G83b: What is the optimal antimicrobial treatment for patients with orthopaedic infections caused by Nontuberculous Mycobacteria (NTM)?

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Response/Recommendation: Prolonged antimicrobial therapy, either empiric or based on drug susceptibility testing (DST), in combination with surgical debridement and/or prosthetic removal is recommended for orthopaedic NTM infection. These infections are complex and need MDT management, whenever available.

Level of Evidence: Moderate

Delegate Vote:

Rationale:

Orthopaedic non-tuberculous mycobacterial (NTM) infection is a rare condition and usually underdiagnosed especially in developing countries. Diagnosis is often difficult to make because of the nonspecific clinical course and difficulty in isolating the pathogen.(1) The standard treatment protocol including the recommended antimicrobial guideline is not currently available. Therefore the treatment recommendation is mostly extrapolated from the existing pulmonary treatment regimen/recommendation. Prolonged antimicrobial therapy either empiric or based on susceptibility testing in combination with surgical debridement and prosthetic material removal is recommended.(2) Among 170 mycobacterium species, over 20 species has been identified to cause infections. We proposed the treatment recommendation for some of the most prevalent NTM in musculoskeletal infections.

Mycobacterium abscessus

M. abcessus belongs to rapidly growing mycobacteria (RGM) subgroup of atypical mycobacterium along with *M. chelonae, M. fortutium, M. smegmatis and M. wolinskyi*. They typically take less than a week to grow on standard blood agar plate and is related with early onset PJI, which may mimic other bacterial PJI presentation.(3) Musculoskeletal *M.abscessus* infection mostly reported in prosthetic joint infection (PJI) cases which was treated with long term Amikacin-based regimen.(4–6) These treatment guidelines is based on drug susceptibility testing result and should be continued for a minimum for 6-12 months after the last positive culture.(7) Some authors avoided long term amikacin due to nephrotoxicity concerns and replaced it with imipenem or clarithromycin.(8,9)

Mycobacterium avium

M. avium infection is the second most common NTM infection of the upper extremity. Clarithromycin or azithromycin is the main component for successful treatment for most NTM including *M. avium*. However, multiple drug regimen is needed to prevent macrolide resistance in the long run. Most studies used the combination of either clarithromycin or azithromycin with ethambutol and rifampin as their antimicrobial regimen for treating musculoskeletal

infection.(10–13) Quinolones were also used in several studies as an adjunct for macrolide-based-regimen.(11,14) Prolonged antimicrobial therapy for at least 12 months past the last positive culture are recommended.

Mycobacterium bovis

Three drug combination: rifampicin, isoniazid and ethambutol is the regimen of choice for most *Mycobacterium bovis* infection including prosthetic joint infection. For severe cases, several studies used four-drug-combination by adding moxifloxacin due to *M. bovis* intrinsic resistance to pyrazinamide.(15,16) Duration of 9 to 12 months of antituberculosis medication resulted in good outcome in most cases.

Mycobacterium chelonae

M. chelonae is typically associated with immunocompromised patients and its presentation in bone has only reported in less than 10 cases.(17) The antimicrobial treatment in those cases were widely varied, ranging from amikacin, clarithromycin, cefoxitin, cotrimoxazole, doxycycline, imipenem and quinolones.(17–20) Therefore the antimicrobial regiment should be tailored based on patient's condition which usually found in immunocompromised condition along with drug susceptibility testing.

Mycobacterium fortutium

M. fortutium is susceptible to agents such as amikacin, cefoxitin, imipenem, sulfonamides and resistant to antituberculous medications.(21,22) Three or four antibiotic combination therapy with an induction and continuation phase is recommended to prevent development of resistance. No specific combination has been determined to be optimal.(7) Combination of amikacin and cefoxitin with or without levofloxacin are usually the initial empirical treatment for *M. fortutium* for the first 2-6 weeks. Then it is usually followed by oral therapy of cotrimoxazole and doxycycline/levofloxacin for 6-12 months.(23)

Mycobacterium kansasii

For *M. kansasii*, rifampin susceptibility testing should be performed prior to initiation of treatment. Rifampicin-sensitive *M.kansasii* should be treated with rifampicin, ethambutol and isoniazid or macrolide (clarithomycin or azithromycin). On the other hand, rifampin-resistant *M.kansasii* should be treated by three drug regimen which is guided by DST results and is recommended to be treated by an expert with MDT discussion. Duration of treatment should be continued after 12 months after culture conversion(24) Two cases of *M.kansasii*-related PJI have been successfully treated with revision arthroplasty and three drug regimen (macrolides, rifampin and ethambutol).(25,26)

Mycobacterium marinum

M. marinum is the most common NTM infection in upper extremity. It is always resistant to isoniazid and frequently also to streptomycin.(27) Combination of two antibiotics including cyclines, macrolides (clarithromycin), ethambutol and rifampin are recommended for deeper infection.(28) Due to its strong bone penetrating ability, rifampicin is usually combined with clarithomycin and ethambutol for patients with osteomyelitis or other deep infections.(7,27) The duration of treatment of deeper infections is also longer, at least 7.5 months compared to the usual 4 months for skin infections.(28)

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