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QUESTION 8: What tests should be used to monitor response to antibiotic treatment in patients with spine infection?

RECOMMENDATION: Serum C-reactive protein (CRP) levels are closely related to clinical response in spine infections and are therefore the preferred marker in monitoring the therapeutic course.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

In two large retrospective studies including 363 patients, criteria for discontinuation of treatment included CRP normalization in addition to resolution of clinical symptoms [1,2]. A weekly decrease of CRP by 50% has been suggested as a therapeutic response in the retrospective study population [3].

Lack of normalization of serum CRP levels is a predictor of treatment failure and warrants additional evaluation, as demonstrated both by a retrospective cohort including 79 patients and a prospective study including 21 patients followed for postsurgical wound infections of the spine [4–5].

Moreover, in a retrospective analysis of 61 patients treated for bacterial spondylodiscitis, the only predictor for de-escalating intravenous therapy to highly bioavailable oral agents was a CRP decrease by week 2 of therapy [6].

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QUESTION 9: Which is the best alternative antimicrobial therapy for fluoroquinolone-resistant gram-negative acute post-surgical infection in spinal surgery?

RECOMMENDATION: The choice of antimicrobial therapy should be based on the pathogen and the susceptibility profile.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

Currently, over 30% of all spinal surgical site infections (SSIs) are secondary to gram-negative bacteria (GNB). Focusing on acute post-surgical infection of spinal surgery, there is no published experience regarding the best therapeutic strategies in case infection by GNB resistant to quinolones. Thus, the treatment criteria used in these cases are the same as those used in the case of fluoroquinolone-resistant GNB periprosthetic join infections (PJIs). The importance of using fluoroquinolones in acute PJIs due to gram-negative bacilli has been demonstrated, but limited antimicrobial agents are available in the case of implant-associated infections caused by fluoroquinolone-resistant GNB [1–3].

The most commonly used antibiotics in the event of fluoroquinolone resistance are β-lactams and carbapenems with or without anti-pseudomonal activity [4]. Grossi et al. described the outcome of 76 GNB-PJIs managed with a curative intent and in their experience, intravenous β-lactams throughout treatment duration (median 90 days) results in an effective alternative to fluoroquinolones [5].

Therapeutic alternatives to β-lactams have been poorly assessed. Cotrimoxazole, which can be switched to oral therapy, has been successfully used in some of these cases [1–6]. Other possible alternatives are the "recovery" of the use of less conventional antibiotics, such as colistin and fosfomycin [7–9]. Colistin shows good spread in bacterial biofilm and a synergistic effect when combined with other antibiotics, especially β-lactams, and has been demonstrated to be effective in vitro against *P. aeruginosa* and enterobacteria [7]. Corvec et al. compared the activities of fosfomycin, tigecycline, colistin and gentamicin (alone and in combination), against a CTX-M15-producing strain of *Escherichia coli* in vitro and in a foreign-body infection model [10]. Fosfomycin was the only single agent, which was able to eradicate *E. coli* biofilms (cure rate, 17% of implanted, infected cages). In combination, colistin plus tigecycline (50%) and fosfomycin plus gentamicin (42%) cured significantly more infected cages than colistin plus gentamicin (33%) or fosfomycin plus tigecycline (25%) ($p < 0.05$). The combination of fosfomycin plus colistin showed the highest cure rate (67%), which was significantly better than that of fosfomycin alone ($p < 0.05$). Therefore, the authors conclude that the combination of fosfomycin plus colistin is a promising treatment option for implant-associated infections caused by fluoroquinolone-resistant GNB, but the effectiveness of this combination should be assessed in vivo.

Other potential therapeutic alternatives are combinations that include tigecycline or rifampin for their demonstrated in vitro synergism with several drugs. Tigecycline has been used for carbapenemase-producing gram-negative PJIs, although bone concentrations of the drug are usually lower than the minimum inhibitory concentrations of these bacteria [11]. Drapeau et al. recently described a literature review of 19 clinical studies on the use of rifampin in treatments for multidrug resistant gram-negative (MDRGN) bacterial infection [12]. Nonetheless, the real clinical benefit of using rifampin-containing therapies for MDRGN bacteria in terms of clinical outcome and survival rates remains to be defined.

The development of new agents (ceftazidime/avibactam, aztreonam/avibactam, cefiderocol, ceftolozane/tazobactam) with activity against MDRGN bacteria will provide important therapeutic options for clinicians, but definitive data showing clinical efficacy is currently lacking [13].

The efficacy of intrawound tobramycin powder in terms of eradicating a known bacterial contamination in an *Escherichia coli*-infected rabbit spinal implantation model was assessed, with the researchers concluding that intrawound tobramycin eliminated *Escherichia coli* surgical site contamination [14].

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