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Intra-cerebrospinal fluid antibiotics to treat central nervous system infections: A review and update

Oliver D. Mrowczynski*, Sara T. Langan, Elias B. Rizk

Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, PA 17033, United States

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ABSTRACT

Central nervous system infections can be complications of neurosurgical procedures or can occur spontaneously, and occasionally lead to devastating neurological complications, increased rate of mortality, and lengthier stays in the hospital, subsequently increasing costs. The use of intrathecal antibiotics to bypass the blood brain barrier and provide effective concentrations to the central nervous system has been described as an adjunct treatment option. However, the regimens of antibiotics utilized intrathecally have not been standardized. Our review of the literature included all articles from MEDLINE/PubMed and Ovid from inception to 2017 and after removing duplicates and checking for relevancy, the final number of articles yielded was 200. This review summarizes the use of antibiotics intrathecally to treat CNS infections, the dosages, therapeutic efficacies, and highlights significant side effects. The current rates of mortality in patients suffering from CNS infections is high, thus intrathecal antibiotic therapy should be considered as a potential therapeutic strategy in this patient population. Multiple antibiotics have demonstrated safety and efficacy when used intrathecally, and further studies, including clinical trials, need to be performed to elucidate their full therapeutic potential and outline proper dosing regimens.

1. Introduction

Central nervous system (CNS) infections can be complications of neurosurgical procedures or occur spontaneously, and occasionally lead to devastating neurological complications, increased rate of mortality, and lengthier stays in the hospital, subsequently increasing costs [1–3]. Previously reported rates of CNS infections [4–6] depend on intervention type, such as craniotomy and drain placement, and can occur in up to 8.6% of patients undergoing a neurosurgical procedure [4]. These infections are complex in nature because bacteria are becoming increasingly resistant to the most common antibiotic therapies [7]. Another challenge when treating CNS infections with intravenous antibiotics is the difficulty of attaining an effective antibiotic concentration within the CNS, as the blood brain barrier (BBB) decreases antibiotic therapy from reaching the desired destination [8]. These factors precipitate high mortality rates of CNS infections. In an attempt to reach effective therapeutic levels within the CNS, the following approaches are utilized: increased dosages of antibiotics with low systemic toxicity, lipophilic antibiotics, antibiotics with small molecular weights, and antibiotics which bind less to plasma proteins, all of which cross the blood brain barrier more effectively [9]. Even with these strategies, adequate drug concentrations within the CNS are difficult to attain, especially without significant systemic toxicity. This has led to increased utilization of intrathecal antibiotics to effectively treat CNS infections, bypassing the blood brain barrier [10,11]. Intrathecal (IT)/intraventricular (IVT) antibiotic therapy can be performed through Ommaya reservoir placement, ventriculostomies, lumbar punctures, or lumbar drains. Ommaya placement is used to treat neoplastic meningitis, without significant surgical morbidity or mortality [12], suggesting this technique may be safe and feasible for administering antibiotics. Intrathecal antibiotic therapy has not been standardized, which complicates the standard of care for patients with CNS infections [8]. Without a standardized protocol for the treatment of CNS infection with intraventricular antibiotics, this review aims to summarize antibiotics used intrathecally to treat CNS infections, the dosages, and therapeutic efficacies.

2. Methods

2.1. Study selection

Our review of the literature included all articles from MEDLINE/PubMed and Ovid from inception to 2017. Search terms included combinations of "intrathecal" OR "intraventricular" OR "IVT" AND

* Corresponding author at: Department of Neurosurgery, Penn State Hershey Medical Center, Hershey, PA 17033, United States.
E-mail address: omrowczynski@pennstatehealth.psu.edu (O.D. Mrowczynski).

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Table 1
Vancomycin.

Study	# patients	Organism	Dose and duration	Response	Toxicity
Arroyo, J. 1983	1	*Staphylococcus aureus*	10 mg/day for 15 days	Patient succumbed to disease	none noted
Czaban, S. 2002	1	*Enterococcus faecalis*	20 mg/day for 10 days	Patient infection cleared	none noted
Richards, S. 1992	1	*Listeria monocytogenes*	20 mg/day for 2 weeks followed by 10 mg/day for 1 week	Patient infection cleared	none noted
Bayston, R. 1987	46	*Coagulase negative staphylococcus, Staphylococcus aureus, enterococcus, Propionibacterium acnes, Streptococcus sanguis*	5, 10, or 20 mg/day for 3–38 days	66% of patient's infections were cleared	none noted
Amod, F. 2005	1	MRSA	5–30 mg/day for 21 days	Patient infection cleared	none noted
Scwabe, M. 2007	1	*Staphylococcus epidermis*	5 mg/day for 18 days	Patient infection cleared	none noted
Sutherland, G. 1981	1	*Staphylococcus epidermis*	0.075 mg for one day	Patient infection cleared	none noted
Bayston, R. 1984	10	*Staphylococci, enterococcus, Staphylococcus aureus*	20 mg/day for 3–38 days	80% of patients had CSF clearance	none noted
Swayne, R. 1987	15	*Staphylococci, streptococci*	20 mg/day for 5–19 days	All patients had clearance of organism	none noted
Reesor, C. 1988	1	*Streptococcus faecalis, Enterobacter cloacae, Escherichia coli,* and *Klebsiella pneumoniae*	50 mg/day, down to 10 mg/2 days with combination gentamicin	Patient infection cleared in one month but patient died	none noted
Pfausler, B. 1997	3	MRSA	10 mg/day for at least 1 day	All patients had clearance of organism	none noted
Young, E. 1981	1	*Staphylococcus aureus*	20 mg/day for 10 days	Patient infection cleared but patient died of enterobacter superinfection thereafter	none noted
Pfausler, B. 2003	10	*Staphylococcus species*	10 mg/day	CSF cleared after 3-4 days	none noted
Morales-Garcia, V. 2003	27	None	10 mg/day for less than 10 days as prophylaxis for infection	None of the patients with IT vancomycin prophylaxis developed infections while almost half of the controls developed ventriculitis	none noted
Soman, R, 2016	1	*Elizabethkingia meningoseptica*	15 mg/day for 15 days	Good treatment response	none noted
Fu, R. 2017	262	None	10 mg/day as prophylaxis for infection	2.7% in the vancomycin group and 11.9% in the control group developed infections	none noted
Patel, T. 2016	1	*Enterococcus faecalis*	10 mg/day every other day for 3 days	Patient infection cleared	none noted
Bao, Y. 2016	35	Multiple species	500kU every 6 h	Recovery rate and time of recovery were better in group treated with combination IV/IT compared to IV alone	3 patients had nerve root irritation which ceased after slowing injection time
Popa, D. 2016	14	Multiple species	10 mg ever 12–48 h for 1–15 days	All patients had clearance of organism	none noted
Lee, K. 2015	1	*Rhodococcus*	25 mg/day vancomycin in combination with amikacin	Patient cleared at 4 month follow up	none noted
Matsunaga, N. 2015	13	Multiple species	5, 10, or 20 mg/day	11 patients had complete CSF clearance of the organism	3 patients with abnormal auditory brain stem response, no convulsions
Chen, K. 2015	14	Multiple species	10 mg twice per day	6 patients with complete CSF clearance, 7 patients with a positive response, and one patient succumbed to infection	none noted
Goto, K. 2011	1	MRSA	10 mg/day	Patient infection cleared	none noted
Nava-Ocampo, A. 2006	1	*Enterococcus faecalis*	10 mg/day	Patient infection cleared	none noted
Knudsen, J. 1994	1	*Corynebacterium jeikeium*	10 mg/day for 4 days	Patient infection cleared	none noted