▪ 2022, 4(2):1-5 ▪ e-ISSN: 2674-7103

Jornal Memorial *da* Medicina

▪ DOI: 10.37085/jmmv4.n2.2022.pp.1-5.

Review

The use of intrathecal antibiotics for bacterial meningitis: what evidence do we have?

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Edited by
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Keywords:
Bacterial meningitis
Intrathecal antibiotics
Drug resistant bacteria
Central Nervous System Infections
Therapeutic Failure

Abstract

The treatment of meningitis is a complex issue when it comes to multi-resistant antibiotic bacteria, limiting the drug options that can cross the blood-brain barrier and effectively reach the subarachnoid space. The impact on the effectiveness of the therapeutic arsenal available, due to the indiscriminate use of antibacterial on a global scale, increases the chances of therapeutic failure of the initial empirical treatment and a persistence of failure despite the culture of targeting the treatment at the pathogens, while not obtaining satisfactory results. Thus, the use of strategies to optimize the delivery of antibacterials to the disease site involves using the pharmacokinetic mechanism in order to achieve the desired effect through intrathecal administration. During this review, we aimed to evaluate the use of intrathecal antibiotic therapy in patients infected with multidrug-resistant bacteria and analyze possible adverse effects.

Submitted: September 10, 2022
Accepted: November 30, 2022
Published: December 19, 2022

Introduction

Nosocomial meningitis (NM) is a complex and important medical issue; due to its urgency, which requires early diagnosis, prompt initiation of therapy and frequent admission to an intensive care unit (ICU). According to a retrospective study, which analyzed patients diagnosed with nosocomial meningitis who required admission to the ICU during 10 years, some predisposing factor for nosocomial meningitis were present in a significative percentage (present in 93% of patients), for example: traumatic brain injury, basal skull fracture and brain hemorrhage.[1] The treatment becomes complex due to the multidrug resistant characteristics of the hospital bacterial population such as *Acinetobacter* spp and *S. epidermidis*, which is causing a great concern, due to its high mortality rate.[2] It is cited as mortality approaching 70%, especially in patients on indwelling ventriculostomy tubes or cerebrospinal fistulae and receiving post-surgical antimicrobial therapy.[3]

The indiscriminate use of antimicrobial drugs by health institutions and the general population has contributed to the natural selection of resistant bacteria, which increases the probability of failure in empirical treatment and its persistence even after the result of bacterial culture, with treatment directed toward the pathogen found, makes intravenous (IV) antibiotic therapy a more challenging management.[4] Therefore, it is of fundamental importance to use less conventional strategies to optimize the delivery of the antibacterial to the disease site, using the mechanism of pharmacokinetics in order to achieve success in the treatment used.[5] Given this scenario, this review aims to summarize scientific evidence to support the use of intrathecal (IT) antibiotics for the establishment of an efficient therapeutic resource for NM.

Methodology

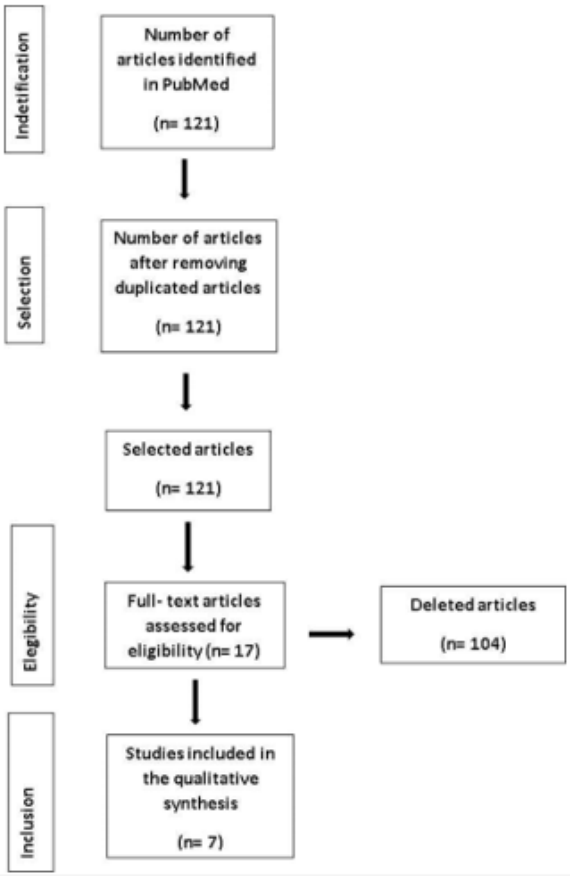
The present review was based on the following research question: "what are the benefits of using intrathecal antibiotic therapy in patients with multidrug-resistant bacterial strains?" formulated by the strategy of the acronym PICOS - Participants, Interventions, Comparisons, Results (Outcomes) and Study Design (Study Design). The strategy is best described in the table represented in Figure 1.

Figure 1 - PICOS strategy used to formulate the research question about the evidence of the benefits in using the IT route in patients with multidrug resistant bacterial strains.

Acronim	Definition	Description
P	Population	Patient with multidrug resistant bacteria refractory to intravenous treatment
I	Intervention	Collect information about treatments and approaches about the patient who component of the macro group P received intrathecal therapy
C	Comparison	Patients who use only the drugs through the conventional intravenous route
O	Result (Outcome)	Expected outcome is associated with good responsiveness to treatment administered via intrathecal administration
S	Study Design	Systematic Review

From the formulation of the question, the descriptors were organized in the PubMed database, a search was made for the corresponding Mesh terms, within which the following combination of descriptors was organized in INL: (Anti-Bacterial Agents AND cerebrospinal fluid AND Central Nervous System Infections) OR (Meningitis OR Cerebral Ventriculitis) AND (Infusions, Spinal OR Injections, Spinal). The following filters were used: Abstract; Full text; in the last years; Humans; English. A total of 121 articles were found in this expansive search on PubMed, no article was discarded for duplication. Among the selected articles, 104 articles were excluded because they did not meet the inclusion criteria: original studies (reviews were not considered) that addressed the topic of intrathecal antibiotic therapy were included. Articles that discussed non-bacterial meningitis or the application of ATB IT for purposes other than central nervous system (CNS) infectious diseases were also excluded. Of the 7 selected, 02 articles were cohorts, 1 was a case series and the others were case reports. The search strategy is described in PRISMA below, as shown in Figure 2.

Figure 2 – The flowchart of the article selection process based on the eligibility criteria of the PRISMA strategy.



Results

Studies have shown that the association between the use of IV ATB and IT route showed benefit in the treatment of meningitis of resistant etiological agents, when compared to conventional treatment by IV, among them strains of the Gram- Negative spectrum, Mycobacterium tuberculosis.

The use of Colistin, also formally known as Polymyxin E, IT associated with already traditional ATB regimens was effective in meningitis caused by Klebsiella pneumoniae of the New Delhi Metalobetalactamase (NDM) variant, resulting in a decrease CSF cell counts., and in Acinetobacter baumannii meningitis, CSF was sterilized in all patients who survived and in 73% of those who had fatal outcomes. Amikacin IT also showed a therapeutic relationship, when combined with ATB regimens administered systemically, in the treatment of Klebsiella pneumoniae meningitis, after ventriculoperitoneal shunt, with no significant side effects and achieving CSF sterilization. In relation to tuberculous meningitis, intrathecal isoniazid may contribute to the improvement of symptoms of meningeal irritation, contributing to a positive prognosis in refractory cases. According to a cohort study including 95 patients with post-operative meningitis caused by Gram-negative bacteria and resistant to carbapenems, mortality and the neurological deterioration of patients who used VIT and IV therapy was significantly lower when compared to those who only received antibiotic

Table 1: articles analyzed in the systematic review that describe the outcomes obtained through the use of ATB used by IT.

Author and year of publication source: Pubmed)	Method	Bacterial pathogen	Utilized therapeutic scheme	Consideration
INAMASU et al.[6]	Case Report	New Delhi Metallo-B-Lactmase 1(NDM-1) producing Klebsiella pneumoniae	Colistin IV (pathogen indicated as sensitive to the drug) and Colistin IT (10mg dissolved in 10 mL saline solution admnistered through lumbar puncture for 14 days)	Despite the administration of IV Colistin (drug sensitive) there were only small improvementes in fever control and cell counts (CSF). After 14 days of IT administration, the fever subsided and the CSF cell Count dropped to <100/ mm^3 (Fig.1) and the level of consciousness retunerd to baseline
EMIROGLU et al.[7]	Case Report	Carbapenem- resistant K. pneumoniae	Amikacin IT (dosage was not describe- for 7 days) Tigecycline IV and Meropenem IV,	On the sixth day of treatment the CSF was sterilized. The antibiotic therapy was managed and consisted of a total of 60 days of meropenem and 20 days of therapy with tigecycline
GOFMAN et al.[8]	Case Report	Pseudomon as Aeruginosa carbapenem- resistant and Klebsiella pneumoniae	Ceftazidie-avibactam IV (2.5g Every 8 hours) for 6 weeks and Amikacin (30mg VIT daily for 28 days)	After 3 days of initiation of therapy, there was of microbiological eradication, wich resulted in CSF sterilization. There weren't any adverse events reported as serious.
LI et al.[9]	Case series	Enterobacteriae Acinetobacter baumannii	Meropenem IVand Meropenem IT (200mg dissolved in 250mL of saline solution, administered through lumbar puncture of 12/12h for 60h)	Meropenem is a drug with low LCR and simply. Increasing the IV dose can increase the risk of adverse effects of the medications (diarrhea, nausea and vomiting, headaches). So, new strategies for administration and dosage should be investigated.
NAKATANI et al.[10]	Case report	Mycobacterium tuberculosis	Intrathecal isoniazid (100mg 3x Weekly) ** dexamethason,heparin	Multimodal therapy, including intrathecal isoniazid and systemic corticosteroids should the considered for cases of refractory tuberculous meningitis, refractory or not, complicated by hepatotoxicity induced by antituberculosis drugs may be na indication for intrathecal isoniazid use.
CHUSRI et al.[11]	Cohort	Carbapene m-resistant acinetobacter baumannii	Of the 33 patientes, 17 received additional intrathecal IV bump and 16 received IV Colistin alone.	Treatmente costs were significantly lower, hospital and intestive care unit (ICU) lengths of stay were significantly shorter, and the number of ventilation days was significantly shorter. Patients who received ITH/IVT Colistin compared with patients who did not receive ITH/ IVT Colistin.
SHOFTY et al.[12]	Cohort	Acinetobacter baumannii or Carbapene m-resistant Gram-negative bactéria (CRGN)	Colistin (average dose 50000 IU/ day range 50000-250000) or Amikacin (average dose 37,5 mg/ day, range 25-50mg/day) for 9 to 12 days*	Mortality was significantly lower with IT therapy/ IV:2/23 (8.7%) versus 9/27 (33.3%), or adjusted by propensity 0.19, 95% CI 0.04-0.99. Death or ne urological deterioration was within 30 days, 14 days and in-hosptital mortality were lower with IT/IV therapy (or<0.4 for all) with no statistically significant diferences.

*In these cases, as they are studies composed of several patients, the dosage was made according to each context

**for approximately 24 weeks, after the period, the dose was administered 1x per week until the condition improved

therapy IV. The results found through the analysis of the articles can be observed more objectively through the Table 1.

Discussion

The treatment of CNS infections is an even more complex issue when it comes to bacteria that are multi-resistant to antibiotics, limiting the drug options that can effectively reach adequate concentrations at the site of infection. Strategies to optimize antibacterial delivery involve utilizing the pharmacokinetic mechanism.[13] Notably, in the case of bacterial meningitis, there was an impact on the effectiveness of the available therapeutic arsenal due to the global emergence of multidrug-resistant bacteria, denoting therapeutic failure in the initial empirical treatment and persistence of failure even after culture and treatment targeting pathogens, therefore, not getting a satisfactory result.[14]

In the researched articles, therapeutic failure in the treatment of meningitis occurs when empirical and guided therapy are administered in a timely manner, but the concentration of bacterial agents remains significant in the CSF, making it impossible to sterilize the material; Reiterating the relevance of scientific research that analyzes strategies to raise alternatives for patients affected by resistant strains. Based on this principle, the administration of ATB via IT is a topic of relevant importance, as it provides an opportunity to achieve high concentrations in the CSF of drugs that cross the blood-CSF barrier poorly, acting as an adjunct to IV therapy, especially in patients who are affected by CNS infections caused by multidrug-resistant bacterial strains that are refractory to IV therapy alone.[5]

However, understanding the distribution of the drug in the subarachnoid compartment and measuring the effectiveness of the procedure is a complex point because it involves anatomical variables such as the dilution of the substance in the CSF; size of ventricles, basal cisterns and subarachnoid space over convexities and spinal cord[15]; and oscillatory pulsations of the CSF flow in drug propagation, factors not well established in literature.[14] Thus, through the inverse reasoning to its main use, in situations in which the pathogens are sensitive and it is possible to use antibiotics that easily overcome the blood-CSF barriers or have low toxicity and therefore, allow an increase in concentration of the daily dose, the drug should not be used for IT therapy. Because it is understood that high concentrations of these drugs or these drugs used in the presence of renal failure, even in situations of IV drug use, can have deleterious neurotoxic effects.[15] In this way, cases that are indicated for the use of ATB IT are protected. In addition, more recent studies suggest that IT administration of drugs such as Colistin, Aminoglycosides and Vancomycin is not associated with severe or irreversible toxicity. Toxicity appears to be dose-related, and in early reports, for example, in the case of streptomycin, it may have been associated with inadequate dosing.[13]

In this review, there was evidence that the use of antibiotic therapy by the IT route, associated with the systemic route, brought benefits to patients infected with multidrug- resistant strains that did not respond to conventional treatment, generating an improvement in the clinical condition, without significant adverse effects, when documented. However, research evidence is very limited and the specific features of the combined use of antibiotic therapy need to be further clarified. In summary, therapy using antibiotic therapy by the IT route associated with the IV route can be useful in specific cases, if administered in a greatly meticulous manner.

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Data Availability

All data generated or analysed during this study are included in this published article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Statement

The authors declare that neither the research nor the publication of this paper was funded by any financially supporting bodies.

Authors' contributions: MEMPD, Conceptualization, Method, Validation, Formal analysis, Investigation, Resources, Writing-Original Draft, Supervision; ACMO, AAPF, LPN, MVAR, ISRD, CBSF, JGSR, Data curation, Writing- Original draft,

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