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REVIEW

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Antibiotic therapy by intrathecal or intraventricular approach for postsurgical meningitis or ventriculitis: a systematic review and meta-analysis

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Abstract

Objective To systematically review the evidence for intrathecal or intraventricular plus intravenous administration of antibiotics compared with standard management for postsurgical meningitis or ventriculitis.

Methods The following databases were searched: MEDLINE, the Central Register of Controlled Trials (CENTRAL); PubMed, EMBASE; and reference list of articles.

Results Administration of intrathecal/intraventricular antibiotics was associated with decreased mortality (OR 0.27 [95% CI 0.15–0.49] p = < 0.00001), increased cure rate (OR 3.4 [95% CI 1.6–7.22] p = 0.001). There was no difference in the occurrence of reinfection rate, and in poor functional outcome (OR 0.57 [95% CI 0.21–1.60] p = 1.6 p = 0.29; OR 0.43 [95% CI 0.11–1.68] p = 0.22).

Conclusions Intrathecal/intraventricular plus intravenous administration of antibiotics improves survival and cure rate in patients with postoperative meningitis or ventriculitis. More high-quality studies are needed.

Keywords Cerebral ventriculitis, Bacterial meningitis, Cerebrospinal fluid shunts, Drug resistance, Intraventricular, Intrathecal infusions, Intravenous infusions, Functional outcome, Systematic review, Meta-analysis

Introduction

Post-surgical meningitis/ventriculitis is a potentially fatal nosocomial infection of the central nervous system that occurs after a brain or spinal surgery since structural defects of the meninges and skull allow the direct spread of bacteria [2]. The incidence tends to increase up to 20% if catheters are used for drainage [3]. If they do not receive adequate treatment, they can reach mortality rates of 56% [4]. Its etiology commonly varies between different hospitals, however, infections by gram-negative bacteria, *P. aeruginosa, A. baumannii*, are usually resistant to multiple antibiotics such as cephalosporins and carbapenems [4, 5].

According to Center for Disease Control (CDC) guidelines, the diagnosis must meet 1 of the following 2 criteria: 1. isolation of organisms in cerebrospinal fluid (CSF) cultures; or 2. clinical presentation of meningitis plus laboratory evidence of infection (altered CSF cytology or biochemistry, including elevated white blood cell count,

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elevated protein levels, decreased glucose levels and/or organisms on Gram stain, and/or positive blood culture). [6] However, the increasing rates of antimicrobial resistance have made these entities difficult to treat [7].

Until now, the intravenous route of administration (IV) is the one used for antibiotic therapy, however, antibiotics show great difficulty in crossing the blood–brain barrier, which makes it difficult to reach their real site of action, and reach therapeutic concentrations in the cerebrospinal fluid [8]. Given the increasing incidence of ventriculitis, the clinical practice guidelines for its management suggest management with adjuvant intraventricular or intrathecal (IT) therapy for the management of cases that are refractory to intravenous management [9] with promising results; however, a consensus is not reached regarding the safety and efficacy of the use of this therapy. In order, we conducted a systematic review and meta-analysis, with the following PICO question: what is the clinical impact of IV therapy compared to IT therapy, or IV plus IT therapy, in terms of mortality, therapeutic success, neurological and functional prognosis? The goal of this review is to systematically review the existing evidence of effectiveness of intraventricular or intrathecal antibiotic management as an adjuvant to standard therapy.

Methods

The following systematic review and meta-analysis will be in accordance with the recommendations of the PRSIMA statement protocol, and the Cochrane manual of systematic reviews and meta-analysis. The quality of the included studies was assessed using the Newcastle Ottawa Scale (NOS) [10]. Risk of bias assessment was performed using the ROBINS-I scale that assesses the risk of bias at "Low Risk", "Moderate Risk", "High Risk", and "Critical Risk". in the domains "selection", "Intervention", "missing data", "confounding", "outcome measurement", "Report" and an overall evaluation expressed in "general bias" [11].

Search

The searching for randomized clinical trials is performed in the following databases: PUBMED (until September 2022); Cochrane Injuries Group Specialized Registry (until September 2022); Cochrane Central Register of Controlled Trials (The Cochrane Library) (to September 2022); MEDLINE (Ovid) (to September 2022); EMBASE (to September 2022); as well as the reference list of included studies and other relevant data other than potentially eligible studies. The search was constructed using terms and descriptors from the Medical Subject Heading (MeSH), all combined with Boolean operators. The search was limited to studies published after the year 2000.

Search strategy

("Cerebral ventriculitis" OR "Meningitis, bacterial" OR "Cerebrospinal fluid Shunts" OR "Drug resistance, multiple"); AND ("Intraventricular infusions" OR "Intrathecal" OR "Spinal infusions") AND "Intravenous infusions" AND ("Eradication" OR "Functional outcome" OR "Infection control" OR "Mortality" OR "Treatment outcome" OR "Cost–benefit analysis").

Inclusion and exclusion criteria

Studies published after the year 2000, case series of more than 15 patients, observational, prospective, and retrospective studies, as well as randomized clinical trials evaluating intrathecal or intraventricular therapy for meningitis or posterior ventriculitis were included separately; to neurosurgical procedures, evaluate mortality, prognosis, and effectiveness of therapy. Pediatric series, and case series of fewer than 15 patients were excluded.

Extraction, management, and statistical analysis of data

Individually and separately, the following data were extracted: Mortality, poor neurological and functional status, cure rate and re-infection. The corresponding author were contacted for missing data. Statistical analysis was performed using the relative risk with the Mantel–Haenszel method for dichotomous variables with a randomized effect calculated using the Review Manager 5.3 software across odds ratio (OR). Heterogeneity was assessed by calculating Chi-squared (I^2), being above 60% as a high heterogeneity of the studies included in the analysis.

Definitions

Mortality

Total deaths at the end of follow-up.

Cure

Patient with sterile cerebrospinal fluid and no clinical evidence of neuroinfectious decease after treatment.

Poor prognosis

Very severe disparity (total dependence), vegetative state, modified Rankin scale (mRS) greater than 4, Glasgow outcome scale equal to 3 points.

Re-infection

Symptom of neuroinfection (fever, headache, meningeal signs, etc.), presence of bacteria, polymorphonuclear

leukocytes in CSF, 10 days after completion of antibiotic treatment, in patients with cure criteria.

Results

After performing systematic search of the information following our strategy, 70 bibliographic citations were identified, of which 22 were considered potentially eligible based on the title or the abstract, or both, and the full texts were obtained. After a review of the full text, 20 trials were considered eligible, 10 studies were discarded for only microbiological outcomes, and 2 because only patients with intrathecal/ventricular therapy plus IV were included, there was no comparison, finally, 8 retrospective observational studies (5 cohort studies and 3 series of cases) were included for qualitative and quantitative analysis [12–19] (Table 1 and Fig. 1).

Eight included studies involved 338 patients with severe infectious disease of the central nervous system, severe meningitis with or without associated ventriculitis, of which 121 were administered specific antibiotic therapy by intraventricular route/intrathecal administration combined by intravenous antibiotics and 217 standard intravenous antibiotic management protocols.

Quality assessment of included studies

The quality of the included studies was evaluated, and it was found that 6 of the included studies obtained a score of 5, considering that 85.71% of the included studies are of moderate quality, one study (14.28%) was of low quality obtaining a score of 4 /7 and the remaining one obtained a score of 7/7, being considered the only included study of high quality (Table 2).

Risk of bias assessment for included studies

The risk of bias for the different studies chosen was assessed using the methodology described and it was found that 50% of the studies showed a risk of bias that was “Moderate” and 15% “Serious” overall risk of bias. 15% of studies showed risk “Serious” in “bias of selection of participants” and “bias due of Missing data”; 50% showed risk “moderate” for measurement of outcomes (Fig. 2).

Chusri et al [12] in this study, "serious risk" was found in "selection of participants" and "missing data". Many of the patients did not complete the follow-up indicated in the study protocol, and were included in the final analysis, the reason for non-follow-up is not specified. However, this methodological weakness did not influence the final statistical analysis, but it did generate great imprecision and low statistical confidence in the data (Fig. 3).

Meta-analysis of included studies

Was found that the administration of antibiotic for Intraventricular/intrathecal plus Intravenous approach decreases 7.09 times the mortality compared to intravenous standard therapy (OR 0.27 [95% CI 0.15–0.49] p = < 0.00001) with low heterogeneity ($Chi^2 = 7.2$ df = 7, $I^2 = 3\%$) (Fig. 4).

In 3 studies poor neurological outcomes were evaluated, they included 89 patients, 36 received antibiotic by intrathecal/intraventricular approach plus intravenous route and 53 by intravenous approach only. No significant differences were found between both groups (OR 0.43 [95% CI 0.11–1.68] p = 0.22) with acceptable homogeneity (Chi2 = 2.74, df = 2; $I^2 = 27\%$) (Fig. 5).

Rate of curation defined as sterile cerebrospinal fluid (CSF) and no clinical evidence of neuroinfectious decease after treatment intrathecal/intraventricular antibiotic treatment increase (OR 3.4 [95% CI 1.6–7.22] p = 0.001) with adequate heterogeneity ($Chi^2 = 10.46$ df = 7, $I^2 = 33\%$) (Fig. 6). Between intrathecal/intraventricular administration of antibiotics combined with intravenous and intravenous administration alone, no statistically significant differences were found in the rate of reinfection (OR 0.57 [95% CI 0.21–1.60] p = 1.6 p = 0.29) with adequate heterogeneity ($Chi^2 = 0.22$ df = 2, $I^2 = 0\%$) (Fig. 7).

Publication bias was evaluated with Funnel plot showing an asymmetric graph possible publication bias (Figs. 8, 9, 10 and 11).

Discussion

Post-surgical meningitis is considered a nosocomial infection, which has Gram-negative and methicillin-resistant Staphylococcus aureus as its causal agent [19–21]. It presents a great variability depending on the geographical distribution and the epidemiological profile of each institution [21]. IDSA guidelines published in 2017 recommend broad-spectrum cephalosporin or carbapenem antibiotics with anti-pseudomonal activity; however, it is known that antimicrobial resistance has increased, so many drugs that do not adequately penetrate the blood–brain barrier are preferred [9].

This systematic review of the effectiveness of intrathecal or intraventricular drug therapy as an adjuvant to systemic therapy classically used for the treatment of meningitis. Eight retrospective studies were included for meta-analysis, where mostly colistin therapies were used. The identified studies had a cohort divided into two groups, a control group, which received systemic therapy, and a group that received ITH/IVT therapy. The studies used different pharmacological treatments for symptom control; none of the studies used non-pharmacological interventions.

Table 1 Characteristics of included studies

Study	Type	Patients	Antibiotic administration	outcome	Length Following
Wang et al. 2014 [19]	Series Cases	N = 109 Intraventricular/intrathecal administration plus Intravenous: 14 Only Intravenous: 95	IV: Imipenem; Meropenem; Meropenem/colistin; Ceftazidime/cefepime; Ceftriaxone; trimethoprim / Sulfamethoxazole IT: Amikacin, Colistin, Gentamicin,	Mortality cure Re-infection	1 year
Chusri et al. 2017 [12]	Retrospective observational cohort	N = 33 Intraventricular/intrathecal administration plus Intravenous: 17 Only Intravenous: 16	IV: Colistin IT: Colistin	Mortality Length of Stay Hospital cure	30 days
From Bonis et al. 2016 [13]	Series cases	N = 17 Intraventricular/intrathecal administration plus Intravenous: 9 Only Intravenous: 8	IV: Colistin IT: Colistin	Mortality Length of Stay Hospital Cure Re-infection unfavorable prognosis	90 days
Rodriguez-Guardado et al. 2008 [16]	Retrospective observational cohort	N = 51 Intraventricular/intrathecal administration plus Intravenous: 21 Only Intravenous: 30	IV: Colistin IT: Colistin	Mortality Length of Stay Hospital cure Re-infection	90 days
Fotakopoulos et al. 2016 [14]	Retrospective observational cohort	N = 34 Intraventricular/intrathecal administration plus Intravenous: 23 Only Intravenous: 11	IV: Colistin IT: Colistin	Mortality Length of Stay Hospital cure	90 days
Moon et al. 2013 [15]	Retrospective observational cohort	N = 22 Intraventricular/intrathecal administration plus Intravenous: 10 Only Intravenous: 12	IV: Colistin IT: Colistin	Mortality cure relapse	30 days
Shofty et al. 2016 [17]	Retrospective observational cohort	N = 50 Intraventricular/intrathecal administration plus Intravenous: 23 Only Intravenous: 27	IV: Ampicillin / sulbactam, Piperaciline /tazobactam, Vancomycin, Gentamicin, Amikacin, Ceftazidime, Ceftriaxone, Merponem ITEM: Ampicilin / sulbctam, Piperaciline /tazobactam, Vancomycin, Gentamicin, Amikacin, Ceftazidime, Ceftriaxone, Meropenem	Mortality cure unfavorable prognosis	30 days
Tuon et al. 2010 [18]	Series cases	N = 22 Intraventricular/intrathecal administration plus Intravenous: 4 Only Intravenous: 18	IV: Ampicillin / sulbactam, Piperacillin /tazobactam, Vancomycin, Gentamicin, Amikacin, Ceftazidime, Ceftriaxone, Meropenem ITEM: Ampicillin / sulbactam, Piperacillin /tazobactam, Vancomycin, Gentamicin, Amikacin, Ceftazidime, Ceftriaxone, Meropenem	Mortality cure unfavorable prognosis	30 days

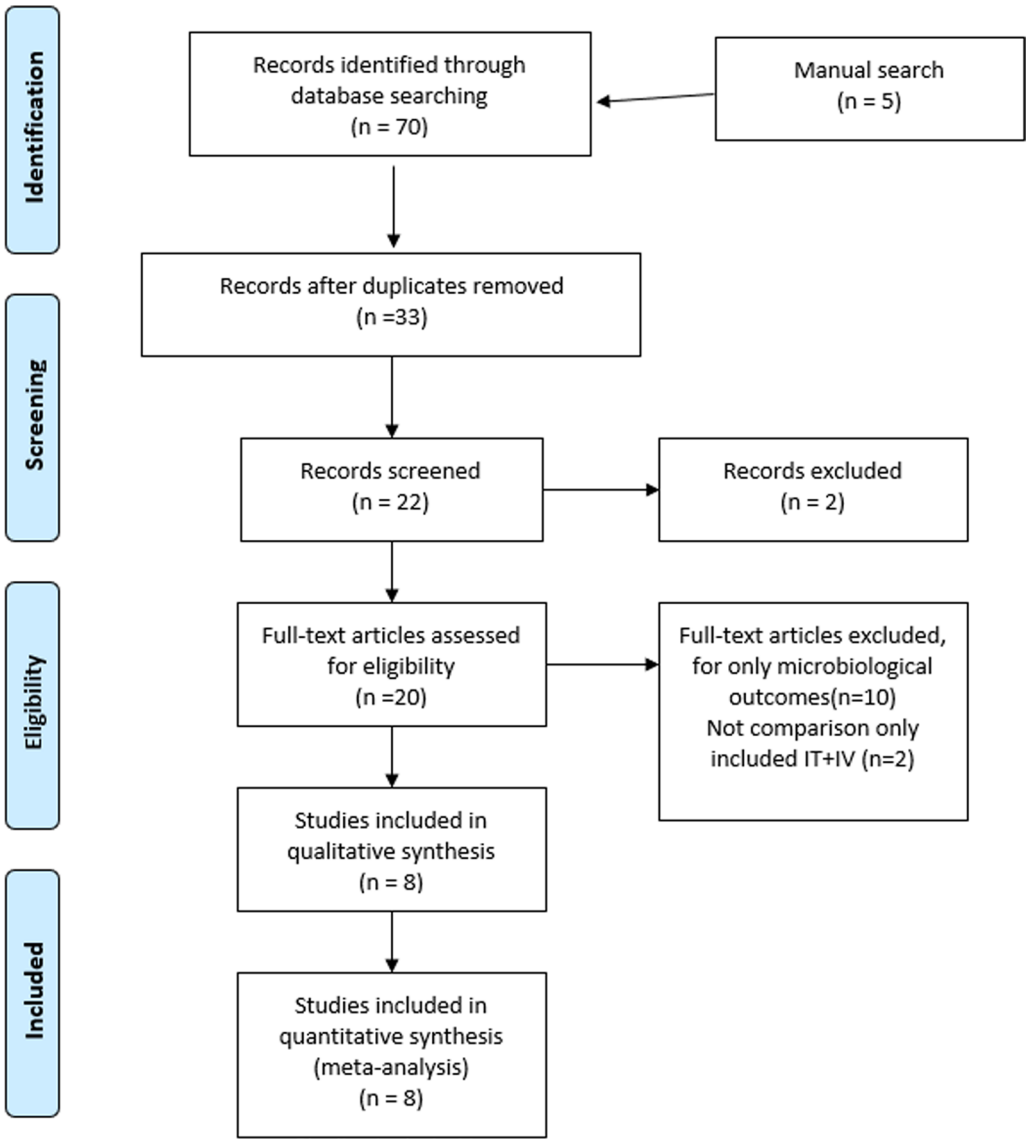

Fig. 1 Process of study selection—flow chart of our search strategy and inclusion and exclusion criteria

In the studies reviewed, patients who received IVT colistin added to IV colistin and compared with those who only had IV colistin were much more effective since they tended to lower mortality, which improved patient outcomes [12–14]. In addition, another study showed the mortality relationship between those resistant to carbapenems and those not resistant to carbapenems, being less in the latter case.

In several retrospective studies including patients with postsurgical meningitis and ventriculitis caused by CRAB carbapenem-resistant Acinetobacter baumannii (showing higher mortality compared to CSAB meningitis), [15] treated with IV colistin alone and with additional IV therapy, demonstrating that IV therapy colistin as an adjunct (combination therapy) was associated with shorter hospital and ICU length of stay, and is much more effective, lower mortality, especially in the seriously ill, contributing to a lower economic burden [12–14, 16–19].

Most of them were significantly associated with the cure of this condition. Moon et al. concluded that in 55% of the cases with colistin regimens in intrathecal or intraventricular administration of antibiotics and combined IV therapy, significant results were obtained in terms of cure, likewise, Wang et al., Bonis et al., Fotopoulos et al., softty et al., Chusri et al., and Rodriguez et al. concluded that IVT therapy in addition to IV therapy allows for favorable results in curing patients. However, of these,

Table 2 Newcastle–Ottawa Scale for quality assessment of studies included in this meta-analysis

Study	Representativeness sample	Size sample	Source of information	Demonstration that outcome was not present at study start	Control variable confusion	Assessment outcome	Enough follow up period	Newcastle Ottawa Scale Score
Tuon et al. 2010 [18]	★			★	★	★	★	**5/7**
Moon et al. 2013 [15]	★		★	★	★		★	**5/7**
Wang et al. 2014 [19]	★	★	★	★	★	★	★	**7/7**
Debonis et al. 2016 [13]	★		★	★		★	★	**5/7**
Fotakopoulos et al. 2016 [14]	★			★	★	★	★	**5/7**
Shofty et al. 2016 [17]	★	★		★	★	★		**5/7**
Chusri et al. 2017 [12]	★		★	★	★	★		**5/7**
Rodriguez-Guardado et al. 2008 [16]	★			★	★	★	★	**5/7**

★Indicates that it meets criteria in Newcastle–Ottawa Scale

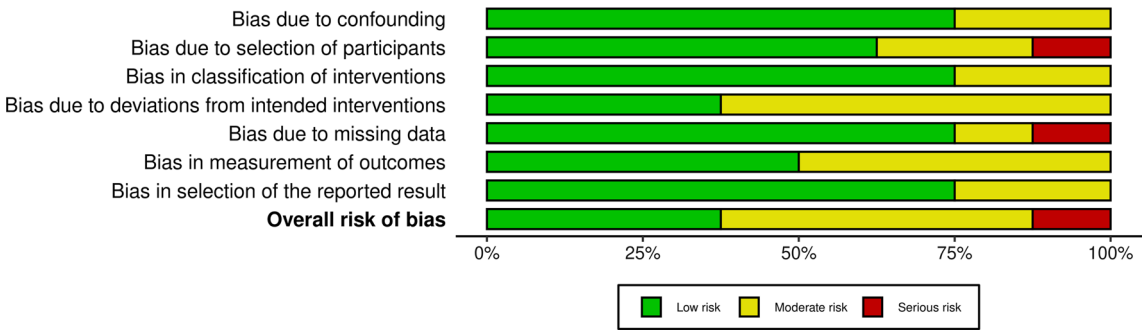

Fig. 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

Tuon et al. showed no significant results when using these therapies.

The prognosis was favorable for patients with IV/IT therapy in the different groups evaluated by Bonis [13], compared to B, Shoffty [17], and Toun [18] who obtained a worse prognosis with these therapies; regarding reported reinfections, only in the study by Wang et al. [19], 4 were reported among the 95 patients who received only IV therapy, with no reports in those who received combined antibiotic therapy.

In the review of the literature, a multicenter retrospective cohort study was found carried out in 2019 [20] where IVT antibiotic therapy is evaluated using drugs such as vancomycin and aminoglycosides, CSF sterilization was achieved in 88.4% compared to this meta-analysis where the results show that patients benefit more from intravenous-only therapy.

In post-surgical meningitis, the meninges are inflamed, decreasing the permeability of the blood–brain barrier with many drugs, including antibiotics, cephalosporins 15%, beta-lactamase inhibitor 5%, carbapenems 4.7% [21, 22]. Intrathecal administration of these antibiotics improves penetration to where the germ is located and therefore its activity, which improves the cure rate and decreases mortality, as shown by the results of this meta-analysis.

Limitations

Our study has several limitations. Studies included in this analysis were retrospective. Publication bias was assessed by assessing funnel plot symmetry, asymmetry is evident in most of the risk factors analyzed, which could be interpreted as the presence of publication bias, however, it should be taken into account that

Fig. 3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

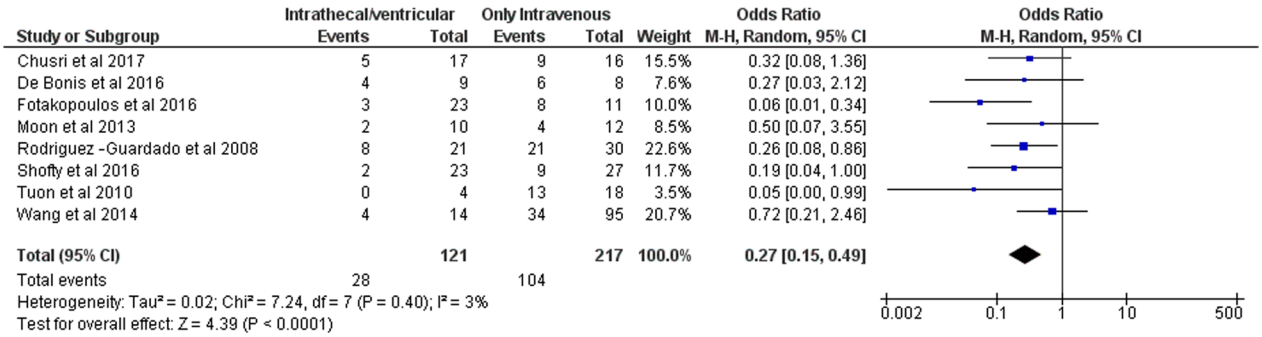

Fig. 4 Forest plot of comparison: 1 intraventricular/intrathecal adjuvant antibiotic therapy vs only Intravenous, outcome: 1.1 mortality

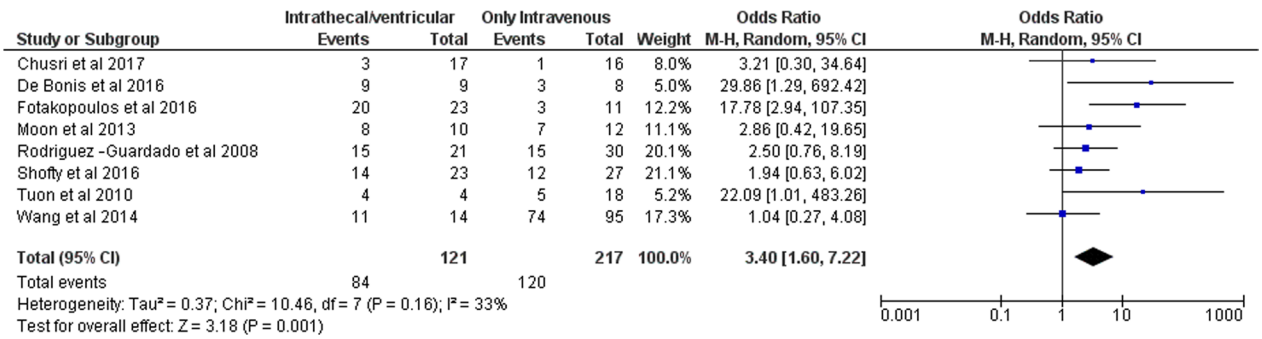

Fig. 5 Forest plot of comparison: 1 intraventricular/intrathecal adjuvant antibiotic therapy Vs only intravenous, outcome: 1.3 unfavorable functional outcome (severe disability and vegetative state)

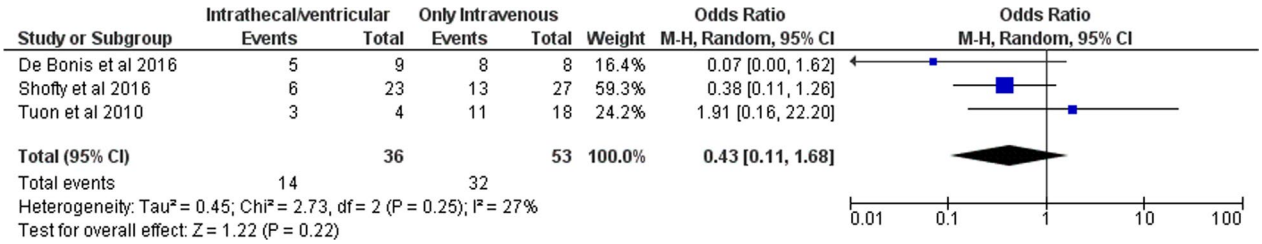

Fig. 6 Forest plot of comparison: 1 intraventricular/Intrathecal adjuvant antibiotic therapy Vs only intravenous, outcome: 1.2 curation

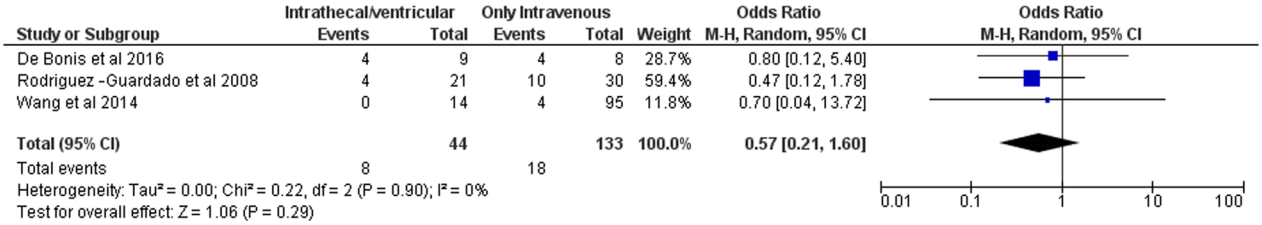

Fig. 7 Forest plot of comparison: 1 intraventricular/intrathecal adjuvant antibiotic therapy Vs only intravenous, outcome: 1.4 reinfection

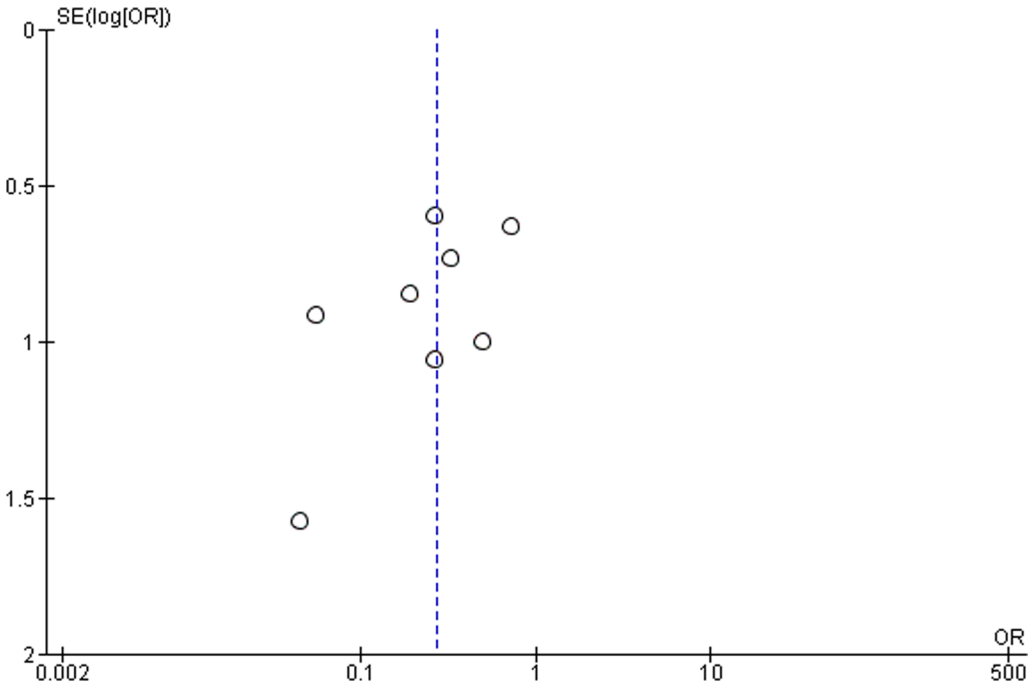

Fig. 8 Funnel plot that assesses the presence of publication bias for the following outcomes: mortality

built with few studies (5), according to the Cochrane manual for systematic reviews This indicates that the assessment of this bias is less than 10 included studies, decreases the statistical power and confidence of the analysis, besides in many included studies show a range of broad confidence, which indicates a possible heterogeneity of the intra-study population. The high heterogeneity of the antibiotic protocols used for each intervention.

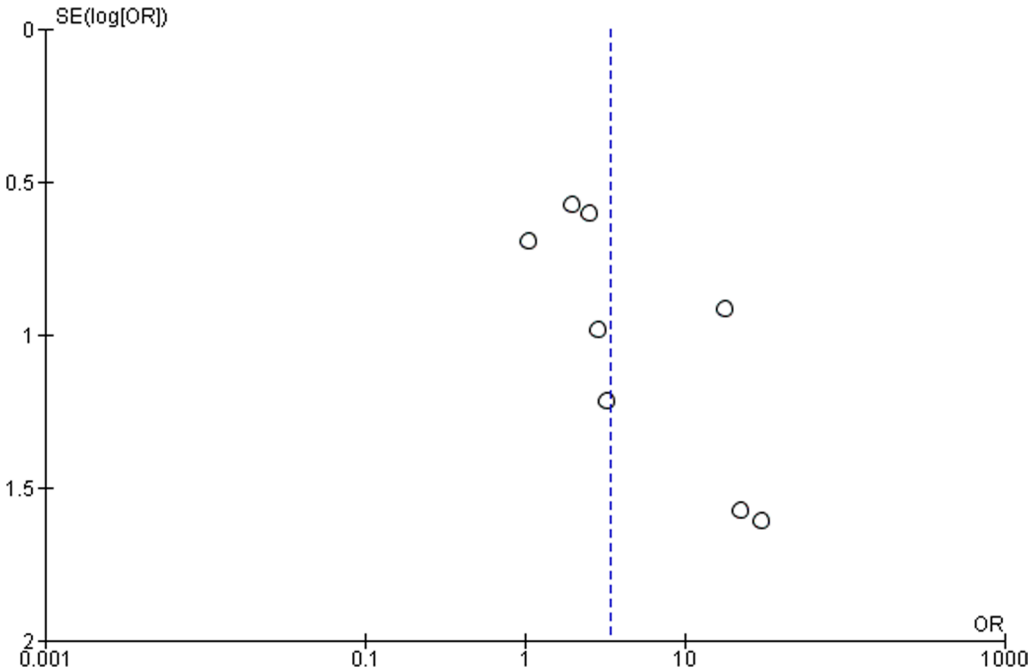

Fig. 9 Funnel plot that assesses the presence of publication bias for the following outcomes: cure

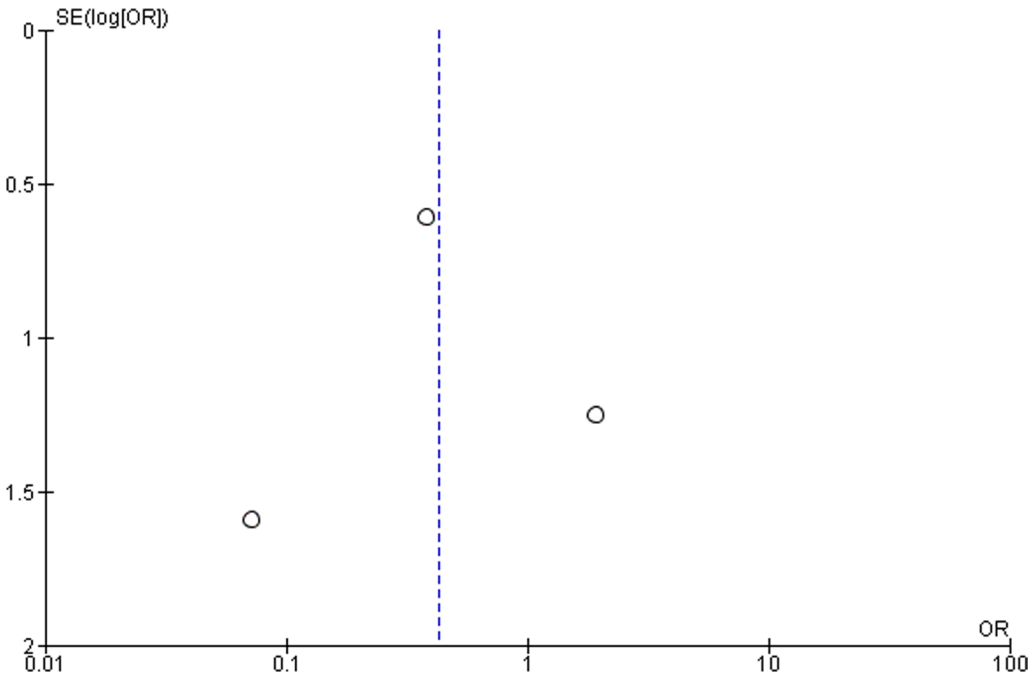

Fig. 10 Funnel plot that assesses the presence of publication bias for the following outcomes: unfavorable outcome

Conclusion

The use of intravenous and intrathecal/intraventricular antibiotics improves survival and the cure rate of patients with postoperative meningitis/ventriculitis; however, it is not superior to standard intravenous therapy in reducing unfavorable functional outcomes or re-infection. The Intrathecal/intraventricular plus intravenous administration is a promising therapy, more studies of high methodological quality are needed.

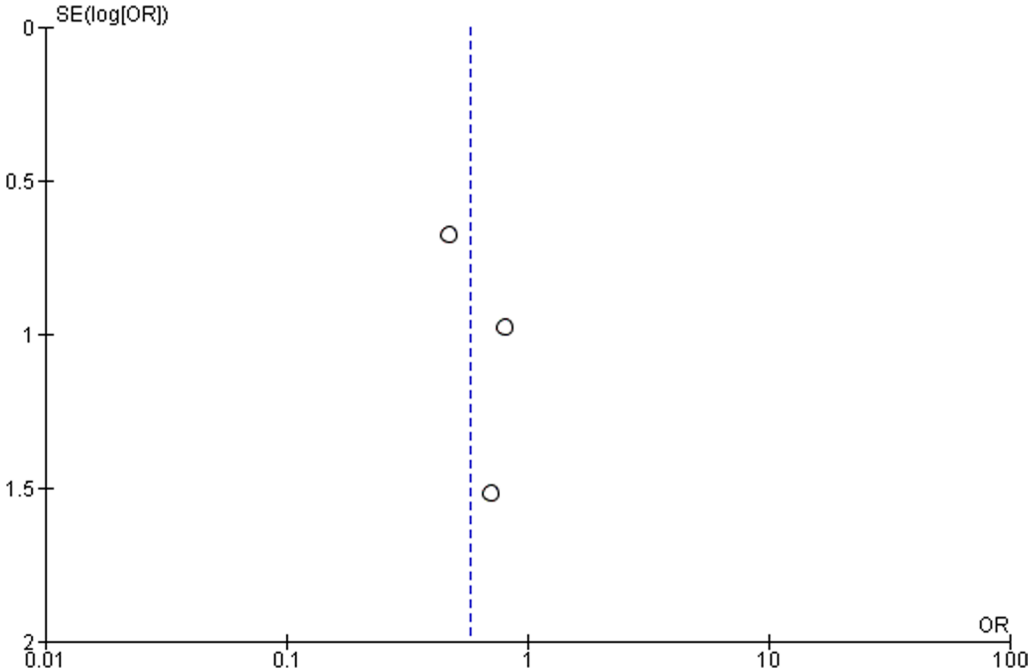

Fig. 11 Funnel plot that assesses the presence of publication bias for the following outcomes: reinfection

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Author contributions
Concept and design: WAFP, HV, AA, and LRM. Analysis and interpretation: WAF. Data collection: WAF. Writing the article: WAF, DEC, IL, TJ, and LRM. Critical revision of the article: IL, DEC, TJ, and AA. Final approval of the article: WAF, IL, AA, DEC, TJ, HV, and LRM. Statistical analysis: WAF. Overall responsibility: WAFP, HV, AA, and LRM. All the authors meet the authorship requirements, they all made substantial contributions to conception of the manuscript regarding the contribution to conception and design, acquisition of data and the correspondent interpretation, drafting the article, and making the critically revision of the intellectual content.

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Declarations

Ethics approval and consent to participate
The present manuscript has not been submitted to other journal for simultaneous consideration. The manuscript has not been published previously and is not split up in other parts, no data have been manipulated or fabricated, and no information is presented as if were from the authors

Consent for publication
All the authors approved the last version of the manuscript and consent for publication.

Competing interests
Not competing interest. The authors declare that they have no conflicts of interest. Dr. Quiñones Ossa has nothing to disclose. Dr. Durango Espinosa has nothing to disclose. Dr. Janjua has nothing to disclose. Dr. Moscote Salazar has nothing to disclose. Dr. Agrawal has nothing to disclose.

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