Intrathecal or intraventricular colistin: a review

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SUMMARY

Central Nervous System (CNS) infections related to external ventricular derivation are a major complication of patients undergoing neurosurgical procedures. Antimicrobial treatment of CNS infections should be based not only on the susceptibility of the isolated microorganism, but also on the treatment's pharmacokinetic properties demonstrating the passage of the molecule through the blood-brain barrier. When CNS infections are caused by multi-drug resistant Gram-negative bacteria, intrathecal colistin is considered an effective and safe option. We review the literature of intrathecal/intraventricular use of colistin, comprehensive of both pharmacokinetic data and clinical experiences.

Keywords: colistin, central nervous system infection, intrathecal, intraventricular, pharmacokinetics.

■ INTRODUCTION

Meningitis and or ventriculitis may be a significant complication in patients undergoing craniotomy and the incidence is up to 8% in patients with external catheter derivation (EVD) [1, 2]. Coagulase-negative staphylococci are predominant amongst Gram-positive and, amongst Gram-negative rods, *Acinetobacter baumannii* has an incidence of 3.6-11% [3]. Risk factors for infection are represented by leakage of the cerebrospinal fluid (CSF), concomitant infection at the time of incision, prolonged or repeated surgery and prolonged ventricular drainage, surgery through the sinuses as well as severity of underlying condition [4, 5]. Aetiology by pseudomonas and carbapenemase-producing Enterobacteriaceae is even more complex and difficult to treat [6-9].
The choice and kinetics of antimicrobials in central nervous system (CNS) infections is of utmost importance and the blood-brain barrier (BBB) has specific features that limit the passage of molecules on several parameters such as size, lypophilia, plasma protein binding and transporter affinity [10]. In patients with acute bacterial meningitis the CNS transfer of drugs may be increased due to opening of intracellular tight junctions, increased CSF outflow resistance, low pH and also by transporters stimulated by proinflammatory cytokines. There is a poor CSF penetration of beta-lactams (AUC_{CSF}/AUC_{serum} <0.15) that increases with inflammation, without requiring intraventricular administration. Other antibiotics such as aminoglycosides, glycopeptides and polymyxins have a very low therapeutic index, with low CSF concentrations and therefore require lumbar, intrathecal or intraventricular (ITH/IVT) administration; only the latter ensure distribution in the hole CSF space.

Pharmacokinetic of colistin
Colistimethate (CSM) is eliminated by the kidneys and has a half-life of 2.7-4.5 hours; after a standard intravenous (IV) administration of 5 mg/Kg/day, the average plasma concentration is 8.1 mg/mL. The few data available on the pharmacokinetics of polymyxins in CSF reported a low diffusion through the CNS, with unclear rate of penetration and a possible role for meningeal inflammation

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[11]. When colistin concentrations were measured by microbiological assay, the low CNS concentrations were not enhanced by meningeal inflammation [12]. Methodological issues in studies before 2009 may be responsible for the low concentration of both colistin and CMS, in a context in heterogeneous patient populations composed by children, adults, neurosurgical patients with EVD and variable amount of daily CSF drainage, with or without meningeal inflammation. Moreover, standard dosage of IV administration of colistin was not universally applied, as we did in a series of three patients [13, 14].

Jimenez Mejitas et al. reported CSF concentrations as high as 25% of serum concentration, with an IV infusion of 1,000,000 IU every 6 hours by a broth-dilution assay of polymyxins, using *Escherichia coli* strain ATCC 25922, whilst Markantonis et al. used high-performance liquid chromatography (HPLC) in five non-consecutive critically ill adult patients receiving intravenous CMS at variable dosages from 150 mg daily to 225 mg three times a day (1,875,000-2,812,500 IU): three patients had meningitis without considerable meningeal inflammation [11, 15, 16]. Serum and CSF samples were collected after two days of treatment by lumbar puncture in four patients and from EVD in one patient, with a ratio of the area under the concentration-time curve (AUC) for CSF-serum of 0.051. It is interesting that the AUC of colistin in CSF were parallel with simultaneous peaks and similar same half-life. According to these results, the conclusion was that the CSF penetration was only of 5%, consistently with previous studies performed by microbiological assays, suggesting a low possibility of eradication of infections by Gram-negative bacteria [12]. Antachopulos et al. used liquid chromatography tandem mass spectrometry (LC-MS-MS) to study the CMS concentrations in three paediatric patients with EVD [17]. Intravenous colistin had low CSF concentrations below 0.2 mcg/mL and higher (34% to 67% of sera concentrations) levels of colistin were observed with meningeal inflammation.

According to these studies, IV colistin alone does not provide CSF concentrations high enough to reach a MIC of 2 mcg/mL for MDR Gram-negative rods and therefore topical administration is needed to support the treatment. Only two studies described the PK of ITH/IVT colistin: Imberti et al. studied by HPLC and by one-compartment model colistin CSF in nine patients only treated with IVT colistin at variable dosages, from 2.61 to 10.44 mg (32,000-130,000 IU) [18]. The C-*trough* concentration ranged between 2,0 and 9,7 mcg/mL and the CSF concentration were always >2 mcg/mL when colistin was administered at a dose >65,200 IU/day, with a great inter-patients variability, perhaps due to the unknown fractions of CMS metabolized to colistin, the diffusion from the CSF to the systemic circulation and the cerebral tissue and the elimination through the external efflux of CSF, in addition to the unpredictable amount of the CSF spontaneously drained through the EVD by the fluctuation of intracranial pressure. Therefore it is not surprising that the ITH/IVT dose of 125,000 IU/day suggested by the IDSA guidelines seems to be more appropriate [19].

Twelve patients treated with IVT-IV colistin (3,000,000 IU every 8 hours and IVT dose of 125,000 IU daily) and EVD were studied by HPLC by Ziaka, of which five were treated only IV, three only by IVT administration and four patients by IVT-IV. The CSF concentrations in the IV group were very low, with a ratio of 0.07 [20]. There was no accumulation of colistin concentration over time, the mean CSF/serum concentration was higher in IVT-IV combination than in the other groups and the mean AUC CSF/AUC serum ratios were 60% higher in patients with ventriculitis than in control patients. Perhaps a greater penetration could be achieved with meningeal inflammation but a median CSF concentration >0.5 mcg/mL was only observed in the combination group, suggesting that IV colistin could increase CSF concentrations of ITH/IVT colistin; the conclusion was that combined treatment had a better chance to eradicate severe CNS infections [20].

Clinical data

Intrathecal/Intraventricular (IVT/ITH) colistin administration was associated with better outcomes compared to IV colistin alone [21-23].

There are guidelines available such as those by the Infectious Diseases Society of America (IDSA) in 2004 that suggested a daily ITH dosage of 10 mg (125,000 IU) [19]. However, in clinical practice, the dose is often chosen empirically, ranging between 1.6 and 40 mg (20,000-500,000 IU) either as a single dose or in divided doses. We synthetized in Table 1 the main data collected from all

Table 1 - Reported cases of Gram-negative CNS infections in adults treated with intrathecal or intraventricular colistin. Dosages reported in the original paper are converted in International Units (1 mg of colistin equals 30.000 IU of colistin and 1 mg of colistimethate equals 12.500 IU of colistin). *ITH: intrathecal, IVT: intraventricular, IV: intravenous, NR: not reported, qd: once daily, bid: twice a day.*

Author, year, reference	Case no.	Microorganisms	ITH, IVT Colistin dose (IU), timing, (days of treatment)	IV Colistin	Other antibiotics	Infection outcome
Price, 1972 [24]	5	*K. aerogenes*	IVT 50,000 bid → qd (NR)	Yes	gentamicin	2/5 Cure
Kaplan, 1990 [25]	1	*A. baumannii*	ITH NR (20)	No	cefotaxime, aminoglycoside	Cure
Fernandez-Viladrich, 1999 [26]	2	*A. baumannii*	ITH 62,000-125,000 bid (17-19)	No	tobramycin	Cure
Vasen, 2000 [27]	1	*A. baumannii*	ITH 62,500→125,000 qd (21)	No	No	Cure
Benifla, 2004 [28]	1	*A. baumannii*	IVT 40,000 qd (17)	No	ampicillin/ sulbactam	Cure
Quinn, 2005 [29]	2	*P. aeruginosa*	ITH 125,000 qd (14-16)	No	No	Cure
Suarez Fernandez, 2005 [30]	7	*A. baumannii*	IVT ITH 300,000 bid (8-21)	Yes	No	5/7 Cure
Gump, 2005 [31]	1	*P. aeruginosa*	ITH 250,000-125,000 qd (10)	Yes	No	Cure
Kasiakou, 2005 [32]	1	*A. baumannii*	IVT 20,000 qd (21)→ 40,000 bid (42)	Yes	amikacin	Relapse → Cure
Bukhary, 2005 [33]	1	*A. baumannii*	IVT 125,000 bid (21)	No	No	Cure
Sueke, 2005 [34]	1	*A. baumannii*	ITH 75,000 bid (14)	No	No	Cure
Berlana, 2005 [35]	2	*A. baumannii, P. aeruginosa*	ITH 125,000-250,000 qd (8-10)	Yes	No	Cure
Charra, 2005 [36]	1	*A. baumannii*	ITH 62,500-125,000 qd (21)	No	No	Cure
Karakitsos, 2006 [37]	6	*A. baumannii*	IVT 125,000-250,000 qd (16-20)	No	No	Cure
Yagmur, 2006 [38]	1	*P. aeruginosa*	ITH 62,500 qd (21)	No	No	Cure
Ng, 2006 [39]	5	*A. baumannii*	ITH IVT 62,500-125,000 qd (3-24)	Yes	amikacin	4/5 Cure
Al Shirawi, 2006 [40]	1	*A. baumannii*	IVT 40,000 qd (28)	No	No	Cure
Motaouakkil, 2006 [41]	1	*A. baumannii*	ITH 62,000-125,000 qd (21)	No	rifampin	Cure
Schina, 2006 [42]	1	*P. aeruginosa*	ITH 20,000-60,000 qd (26)	Yes	ceftazidime, amikacin	Cure
Metan, 2007 [43]	1	*A. baumannii*	ITH 125,000 qd (21)	No	meropenem	Death
Enfanto, 2007 [44]	1	*K. pneumoniae*	ITH 125,000 qd (7)	No	vancomycin, meropenem	Cure
Ho, 2007 [45]	1	*A. baumannii*	ITH 80,000 qd (28)	Yes	No	Cure
Paramythiotou, 2007 [46]	1	*A. baumannii*	IVT 125,000 qd (20)	Yes	No	Cure
Lee, 2008 [47]	1	*A. baumannii*	IVT 62,500 qd (3)	Yes	meropenem, sulbactam	Cure
Rodriguez Guardado, 2008 [48]	8	*A. baumannii*	IVT 125,000 bid (21)	Yes	No	Cure
Hachimi, 2008 [49]	1	*A. baumannii*	IVT 62,000-125,000 qd (22)	No	amikacin	Cure
Rodriguez, 2009 [50]	1	*A. baumannii*	ITH 125,000 qd (NR)	No	rifampin	Cure

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Author, year, reference	Case no.	Microorganisms	ITH, IVT Colistin dose (IU), timing, (days of treatment)	IV Colistin	Other antibiotics	Infection outcome
Lopez-alvarez, 2009 [51]	3	*A. baumannii*	IVT 62,500-100,000 bid (9-29)	Yes	No	Cure
Dalgic, 2009 [52]	1	*A. baumannii*	IVT 12,500→125,000 qd (20)	Yes	No	Cure
Baiocchi, 2010 [53]	1	*P. aeruginosa*	ITH 125,000 qd (NR)	No	aztreonam, amikacin	Cure
De Pascale, 2010 [54]	1	*A. baumannii*	ITH 75,000-150,000 qd (22)	Yes	No	Cure
Khawcharoenporn, 2010 [55]	7	*A. baumannii*	ITH 300,000-500,000 qd (2-21)	No	imipenem, sulbactam, ciprofloxacin	5/7 Cure
Cascio, 2010 [56]	1	*A. baumannii*	ITH 125,000 qd (10)	No	No	Cure
Kim, 2010 [57]	1	*A. baumannii*	ITH 62,500 bid (17)	Yes	rifampin	Cure
Ozdemir, 2010 [58]	1	*A. baumannii*	ITH 125,000 qd (35)	Yes	meropenem, sulbactam, amikacin	Cure
Razmkon, 2011 [59]	6	*A. baumannii*	IVT 125,000 qd (NR)	Yes	No	3/6 Cure
Patel, 2011 [60]	1	*A. baumannii*	IVT 125,000 qd (36)	Yes	No	Cure
Saleem, 2011 [61]	5	*A. baumannii*	ITH 4,800/kg-12,000/kg qd (5-21)	Yes	No	4/5 Cure
Alaoui, 2011 [62]	1	*A. baumannii*	ITH 48,000 qd (NR)	Yes	No	Cure
Wang, 2012 [63]	4	*A. baumannii*	IVT 25,000-200,000 bid or qd (7-27)	Yes	meropenem, sulbactam, imipenem,	3/4 Cure
Imberti, 2012 [18]	9	*A. baumannii (2) K. pneumoniae (6) P. aeruginosa (1)*	IVT 31,250-62,500 qd – bid (11-36)	Yes (5/9)	rifampin, meropenem, linezolid, sulbactam, amikacin, ceftazidime, fosfomycin, vancomycin	8/9 Cure
Ziaka, 2013 [20]	7	*A. baumannii (3) K. pneumoniae (2) Negative cultures (2)*	IVT 125,000 qd (NR)	4/7 Yes	NR	4/5 Cure
Karaiskos, 2013 [64]	6	*A.baumannii*	IVT 500,000→125,000 qd→ every 48h (12-21)	Yes	No	Cure
Bargiacchi, 2014 [14]	3	*A. baumannii (1) K. pneumoniae (1) P. aeruginosa (1)*	IVT 250,000 qd (14-20)	Yes	rifampin, tigecycline	Cure
De Bonis, 2015 [23]	9	*A. baumannii*	IVT 125,000-250,000 qd (14-40)	Yes	NR	Cure
Shofty, 2016 [22]	22 (+15 ITH amikacin)	*A. baumannii (51% in whole)*	ITH/IVT 50,000-250,000 qd (median duration 9 days)	Yes	NR	5/37 in whole Cure
Fotakopulos, 2016 [21]	23	*A. baumannii (15) K. pneumoniae (2) P. aeruginosa (8) E. cloacae (1)*	150,000-200,000 qd (8-24)	Yes	NR	20/23 Cure

the published cases and case series with IVT/ITH colistin [14, 18, 20-23, 24-64].

In a recent paper, Karaiskos and coll. proposed an interesting schedule of IVT administration with a loading dose of 500,000 IU followed by a dose of 125,000-250,000 IU every 24h, followed by a q48h ITH administration after the CSF culture becomes negative, to reduce the risk of chemical meningitis or ventriculitis and the numbers of manipulations of the EVD [64]. However, in published studies, where ITH/IVT colistin was mainly used for infections by *A. baumannii*, there was no difference in the cure rate and the time to CSF sterilization with daily ITH/IVT dosages higher or lower than 125,000 IU. Moreover, this dosage should be high enough to treat even *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Figure 1 shows that a cumulative dose above 1,750,000 IU of ITH/IVT colistin (which correspond to 125,000 IU once daily for 14 days) is associated to better outcomes.

The duration of therapy described is quite variable, from one to four weeks. Shorter treatments (less than a week) seem to correlate with a higher mortality, although in critical patients death may occur for other underlying conditions before the conclusion of the scheduled treatment (Figure 2). By converse, higher dosages may be administered in more severe patients, with a consistent bias toward higher and early mortality in those patients (Figures 3 and 4). An important issue influencing the duration of

Figure 1 - Cure rate according to cumulative dose of intrathecal/intraventricular colistin. The cumulative dose of 1.750.000 correspond to 125.000 IU of colistin once daily (dose suggested by IDSA Guidelines) for 14 days.
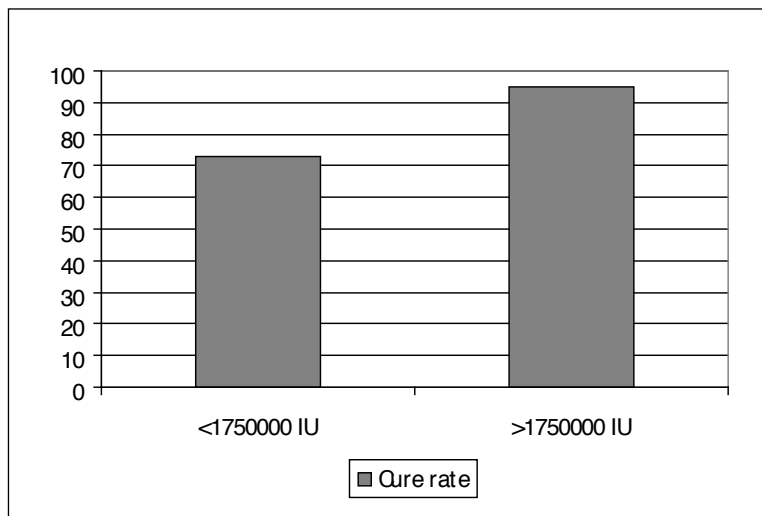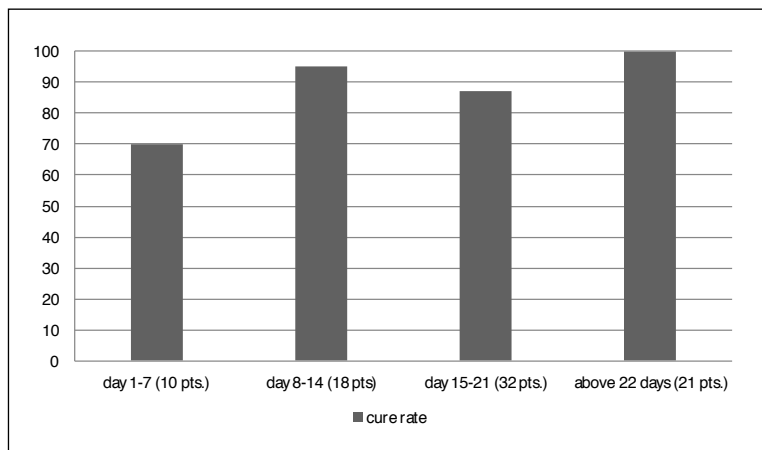

Figure 2 - Cure rates according to duration of treatment. In brackets the number of patients, whose duration of treatment was defined.
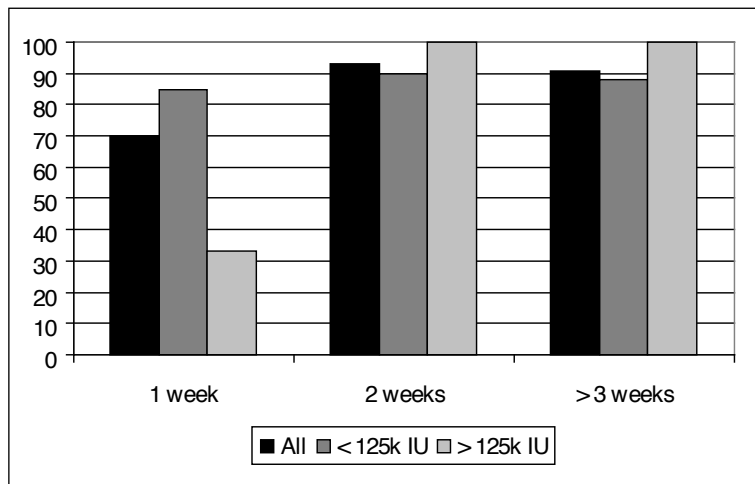
Figure 3 - Cure rates according to duration of treatment and dose of intrathecal colistin for those patients whose duration and dose of treatment was defined.
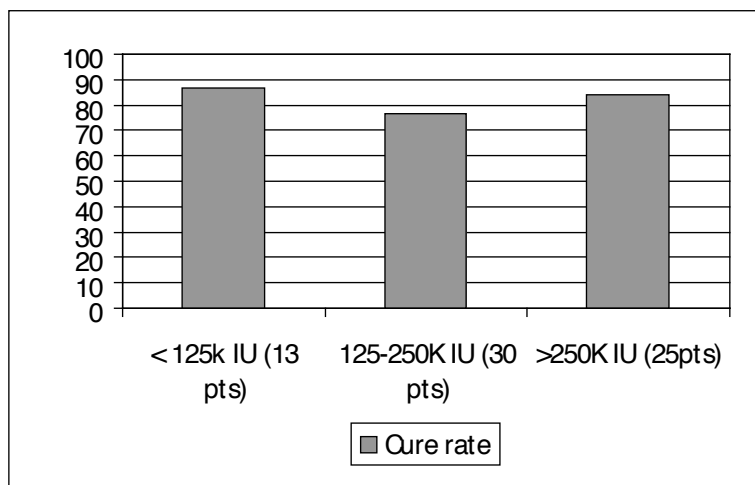

Figure 4 - Cure rates according to dose of intrathecal/intraventricular colistin. In brackets the number of patients, whose duration of treatment was defined.

treatment is the time to the first negative culture suggesting that a fast clearance of the infection may result in a better outcome with an earlier chance to change an infected catheter or to replace the external catheter, an essential factor to destroy the bacterial biofilm adhering to the device.

It is unclear which role IV colistin may play on the outcome of the CNS infection, when ITH/IVT colistin is used. Therefore, if the source of infection is strictly related to the colonization of the EVD and the infection is limited to the CNS, ITH/IVT treatment may be sufficient to sterilize CSF, but if ventriculitis is the result of a bacteraemia or there are other sites infected, IV colistin should be added to ITH/IVT colistin and perhaps a second systemic antimicrobial, chosen according to the susceptibility and synergy tests [65].

Combination antimicrobial treatment is reported in many cases choosing antibiotics according to the susceptibility tests. Rifampin has optimal CNS diffusion and may have a synergistic effect with colistin against Gram negative bacteria, such as *A. baumannii, P. aeruginosa* and, perhaps, KPC [18, 41, 50, 57, 66-69].

Side effects are reported: seizures, controlled by anticonvulsant therapy (1 case), chemical meningitis (5 cases), and *cauda equina* syndrome (1 case), with complete resolution after ITH administration discontinuation [39, 51, 57, 64]. No nephrotoxicity is reported with ITH/IVT administration.

CONCLUSIONS

PK studies and clinical data suggest that intravenous colistin alone is not sufficient to treat meningitis and ventriculitis caused by Gram-negative multidrug resistant bacteria. Intrathecal or intraventricular colistin has proved to be effective and safe. The suggested dose of 125,000 IU by IDSA Guidelines is still valid if administered once daily for at least 14 days. IV and IVT colistin (at least 125,000 IU/die) for at least 10-14 days are probably required in most patients with CNS infections.

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