serious nephrotoxic effect was observed during the period of administration. Presumably, physicians were aware of the potential adverse effects of colistin and managed adequately the fluid–electrolyte balance and other possible risk factors for renal injury during the period of treatment.

The duration of hospitalization in our study was 87.9 ± 11.0 days in the ITC group and 68.0 ± 22.1 days in the IVC group. The long duration of stay was probably due to the burden of the neurosurgical disease. Previous studies have reported various lengths of stay in these patients. For example, in Wang et al.'s study [39], the mean duration was approximately 122 days, in Remes et al.'s [31] study, 42 days, and in De Bonis et al.'s [8] study the median length was 48 days (range, 25–184).

We acknowledge that there are several points of our study that have to be considered when interpreting its results. Firstly, this is a one-center study. The population studied was small, and therefore the statistical power is low and statistical comparisons may not provide reliable results for such small samples. Secondly, data were retrospectively collected and thus

most sources of error due to confounding and bias are more common compared to a randomized study. For example, we cannot ascertain for the reasons for which physicians decided for intravenous or intravenous plus intrathecal treatment. In addition, most patients stayed in the ICU for some period of time together with patients with different pathologies. This may have influenced the incidence of meningitis and outcome. Furthermore, other antibiotics than colistin were not used for intrathecal treatment—the latter could offer further insight in the role of intrathecal treatment in CNS infections. Consequently, the number of EVD-related meningitis cases was relatively low and we could not identify independent risk factors for MDR cases. In this respect, a definitive conclusion is hard to be drawn. Moreover, there were no data regarding brain magnetic resonance imaging that could provide insight for a potential adverse effect of intrathecal treatment in the epithelium of the brain ventricle and the risk of chemical meningitis. This could be done in a prospective study with a different design than ours. Finally, we acknowledge that different clinical conditions or characteristics of treatment could affect outcomes in this study. In order to clarify this point, we introduced variables in the analyses that describe different clinical parameters, i.e., causes of admission and treatment modalities (different dosing schemes, length of therapy). Only intrathecal treatment and duration of fever were found to be independently associated with mortality. In this respect, our findings could be helpful as the basis for prospective studies in the future that could provide further insight in the role of intrathecal colistin in EVD-related infections.

Conclusions

In conclusion, these data show that the combination IV-IVT colistin therapy may improve outcomes in patients presenting with meningitis due to MDR infections after neurosurgical interventions. In this respect, combined IV-IVT therapy may be one of the few treatment options for multi-resistant microorganisms in CNS.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed patient consent Informed consent was obtained from all individual participants included in the study.

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Comments

Fotakopoulos and coworkers present a study retrospectively assessing "outcomes in meningitis/ventriculitis treated with intravenous or intraventricular plus intravenous colistin" in 34 patients. Meningitis/ventriculitis, especially in multi-drug resistant bacteria, is still a life-threatening disease with therapeutic challenges. Thus, in my opinion the analysis of the described regimen deserves publication on the one hand, and on the other hand, we have to consider the limitations of the study, discussed by the authors themselves. The most important limitation is the retrospective design of the study, making it difficult to draw definite conclusions. The authors should try to initiate a prospective controlled study to critically review the present results and conclusions.

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