International Journal of Antimicrobial Agents 54 (2019) 556–561

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

# Intrathecal or intraventricular antimicrobial therapy for post-neurosurgical intracranial infection due to multidrug-resistant and extensively drug-resistant Gram-negative bacteria: A systematic review and meta-analysis

Yangmin Hu, Wei He, Difei Yao, Haibin Dai*

*Department of Pharmacy, Second Affiliated Hospital, Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou 310009, China*

ARTICLE INFO

*Article history:*
Received 11 February 2019
Accepted 1 August 2019

Editor: Po-Ren Hsueh

*Keywords:*
Intrathecal
Intraventricular
Intracranial infection
Gram-negative bacteria
Multidrug-resistant
Extensively drug-resistant

ABSTRACT

This review investigated the effectiveness and safety of intrathecal (ITH) or intraventricular (IVT) antimicrobial therapy for post-neurosurgical intracranial infection due to multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria. Electronic databases including PubMed, EMBASE and the Cochrane Library databases were searched for clinical studies that compared the addition of ITH/IVT therapy with intravenous (IV) monotherapy in the treatment of post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria. Eligible articles were analysed using Stata/SE software v.12.0. Publication bias was assessed using Begg's funnel plot and Egger's test. Nine studies involving 296 patients were included. The odds ratio (OR) for death (IV+ITH/IVT versus IV) reported in the included studies ranged from 0.02–0.93. The overall pooled OR was 0.15 [95% confidence interval (CI) 0.08–0.28; $P < 0.001$] and the risk of mortality was significantly different between the two groups. Microbiological clearance was significantly different between the two groups, with a pooled OR of 0.02 (95% CI 0.01–0.10; $P < 0.001$). In observational studies, addition of ITH/IVT antimicrobial therapy is associated with a lower risk of mortality and a higher microbiological clearance rate, with mild adverse effects, in patients with post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria. A well-designed randomised controlled trial is necessary to address this important issue.



## 1. Introduction

Post-neurosurgical intracranial infection is one of the serious complications of neurosurgical procedures and is associated with significant morbidity and mortality [1–3]. Cerebrospinal fluid (CSF) shunts and drains, neurosurgery or head trauma, and intrathecal infusion pumps are associated with infection [4]. Staphylococci and resistant Gram-negative bacilli are the most likely aetiological agents [4,5]. The mortality rate is higher among patients with Gram-negative bacterial intracranial infection than among those with other pathogenic bacteria [6] and, even worse, treatment of the infection has become extremely difficult because of the increasing emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) isolates of *Acinetobacter baumannii, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [7]. Post-neurosurgical intracranial infection is an emergency and requires early diagnosis and treatment with appropriate antibiotics.

According to drug susceptibility analyses, there are only a few drugs, such as the polymyxins and aminoglycosides, that are effective against MDR/XDR Gram-negative bacteria. However, due to very low brain penetration, intracranial infection does not show any improvement when treated with these antimicrobial agents intravenously alone. Thus, intrathecal (ITH) or intraventricular (IVT) administration of antibiotics has been considered the last resort for MDR/XDR Gram-negative bacteria ventriculitis and meningitis not responding to intravenous (IV) regimens [8]. ITH/IVT administration can bypass the blood–brain barrier, achieve a more effective concentration of antibiotics in the CSF and reduce systemic side effects [9,10]. However, there is insufficient evidence to support ITH/IVT therapy and it is not approved by the US Food and Drug Administration (FDA). In addition, its potential neurotoxicity, such as chemical meningitis and ventriculitis, cannot be ignored, although these reactions have been reported to be mild and reversible [8,11–13]. Therefore, the aim of this systematic review and meta-analysis was to compare the mortality and microbiological

* Corresponding author. Tel.: +86 571 8778 3891; fax: +86 571 8778 3891.
*E-mail address:* haibindai@zju.edu.cn (H. Dai).

https://doi.org/10.1016/j.ijantimicag.2019.08.002

clearance of the addition of ITH/IVT therapy with IV monotherapy in the treatment of post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria and to evaluate the safety of ITH/IVT administration.

## 2. Methods

### *2.1. Sources of information and search strategy*

Relevant studies were identified by searching electronic databases including PubMed, EMBASE and the Cochrane Library up to 31 July 2018. References of each article selected were searched manually to identify additional potentially relevant studies. Conference abstracts were not searched for. No language restrictions were applied. The search terms used were 'intrathecal' or 'intraventricular', 'Gram-negative bacteria', 'intracranial infection' or 'central nervous system infection' or 'meningitis' or 'ventriculitis'.

### *2.2. Inclusion and exclusion criteria*

The study inclusion criteria were: (i) study design: randomised controlled trial (RCT), prospective or retrospective study; (ii) study population: patients with post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria; (iii) studies that compared the effects of IV plus ITH/ IVT administration therapy with IV monotherapy; and (iv) outcome of mortality reported by the study. Case reports or case series were excluded.

### *2.3. Data extraction and quality assessment*

Two researchers independently reviewed the included studies and extracted relevant information from each study. Disagreement between the two reviewers was resolved by consensus. The following variables were extracted from each study if available: first author's surname; publication year; study design; study setting; study period; type of infection; organism; demographic characteristics of the patients; ITH/IVT drug administration; microbiological clearance; mortality; and odds ratio (OR) with 95% confidence interval (CI) of outcomes. Study quality was assessed using the nine-star Newcastle–Ottawa Scale for assessing the quality of observational studies in meta-analyses (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

### *2.4. Statistical analysis*

For each study, ORs with 95% CIs were retrieved to estimate outcomes. Heterogeneity of studies was assessed by $\chi^2$ test and the $I^2$ measure of inconsistency. A fixed-effects model was applied unless statistical heterogeneity was found ($P < 0.1$ or $I^2 > 50\%$); otherwise, a random-effects model was used. Potential publication bias was assessed with Begg's funnel plot and Egger precision weighted linear regression test. All statistical analyses were conducted using Stata Statistical Software: Release 12 (StataCorp LP, College Station, TX, USA).

## 3. Results

A total of 166 articles were retrieved; the process of identifying relevant studies is shown in Fig. 1. After reviewing titles and abstracts, 21 articles were identified as potentially eligible for inclusion. Among the 21 studies, 12 were excluded from further analysis for various reasons (3 studies were excluded because they did not involve MDR/XDR Gram-negative bacteria, 6 were excluded because they did not compare IV plus ITH/IVT with IV administration and 3 were excluded because they were case reports) (Fig. 1). Finally, nine retrospective studies involving 296 patients were included in the meta-analysis [11,14–21]. Four studies were conducted in Asia [11,17–19], another four in Europe [14–16,20] and

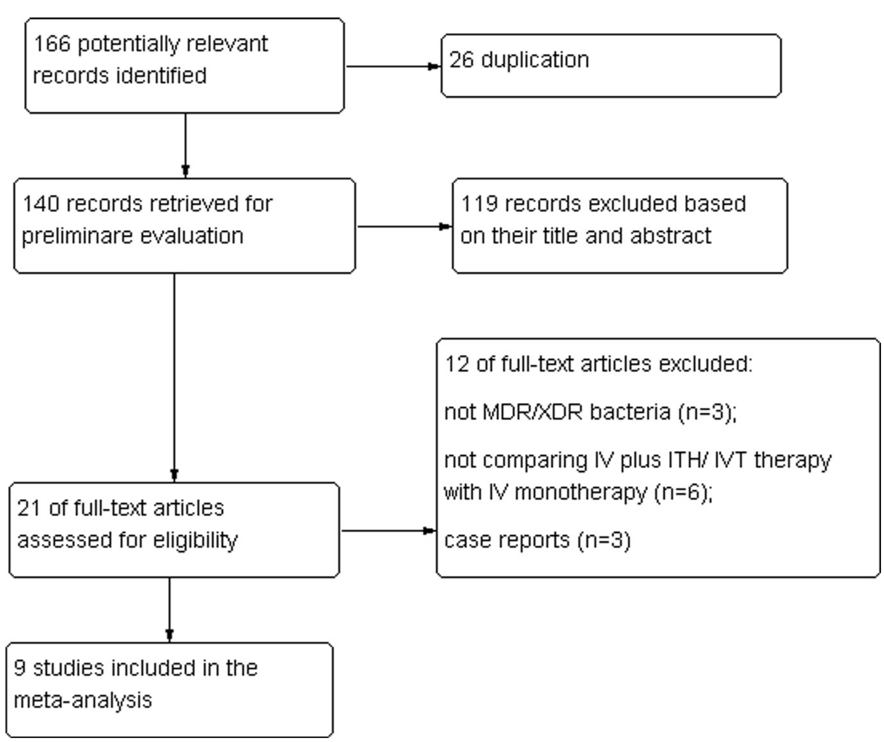


**Fig. 1.** Flowchart of included studies and the selection process. MDR, multidrug-resistant; XDR, extensively drug- resistant; IV, intravenous; ITH, intrathecal; IVT, intraventricular.

**Table 1**
Characteristics of the included studies

| Author/publication year | Study design | Country | Study period | Type of infection | Organism | No. of patients | Mean age (years) | Sex ratio (M/F) |
|---|---|---|---|---|---|---|---|---|
| Chusri, 2018 [11] | Retrospective | Thailand | Jan. 2006–Dec. 2015 | Post-neurosurgical meningitis and ventriculitis | CR *Acinetobacter baumannii* | 33 | 42[a] | 1.36:1 |
| De Bonis, 2016 [14] | Retrospective | Italy | Jan. 2003–Dec. 2012 | Post-neurosurgical ventriculitis/meningitis | XDR *A. baumannii* | 18 | 52.1 ± 14.8 | 1.25:1 |
| Fotakopoulos, 2016 [15] | Retrospective | Greece | 2006–2014 | Nosocomial meningitis/ventriculitis following neurosurgical intervention | MDR Gram-negative bacteria (*A. baumannii*, 70.5%) | 34 | 50.6 | 0.62:1 |
| Guardado, 2008 [16] | Retrospective | Spain | 1990–2004 | Nosocomial postsurgical meningitis | MDR *A. baumannii* | 46 | 44 ± 16 | 3:1 |
| Moon, 2013 [17] | Retrospective | Korea | Jan. 2005–May 2011 | Post-neurosurgical meningitis | CR *A. baumannii* | 22 | 56[a] (20–83) | 2.14:1 |
| Pan, 2019 [18] | Retrospective | China | Jan. 2013–Sept. 2017 | Post-neurosurgical intracranial infection | MDR/XDR A. *baumannii* | 61 | 54.1 | 0.97:1 |
| Shofty, 2016 [19] | Retrospective | Israel | 2005–2014 | Post-neurosurgical meningitis | CR Gram-negative bacteria | 50 | 52.3 | 1.94:1 |
| Sipahi, 2018 [20] | Retrospective | Turkey, France | Jan. 2007–Apr. 2016 | Nosocomial post-neurosurgical meningitis | MDR *A. baumannii* | 15 | 49.5 ± 18.2 | 1.5:1 |
| Tuon, 2010 [21] | Retrospective | Brazil | Jan 2006–Jan. 2009.1 | Nosocomial post-neurosurgical meningitis | MDR *A. baumannii* | 17 | 43.6 | 1.2:1 |

CR, carbapenem-resistant; XDR, extensively drug-resistant; MDR, multidrug-resistant.
[a] Data were expressed as the median.

**Table 2**
Administration of intrathecal or intraventricular (ITH/IVT) antibiotic therapy, outcomes and quality of the included studies

| Author/publication year | ITH/IVT administration | Microbiological clearance | | Mortality | Death (*n*/*N*) | | OR (95% CI) of outcome | Study quality |
|---|---|---|---|---|---|---|---|---|
| | | IV+ITH/IVT | IV | | IV+ITH/IVT | IV | | |
| Chusri, 2018 [11] | Colistin (dosage regimen of 150 000–200 000 IU daily); the duration of consolidative IV treatment was 18 days | N/A | N/A | 30-day mortality | 5/17 | 9/16 | 0.32 (0.08–1.36) | 8 |
| De Bonis, 2016 [14] | IVT colistin (10–20 mg/day); the median length of therapy was 26.5 days | 9/9 | 3/9 | Hospital mortality | 3/9 | 7/9 | 0.14 (0.02–1.16) | 8 |
| Fotakopoulos, 2016 [15] | IVT colistimethate sodium (mean dose 170 000 ± 400 IU); the duration of treatment was 16.0 ± 8.3 days | N/A | N/A | Hospital mortality | 3/23 | 8/11 | 0.06 (0.01–0.34) | 8 |
| Guardado, 2008 [16] | ITH therapy with colistin (8 cases) and aminoglycosides (9 cases) | N/A | N/A | Hospital mortality | 2/17 | 11/29 | 0.22 (0.04–1.14) | 7 |
| Moon, 2013 [17] | ITH/IVT colistimethate (8 cases) and aminoglycoside (2 cases) | N/A | N/A | Hospital mortality | 2/10 | 11/12 | 0.02 (0.00–0.30) | 6 |
| Pan, 2019 [18] | ITH polymyxin B 50 000 U/day | 21/23 | 7/38 | 28-day mortality | 2/23 | 21/38 | 0.08 (0.02–0.38) | 8 |
| Shofty, 2016 [19] | 10 with colistin (median dose 50000 IU/day) and 13 with amikacin (median dose 37.5 mg/day) for a total median duration of 9 days and 12 days, respectively | N/A | N/A | 30-day mortality | 2/23 | 9/27 | 0.19 (0.04–1.00) | 9 |
| Sipahi, 2018 [20] | ITH colistin 2 × 5 mg (19 days, 20 days, 22 days) | N/A | N/A | 1 month post-therapy mortality | 1/3 | 6/12 | 0.50 (0.04–7.10) | 6 |
| Tuon, 2010 [21] | N/A | N/A | N/A | Hospital mortality | 2/2 | 13/15 | 0.93 (0.03–25.68) | 5 |

IV, intravenous; OR, odds ratio; CI, confidence interval; N/A, not available.

one in South America [21] (Table 1). According to the Newcastle–Ottawa Scale, one retrospective study was fair (score 5) and the remaining eight studies were rated as good or excellent quality (score range, 6–9) (Table 2).

The OR for death (IV+ITH/IVT versus IV) reported in the included studies ranged from 0.02–0.93 (Table 2). No significant heterogeneity ($P = 0.51$; $I^2 = 0\%$) was observed across the nine included studies; thus, a fixed-effects model was used to analyse the studies (Fig. 2). The overall pooled OR was 0.15 (95% CI 0.08–0.28; $P < 0.001$) and the risk of mortality was significantly different between the two groups. Based on variable descriptions of microbiological clearance, only two studies were analysed. Microbiological

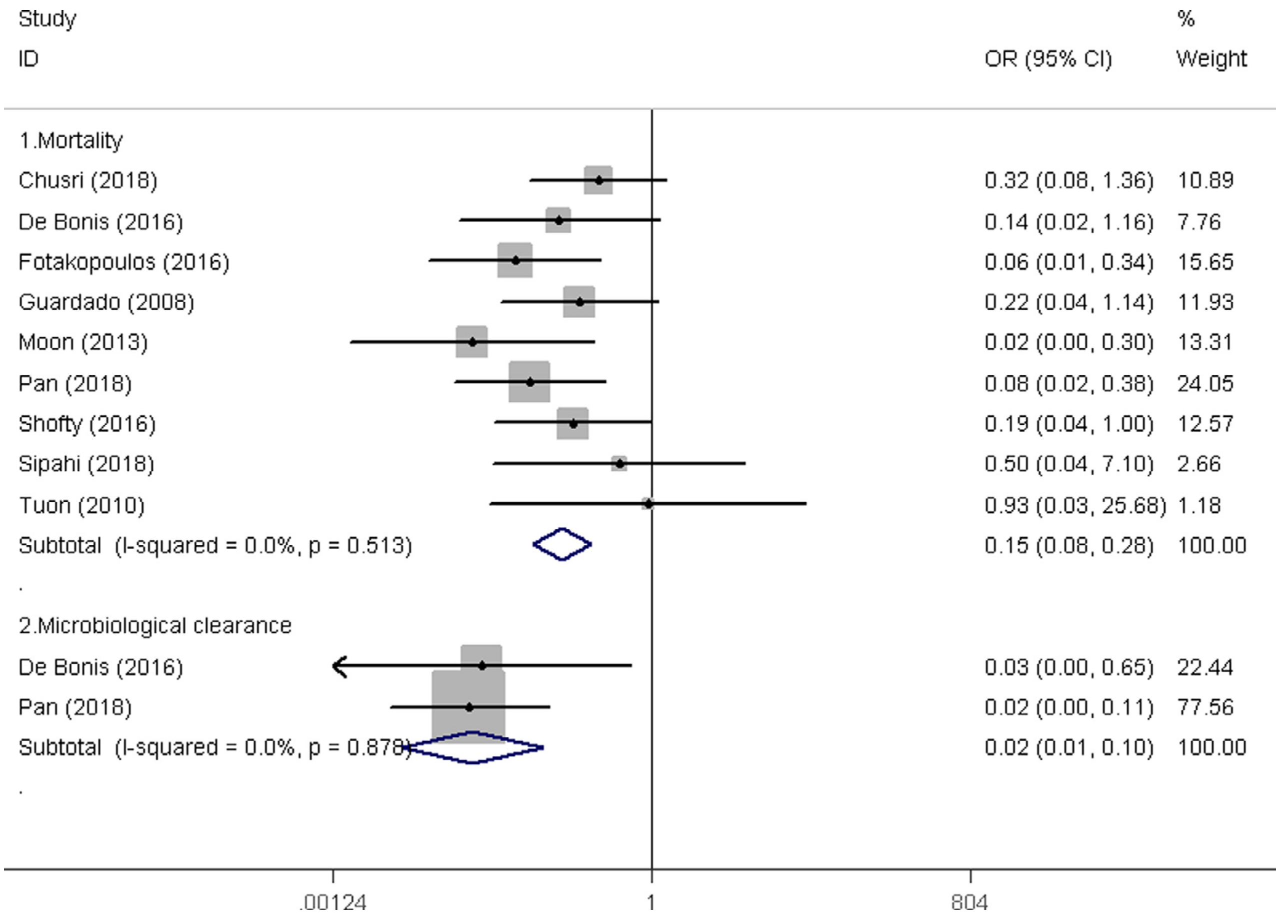


**Fig. 2.** Forest plots of the comparisons of (1) mortality and (2) microbiological clearance. OR, odds ratio; CI, confidence interval.

clearance was significantly different between the two groups, with a pooled OR of 0.02 (95% CI 0.01–0.10) without significant heterogeneity ($P = 0.88$, $I^2 = 0\%$) (Fig. 2). Only one study described side effects, showing no significant difference between the two groups [5/17 (29.4%) vs. 6/16 (37.5%); $P = 0.62$] [11]. Other studies had no serious adverse reactions observed or they were not described. Graphical inspection through Begg's funnel plot (Fig. 3) and quantitative evaluation through Egger's test ($P = 0.87$) did not reveal any evidence of publication bias.

## 4. Discussion

In this meta-analysis, nine studies comparing IV+ITH/IVT with IV monotherapy for post-neurosurgical intracranial infection due to MDR/XDR Gram-negative bacteria were systematically reviewed. MDR/XDR *A. baumannii* was the most commonly isolated bacterial agent. Polymyxins were the most common drug used for ITH/IVT, followed by aminoglycosides. The risk of mortality and microbiological clearance were significantly different between the two groups.

Post-neurosurgical intracranial infection has been classified as a nosocomial infection, and resistant Gram-negative bacteria and staphylococci are most likely to be the pathogenic agents [4]. MDR/XDR Gram-negative bacteria-related ventriculitis/meningitis has become increasingly frequent in recent years, among which *Acinetobacter* spp. are the most common organisms isolated in CSF cultures, followed by *K. pneumoniae* and *P. aeruginosa* [22,23]. Mortality due to *A. baumannii* ventriculitis/meningitis has been reported to be as high as 72.7% [21]. A multicentre retrospective case–control study showed that even with IVT treatment, the mortality rate in patients with MDR/XDR *A. baumannii* central nervous system (CNS) infection reached 48% [13].

Penetration of many drugs through the blood–brain barrier is poor, and the presence of MDR/XDR bacteria has forced the use of topical therapies to achieve an effective therapeutic concentration of antibiotics at the site of infection [1]. The most recent meta-analysis revealed an 84% lower risk of mortality in the ITH/IVT+IV antimicrobial therapy group treated for post-neurosurgical *A. baumannii* infection [24]. ITH/IVT is usually used as a remedial treatment when systemic treatment is ineffective rather than as an initial treatment. A previous study showed that the mean time from diagnosis to initiation of ITH/IVT treatment was 25.4 days [25]. Compared with survival, death is associated with delayed ITH/IVT therapy [26], and early administration of effective ITH/IVT therapy might increase the clinical cure rate for post-neurosurgical intracranial infection [19,25]. However, there have been few clinical studies on the correlation between the timing of ITH/IVT administration and mortality to date.

The dosage regimen of ITH/IVT antimicrobial therapy is controversial because of the minimum inhibitory concentration (MIC) of the causative micro-organism, variable volumes of CSF, circulation and drainage of CSF, and differing degrees of meningeal inflammation [9,10]. Guidelines suggest that the IVT dosage of colistin or polymyxin B should be 10 mg or 5 mg daily and the duration of therapy should be 21 days for ventriculitis/meningitis caused by Gram-negative bacteria [4]. The dosages and treatment courses of polymyxins in studies included in the current review varied, indicating that the ITH/IVT administration of the drug was still based on expert opinion or clinical experience. The duration of therapy described was also quite variable (2–4 weeks). Shorter treatments

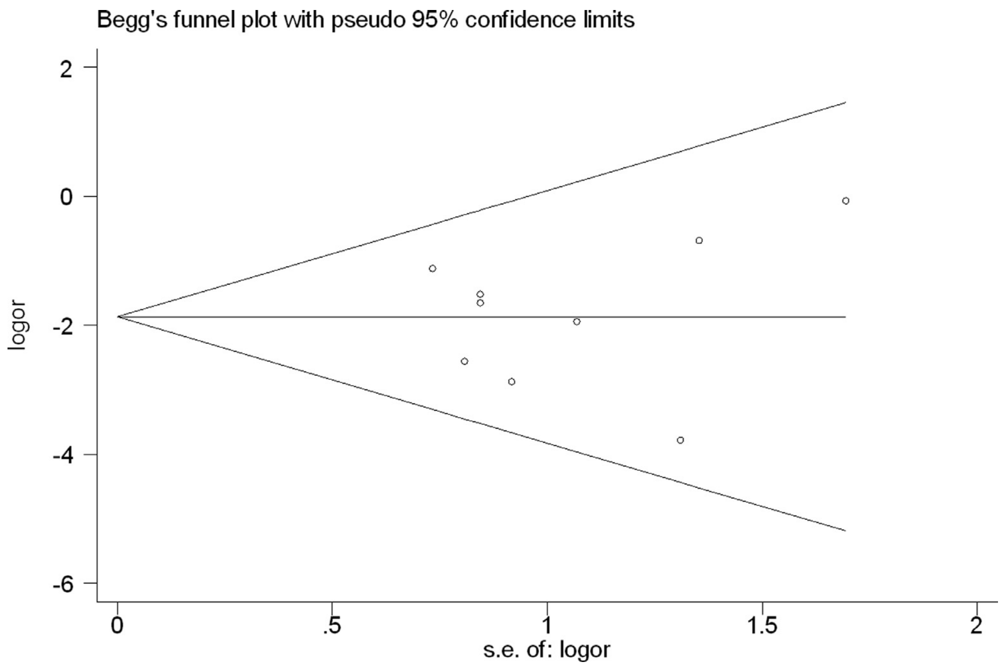


**Fig. 3.** Publication bias plot. s.e., standard error; logor, log of odds ratio.

(<1 week) correlate with higher mortality, although death may occur for other potential reasons before the conclusion of the scheduled treatment in critically ill patients [27].

CSF sterilisation is likely to be an important factor for mortality [11]. A lack of CSF sterilisation with treatment may lead to increased mortality during hospitalisation [13]. In addition, seizures, subdural effusions and hemiparesis are found significantly more often in those with delayed CSF sterilisation [28]. ITH/IVT antibiotics can likely lead to rapid CSF sterilisation in post-neurosurgical patients with meningitis and ventriculitis. Remeš et al. showed that the mean time necessary to obtain CSF sterilisation was 2.9 ± 2.7 days (range 1–12 days) of ITH/IVT administration of antibiotics in critically ill patients [29]. However, in other studies the mean time to CSF sterilisation was 4–21 days [8,14].

Adverse effects of ITH/IVT polymyxins are not negligible. Previous studies reported that toxicity was mostly caused by chemical meningitis (~15.4–60% of patients) and the occurrence of neurotoxicity was apparently dose-independent [7,30]. Most studies have shown that adverse effects are not observed or are mild [11,12,14,29]. Adverse effects following high-dose ITH/IVT antibiotics can lead to poor treatment outcomes owing to complications in critically ill patients [31]. In some critically ill patients who were mechanically ventilated and sedated, the signs or symptoms of CNS toxicity were ignored [9]. This indicates that ITH/IVT therapy is safe, but further well-designed studies are required to validate this.

This study has several limitations that need to be acknowledged. First, all of the studies included in the review were retrospective observational studies with small sample sizes. The possibility of unmeasured confounding factors between the two groups remains, although prospective RCTs for such studies are ethically difficult. Second, the total mortality data of the included studies was extracted. Some of the deaths were not directly related to intracranial infection but to the disease itself or to nosocomial pneumonia; however, these deaths do not affect the credibility of the results. Finally, we did not assess the association of antimicrobial choice and duration of treatment with outcome measures because it was difficult to define the optimal dosage, duration and indications in ITH/IVT antimicrobial therapy for post-neurosurgical intracranial infections in different studies.

Based on this meta-analysis, we conclude that ITH/IVT antimicrobial therapy is associated with a lower risk of mortality and a higher microbial clearance rate in patients with post-neurosurgical intracranial infections due to MDR/XDR Gram-negative bacteria. More prospective RCTs on this topic are urgently required to provide more conclusive guidelines for clinical practice.

## Declaration

**Funding:** This study was supported by research grants from the Zhejiang Provincial Natural Science Foundation of China [LY15H310006 and LY16H310001] and the Department of Education of the Zhejiang Province of China [Y201328670].

**Competing interests:** None declared.

**Ethical approval:** Not required.

## References

[1] Kim BN, Peleg AY, Lodise TP, Lipman J, Li J, Nation R, et al. Management of meningitis due to antibiotic-resistant *Acinetobacter* species. Lancet Infect Dis 2009;9:245–55.
[2] Lee JJ, Lien CY, Huang CR, Tsai NW, Chang CC, Lu CH, et al. Clinical characteristics and therapeutic outcomes of postneurosurgical bacterial meningitis in elderly patients over 65: a hospital-based study. Acta Neurol Taiwan 2017;26:144–53.
[3] Demiraslan H, Ulutabanca H, Ercal BD, Metan G, Alp E. Does antimicrobial usage before meningitis lead to a higher risk of adult postsurgical *Acinetobacter baumannii* meningitis than that of Enterobacteriaceae meningitis? Infez Med 2016;24:293–8.
[4] Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Scheld MW, et al. Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis 2017;201764:e34–65.
[5] Tsimogianni A, Alexandropoulos P, Chantziara V, Vassi A, Micha G, Lagiou F, et al. Intrathecal or intraventricular administration of colistin, vancomycin and amikacin for central nervous system infections in neurosurgical patients in an intensive care unit. Int J Antimicrob Agents 2017;49:389–90.
[6] Pomar V, Benito N, Lopez-Contreras J, Coll P, Gurgui M, Domingo P. Spontaneous Gram-negative bacillary meningitis in adult patients: characteristics and outcome. BMC Infect Dis 2013;13:451.
[7] Imberti R, Iotti GA, Regazzi M. Intraventricular or intrathecal colistin for the treatment of central nervous system infections caused by multidrug-resistant Gram-negative bacteria. Expert Rev Anti Infect Ther 2014;12:471–8.

[8] Karaiskos I, Galani L, Baziaka F, Giamarellou H. 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.
[9] Imberti R, Cusato M, Accetta G, Marino V, Procaccio F, Del Gaudio A, et al. Pharmacokinetics of colistin in cerebrospinal fluid after intraventricular administration of colistin methanesulfonate. Antimicrob Agents Chemother 2012;56:4416–21.
[10] Velkov T, Dai C, Ciccotosto GD, Cappai R, Hoyer D, Li J. Polymyxins for CNS infections: pharmacology and neurotoxicity. Pharmacol Ther 2018;181:85–90.
[11] Chusri S, Sakarunchai I, Kositpantawong N, Panthuwong S, Santimaleeworagun W, Pattharachayakul S, et al. Outcomes of adjunctive therapy with intrathecal or intraventricular administration of colistin for post-neurosurgical meningitis and ventriculitis due to carbapenem-resistant *Acinetobacter baumannii*. Int J Antimicrob Agents 2018;51:646–50.
[12] Falagas ME, Bliziotis IA, Tam VH. Intraventricular or intrathecal use of polymyxins in patients with Gram-negative meningitis: a systematic review of the available evidence. Int J Antimicrob Agents 2007;29:9–25.
[13] Ceylan B, Arslan F, Sipahi OR, Sunbul M, Ormen B, Hakyemez İN, et al. Variables determining mortality in patients with *Acinetobacter baumannii* meningitis/ventriculitis treated with intrathecal colistin. Clin Neurol Neurosurg 2017;153:43–9.
[14] De Bonis P, Lofrese G, Scoppettuolo G, Spanu T, Cultrera R, Labonia M, et al. Intraventricular versus intravenous colistin for the treatment of extensively drug resistant *Acinetobacter baumannii* meningitis. Eur J Neurol 2016;23:68–75.
[15] Fotakopoulos G, Makris D, Chatzi M, Tsimitrea E, Zakynthinos E, Fountas K. Outcomes in meningitis/ventriculitis treated with intravenous or intraventricular plus intravenous colistin. Acta Neurochir (Wien) 2016;158:603–10.
[16] Guardado AR, Blanco A, Asensi V, Pérez F, Rial JC, Pintado V, et al. Multidrug-resistant *Acinetobacter* meningitis in neurosurgical patients with intraventricular catheters: assessment of different treatments. J Antimicrob Chemother 2008;61:908–13.
[17] Moon C, Kwak YG, Kim BN, Kim ES, Lee CS. Implications of postneurosurgical meningitis caused by carbapenem-resistant *Acinetobacter baumannii*. J Infect Chemother 2013;19:916–19.
[18] Pan S, Huang X, Wang Y, Li L, Zhao C, Yao Z, et al. Efficacy of intravenous plus intrathecal/intracerebral ventricle injection of polymyxin B for post-neurosurgical intracranial infections due to MDR/XDR *Acinetobacter baumannii*: a retrospective cohort study. Antimicrob Resist Infect Control 2018;7:8 Erratum in: Antimicrob Resist Infect Control 2019;8:11.
[19] Shofty B, Neuberger A, Naffaa ME, Binawi T, Babitch T, Rappaport ZH, et al. Intrathecal or intraventricular therapy for post-neurosurgical Gram-negative meningitis: matched cohort study. Clin Microbiol Infect 2016;22:66–70.
[20] Sipahi OR, Mermer S, Demirdal T, Ulu AC, Fillatre P, Ozcem SB, et al. Tigecycline in the treatment of multidrug-resistant *Acinetobacter baumannii* meningitis: results of the Ege study. Clin Neurol Neurosurg 2018;172:31–8.
[21] Tuon FF, Penteado-Filho SR, Amarante D, Andrade MA, Borba LA. Mortality rate in patients with nosocomial *Acinetobacter* meningitis from a Brazilian hospital. Braz J Infect Dis 2010;14:437–40.
[22] Albornoz H, Ibias L, Gadea A, Porcires F, Brinckhaus R, Ramos N, et al. Central nervous system infections in postneurosurgical patients. BMC Proc 2011;5(Suppl 6):P191.
[23] Khan SA, Waqas M, Siddiqui UT, Shamim MS, Nathani KR, Jooma R, et al. Intrathecal and intraventricular antibiotics for postoperative Gram-negative meningitis and ventriculitis. Surg Neurol Int 2017;8:226.
[24] Mohammed N, Savardekar AR, Patra DP, Narayan V, Nanda A. The 21st-century challenge to neurocritical care: the rise of the superbug *Acinetobacter baumannii*. A meta-analysis of the role of intrathecal or intraventricular antimicrobial therapy in reduction of mortality. Neurosurg Focus 2017;43:E8.
[25] Wang JH, Lin PC, Chou CH, Ho CM, Lin KH, Tsai CT, et al. Intraventricular antimicrobial therapy in postneurosurgical Gram-negative bacillary meningitis or ventriculitis: a hospital-based retrospective study. J Microbiol Immunol Infect 2014;47:204–10.
[26] Khawcharoenporn T, Apisarnthanarak A, Mundy LM. Intrathecal colistin for drug-resistant *Acinetobacter baumannii* central nervous system infection: a case series and systematic review. Clin Microbiol Infect 2010;16:888–94.
[27] Bargiacchi O, De Rosa FG. Intrathecal or intraventricular colistin: a review. Infez Med 2016;24:3–11.
[28] Lebel MH, McCracken GH Jr. Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics 1989;83:161–7.
[29] Remeš F, Tomáš R, Jindrák V, Vaniš V, Setlík M. Intraventricular and lumbar intrathecal administration of antibiotics in postneurosurgical patients with meningitis and/or ventriculitis in a serious clinical state. J Neurosurg 2013;119:1596–602.
[30] Ng J, Gosbell IB, Kelly JA, Boyle MJ, Ferguson JK. Cure of multiresistant *Acinetobacter baumannii* central nervous system infections with intraventricular or intrathecal colistin: case series and literature review. J Antimicrob Chemother 2006;58:1078–81.
[31] Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. Br J Clin Pharmacol 2011;72:381–93.