Intraventricular or intrathecal use of polymyxins in patients with Gram-negative meningitis: a systematic review of the available evidence
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CRD summary
The authors concluded that limited evidence suggests that intraventricular and intrathecal polymyxins (alone or with systemic antibiotics) are effective for Gram-negative meningitis, and that toxicity is not uncommon but is usually dose-dependant and reversible. The conclusions appear to be supported by the data but the limited search and poor reporting of review methods make it difficult to assess their reliability.

Authors’ objectives
To investigate the effectiveness and safety of polymyxins for meningitis.

Searching
PubMed was searched from 1950 to 2006 to identify eligible studies, and the reference lists of relevant studies and reviews were also examined; the search terms were reported. Studies were excluded unless they were written in English, French, Italian, German, Spanish or Greek.

Study selection
Study designs of evaluations included in the review
There were no inclusion criteria with respect to study design. The review included case reports and case series.

Specific interventions included in the review
Studies of intraventricular or intrathecal polymyxin B or E (colistin) were eligible for inclusion.

The included interventions comprised monotherapy or combined therapy with intraventricular or intrathecal polymyxin B or E, often used after the failure of prior antibiotic regimens. Polymyxins were the only agents used in the final therapeutic regimen in 56% of episodes of Gram-negative meningitis. Where other agents were used in combination with polymyxins in the final regimen, they comprised adjuvant systemic beta-lactams or local penicillin, amikacin, streptomycin, cefaloridine or gentamycin. The daily dose of polymyxins ranged from 20,000 to 250,000 IU in adults and from 5,000 to 120,000 IU in children. The duration of treatment ranged from 1 to 9 weeks, approximately.

Participants included in the review
Studies were eligible for inclusion if they enrolled participants with culture-proven bacterial infection from cerebrospinal fluid (CSF) or central nervous system (CNS) tissue.

The participants included adults and children with primary meningitis, or (in more recent studies) Gram-negative meningitis secondary to a neurosurgical procedure and often involving a ventriculoperitoneal or ventriculoatrial shunt. The most common infective organisms were Pseudomonas aeruginosa and Acinetobacter baumannii, in many cases described as multidrug-resistant and susceptible only to polymyxins. The review included older studies that used polymyxins for organisms for which they would not be used nowadays.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported clinical effectiveness or safety. Effectiveness was defined in terms of clinical outcome: success, failure or intermediate. Success was defined as clinical improvement or resolution with negative CSF cultures at follow-up. Failure was defined as deterioration or death associated with the uncontrolled progression of meningitis, discontinuation of therapy due to adverse effects, or change to other antimicrobial therapy. An intermediate result was defined as a good clinical response with respect to meningitis but with mortality due to co-morbidity, or discontinuation of therapy due to toxicity after at least 5 days of treatment. The review also reported the incidence and (where relevant) the nature of toxicity in each primary study.
How were decisions on the relevance of primary studies made?
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Assessment of study quality
The authors did not state that they assessed validity

Data extraction
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Outcomes were presented in textual form in a table summarising clinical effectiveness (categorised as cure, failure or intermediate) and toxicity.

Methods of synthesis
How were the studies combined?
The studies were presented in a narrative synthesis.

How were differences between studies investigated?
Differences between the studies were discussed in terms of the age of the study and clinical factors such as the causative organism, drug regimen used and age of the participants.

Results of the review
Thirty-one studies (n=60) were included. These comprised 26 case reports (n=32) and 4 case series (n=26) on the use of intrathecal or intraventricular polymyxins, plus 1 larger case series on the use of polymyxins in general, from which 2 of 80 relevant cases were extracted.

The authors noted a number of limitations and sources of potential bias in their review. Publication bias was possible, as case reports with a successful outcome or describing toxicity were more likely to have been published; problems with indexing or terminology may have caused potentially relevant older publications to be missed in the literature search; and changes in methods of bacterial testing may have limited the comparability of studies over time.

Among 60 patients who experienced 64 episodes of bacterial meningitis and who were treated with regimens that included local polymyxins, the outcome was cure in 80% (51 of 64) of episodes. Among adults, outcomes were cure in 79% (27 of 34), failure in 12% (4 of 34) and intermediate in 9% (3 of 34). Among children, outcomes were cure in 80% (24 of 30) of episodes, failure in 10% (3 of 30) and intermediate in 10% (3 of 30). By causative organism, the cure rates were Pseudomonas (usually aeruginosa) in 87% (27 of 31) of episodes, Acinetobacter (usually baumannii) in 91% (10 of 11) and Klebsiella in 63% (5 of 8). Toxicity was reported in the primary studies in 28% (17 of 60) of patients. Irreversible toxicity was not reported in any study. The most common form of toxicity was dose-dependant reversible meningeal irritation in 71% (12 of 17) of cases; this was less commonly reported in more recent studies. Discontinuation of treatment occurred in 4 patients, and dose reduction in another 4.

There was limited evidence from 8 studies that intraventricular polymyxins may be highly effective in cases of catheter- or shunt-related multidrug-resistant Gram-negative CNS infections. There was a lack of evidence on the appropriate timing of initiation of polymyxin therapy, the comparative effectiveness and toxicity of polymyxins and other antibiotics, the role of combining systemic antibiotics with local CNS polymyxins, and the optimal dosing regimen.

Authors' conclusions
The limited evidence available suggested that intraventricular or intrathecal polymyxins, alone or in combination with systemic antibiotics, are effective against Gram-negative bacillary meningitis. Toxicity is not uncommon but usually constitutes dose-dependant reversible meningeal irritation. Further research is required to determine a suitable regimen.
for intraventricular or intrathecal polymyxins.

**CRD commentary**
The review question and inclusion criteria were clear. The search was limited to one database, which might mean that studies were missed. It was also somewhat limited by language restrictions, which necessitated the exclusion of two potentially relevant studies. It is unclear what steps were taken to minimise bias and error in the review process, as the authors did not state that they assessed validity, nor did they describe how papers were selected for the review, how the data were extracted, or how many reviewers performed these processes.

Adequate detail was provided about the included studies, though there were minor discrepancies in sample numbers between the table and the text. The narrative synthesis was clear and addressed historical factors and other possible reasons for differences between the studies. The authors discussed the limitations of the evidence and the lack of comparative studies and, appropriately, their conclusions highlighted the need for further research. The conclusions appear to be supported by the data but limitations in the search and lack of reporting of review methods make it difficult to assess their reliability.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research is needed to determine the criteria for initiation of local CNS polymyxin therapy, the optimal dosing regimen, and the role of other systemic or local treatment on Gram-negative bacillary CNS meningitis.

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