

Sp55: What is the optimal treatment of patients with culture negative spinal infection?

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Recommendation

The evidences are in favor of combination of drugs rather than monotherapy in treatment of culture-negative spinal infections.

With the available evidence, cephalosporins are first line of drugs recommended in view of it's broad spectrum of activity when the incidence of resistance is low. Alternatively, fluroquinolones can be added to cephalosporins to increase the efficacy of the regimen.

When MRSA is suspected, Vancomycin can be combined with fluroquinolones or third-generation cephalosporins or with carbapenems.

When resistant strains of gram-negative bacilli are suspected carbapenems or fourth-generation cephalosporins can be utilized.

Level of Evidence: Low

Rationale

This systematic review was conducted in concordance with guidelines of the Cochrane Handbook of Systematic Reviews for Interventions to analyze the optimal treatment of patients with culture-negative spinal infection. A thorough search was made in PubMed, Scopus, Web of Science and Clinicaltrials.org from inception till January 01, 2024, for original articles reporting medical management in culture-negative spinal infections. Exclusion criteria were case reports, articles in non-English language, review articles, registry-based studies, and studies on postoperative spinal infections, studies describing surgical techniques and studies on tubercular spondylodiscitis.

Initial database screening resulted in 488 articles which after duplicate removal resulted in 362 articles that were subjected to title and abstract screening. We shortlisted 28 articles for full-text screening from the 362 articles and included 6 articles in the review that met the inclusion criteria. All the studies were of retrospective nature and were of level IV evidence.

Microbiological diagnosis is an important predictive factor for successful treatment of pyogenic spinal infections. However, despite refinements in biopsy techniques and culture methods more than one-third have negative cultures (1). Culture negativity can be resultant of prior antibiotic exposure, fastidious organisms that are difficult to culture or due to faulty biopsy technique (2). Recent reports indicate that clinical characteristics, laboratory values of ESR, CRP and relapse rate in culture-negative patients differ from culture-positive spinal infections (3). Negative cultures also pose a significant challenge in deciding the appropriate antibiotic regimen. While choosing a suitable antibiotic regimen careful consideration of host factors including patient's profile, co-morbidities, epidemiology, prevalent resistance pattern in the community must be made along with pharmacological properties of antibiotics including spectrum of activity, bone and disc penetration capability, potential adverse effects, and administration feasibility. However, our review finds that there is no clear consensus on the choice of antibiotic. The included studies were heterogenous and retrospective. The sparse data of low-quality evidence precludes a comprehensive assessment and algorithmic proposal. The

sample size, antibiotic regimen employed in the studies and duration of treatment are listed in **Table 1**.

Sl. No	Author	Year	Sample size	Antibiotic Protocol	Duration of Antibiotics
1	Kim et al.	2014	151	First gen Cephalosporins	8 weeks
2	J Urrutia et al.	2015	97	Ciprofloxacin + Cephalosporins	12 weeks
3	Gouse Mohamad et al.	2018	42	I.V Cloxacillin/ Cefazolin + Ciprofloxacin – 2 weeks followed by 10 weeks oral cloxacillin / cephalixin+ ciprofloxacin	12 weeks
4	Yu D et al.	2020	41	β -Lactam and glycopeptide	14.4 weeks
5	Lee SH et al.	2022	183	3rd gen Cephalosporins, When non responsive Fourth gen Cephalosporins / Carbapenems + Vancomycin	6 weeks
6	Dai et al.	2024	126	Vancomycin + Imipenem or Vancomycin + Fluoroquinolones or Fluoroquinolones + Third-generation cephalosporins	7.13 weeks

Kim et al. utilized first generation cephalosporins in their antibiotic regimen and was able to achieve a cure rate of 91.5 % (3). No significant difference in relapse rate between culture positive and negative patients was found in their study when the treatment duration was 8 weeks. Lee et al. also utilized Cephalosporins as their first choice and supplemented it with Carbapenems for gram negative coverage and Vancomycin for MRSA coverage when patients were non-responsive to cephalosporins monotherapy (4). Gouse Mohammed et al. utilized a combination of Cloxacillin/ cephalosporins along with fluoroquinolones for twelve weeks and were able to achieve good outcomes (5). Infectious Diseases Society of America (IDSA) Guidelines (2015) recommends using a combination of vancomycin and a third- or fourth-generation cephalosporin for a period of six weeks (09). Alternatively, a combination of daptomycin and fluroquinolone can be employed in case of intolerance or allergy to Vancomycin.

When choosing appropriate antibiotics clinical and demographic characteristics have to be also considered. Though the majority of native pyogenic spinal infections are by *Staphylococcal aureus*, it varies with demography and geography. Research has documented that younger

individuals and men have higher incidence of *Staph. aureus*. Women and Elderly >60 yrs have increased incidence of gram-negative infections and, MRSA is prevalent in chronic renal disease and haemodialysis patients (10). A Recent study has identified risk factors for multidrug-resistant spinal infection including autoimmune conditions immunocompromised state, central venous catheter, prolonged use of broad-spectrum antibiotics and recommended use of antibiotics with MRSA coverage in such scenarios (11).

The duration of antibiotic treatment in the studies under review ranges from 6-12 weeks. A randomized non-inferiority clinical trial showed that 6 weeks of antibiotic treatment was not inferior to 12 weeks in pyogenic spinal infections (12). Most studies recommend that a minimum of six weeks of antibiotic treatment is required to reduce relapse rates though there is no consensus on the duration of I.V antibiotics and a switch to oral therapy (13).

The major limitation of our review is the retrospective nature of included studies and a significant heterogeneity. The antibiotic protocols and the duration of treatment also varied considerably which precludes a strong recommendation based on the available data.

Conclusion:

Adhering to the WHO's rational antibiotic usage careful consideration of clinical and demographic profile of patient along with the invitro susceptibility pattern prevalent in the community must be made when choosing an appropriate antibiotic regimen. With the available evidence, cephalosporins are first line of drugs recommended in view of its broad spectrum of activity when the incidence of resistance is low. Alternatively, fluoroquinolones can be added to cephalosporins to increase the efficacy of the regimen. When MRSA is suspected, Vancomycin can be combined with fluoroquinolones or third-generation cephalosporins or with carbapenems. When resistant strains of gram-negative bacilli are suspected carbapenems or fourth-generation cephalosporins can be utilized. The evidences are in favor of combination of drugs rather than monotherapy in treatment of culture-negative spinal infections.

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