URL: http://www.mjima.org/ • DOİ: 10.5578/mjima.6117

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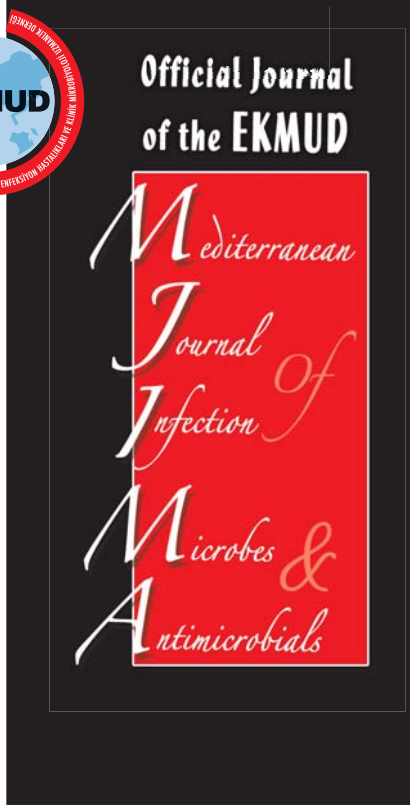

Modern Antibiotic Treatment of Chronic Long Bone Infections in Adults-Theory, Evidence and Practice

Uzun Kemiklerin Kronik Osteomiyelit Tedavisi-Teori, Kanıt ve Uygulamalar

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ABSTRACT

Implant-free chronic osteomyelitis in adults is a bacterial bone infection requiring surgery for treatment. The pharmacokinetic and pharmacodynamic parameters (PK/PD) of concomitant administration of antimicrobial agents for bone penetration are mostly known, but are complex and unpractical. Whether improvement of a PK/PD-driven therapy improves outcome remains unresolved. Equally, the ideal duration of antibiotic therapy concomitant to surgery remains unknown. The traditional recommendation of 6 to maximal 12 weeks of therapy, of which the first 2-4 weeks are intravenously, is more and more being challenged and discussed in favour of an oral antibiotic treatment from the start. Randomized trials in adult patients are urgently needed; allowing optimal timing and duration for therapy avoiding unnecessary prescriptions and antibiotic resistance development.

Key words: Osteomyelitis, antibiotic therapy, duration, penetration, PK/PD

Received: 26.02.2014 • ***Accepted:*** 23.06.2014 • ***Published:*** 07.07.2014

ÖZET

Erişkin hastalarda implantsız kronik osteomyelitlerin tedavisi cerrahi gerektirmektedir. Antimikrobiyal ajanların kemik içine penetrasyonunda farmakokinetik ve farmakodinamik (PK/PD) parametreler hakkında çeşitli veriler mevcut olsa da konu karmaşıktır ve uygulanabilir değildir. PK/PD bazlı tedavinin, sonucu iyileştirip iyileştirmediği hala çözümlenmemiş bir konudur. Ayrıca cerrahiye eşlik eden antibiyotik tedavisinin ideal süresi de bilinmemektedir. İlk 2-4 haftası intravenöz olmak üzere 6-12 haftalık tedaviler gibi geleneksel öneriler artık, başlangıçtan itibaren oral antibiyotik tedavilerin lehine tartışılmaya başlanmıştır. Erişkinlerde acilen optimal başlama zamanı ve gereksiz reçetelemeyi ve antibiyotik direncini ortadan kaldıran süreleri belirleyen randomize çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Osteomyelit, antibiyotik tedavisi, süre, penetrasyon, PK/PD

Geliş Tarihi: 26.02.2014 • ***Kabul Ediliş Tarihi:*** 23.06.2014 • ***Yayınlanma Tarihi:*** 07.07.2014

INTRODUCTION

Chronic osteomyelitis in adults always requires surgical debridement[1]. While surgical science consists many publications demonstrating results, the optimal antibiotic treatment post-debridement for implant-free, non-diabetic long bone osteomyelitis among adults remains less known[2-4]. Studies have primarily investigated the selection of antibiotic agents, rather than their duration, dosage, or route of administration[4-6]. Different series recommend different durations without consistent results, and international guidelines are currently lacking[2-5].

Meanwhile, optimal management of chronic bone infections remains a challenge, and there have been no significant therapeutic developments in medical science in the last two decades. Besides surgery, chronic osteomyelitis still requires prolonged course of parenteral and oral antibiotics, and reveals a relatively high relapse risk after an apparently successful treatment of about 10-20%[2,7-9]. However, the required prolonged exposure of pathogens to antimicrobials, coupled with the peculiar characteristics of antibiotic penetration into bone tissue, also raise the threat of promoting antimicrobial resistance[9]. This short review gives a general assessment and focuses on new insights in the antibiotic treatment of chronic implant-free long bone osteomyelitis in adults.

Antibiotic Treatment-Rationales and Theoretical Concepts

Traditionally, the spectrum of activity and the in vitro susceptibility to antimicrobials have been the cornerstones in the selection of antimicrobial regimens. However, it has progressively become clear that the pharmacokinetic (PK) characteristics of antimicrobials and the optimal pharmacodynamic (PD) exposure, not only in the plasma but also at the infection site, should be taken into account to improve antimicrobial use[10]. For antimicrobials acting with a concentration-dependent mechanism (e.g. aminoglycosides and quinolones), maximal drug efficacy is achieved through an optimized peak concentration (C_{max})/minimum inhibitory concentration (MIC) ratio, meaning that high-dosage may yield more rapid bacterial killing and, possibly, prevent resistance development[11,12]. For time-dependent antimicrobials, such as beta-lactams, carbapenems, linezolid and glycopeptides, the most predictive PD parameter of maximal bactericidal activity is the duration above the MIC during dosing intervals ($\int T > MIC$)[13,14]. Therefore, prolonging the infusion time of beta-lactams could maximize the likelihood of achieving therapeutic concentrations over the MIC for the majority of dosing intervals, especially against pathogens with high MIC values. This prolonged infusion of beta-lactams is not only associated with the improved likelihood of target concentration attainment but also with the possible cost savings and greater potential for reducing the emergence of resistance in comparison with intermittent infusion, even if concrete and convincing trials among patients with osteoarticular infections are lacking[15,16].

To further elaborate, antimicrobials can be divided into hydrophilic and lipophilic compounds, with different volumes of distribution (V_d), protein binding and disposition. All beta-lactams, carbapenems, glycopeptides, and aminoglycosides are typically hydrophilic with a small V_d -generally < 1 L/kg, are unable to penetrate into cell membranes (are inactive against intracellular pathogens), and their disposition is affected by renal clearance or variation in extracellular fluids in most cases[11]. On the contrary, lipophilic drugs, such as quinolones, linezolid, or rifampin, exhibit the capability to diffuse into cell membranes, are active against intracellular pathogens, have an extensive V_d, and feature a non-renal metabolism in most cases. Their disposition, therefore, is minimally affected by renal clearance or variation of extracellular fluids, such as in the case of sepsis.

The potential influence of an underlying disease in antimicrobial penetration into bone is another issue. Patients with osteomyelitis and disorders of peripheral vessels may have impaired blood flow circulation lowering target concentration. Additionally, since the composition of the bone is different from those of other tissues, penetration of the agent into the bone is barely unpredictable. Bone is less vascularized than other tissues and functionally composed of two distinct parts: the cortical bone and the cancellous bone. The presence of pus and ischemic districts within the site of infection may decrease blood circulation, and consequently, the availability of therapeutic concentrations of antibacterials. The efficacy of an antibacterial in bone, in relationship to the antimicrobial plasma concentration after systemic administration, may be influenced by several factors, such as the physicochemical properties of the drug, its degree of protein binding, compartmental clearance, and by the particular structure of the bone tissue itself[17,18]. Macrolides, linezolid and

quinolones reveal mean bone-serum concentrations ratios ranging between 0.3 and 1.2, whereas the mean ratio is between 0.15 and 0.3 for cephalosporins and glycopeptides, and between 0.1 and 0.3 for penicillins[17]. Previous studies have demonstrated different penetration (that is different bone to plasma ratio) of common antimicrobials within cancellous and cortical bone[17-21]. For most antimicrobials, the ratio is higher for cancellous than for cortical bone[17,18]. It should be also be considered that the bone to plasma ratio might change over time until equilibrium is reached between compartments (system hysteresis phenomenon).

Despite improved knowledge on pharmacologic characteristics of antimicrobials, the available literature about clinical practice in the treatment of chronic osteomyelitis is still inadequate to determine the best agent, route, or duration of antibiotic therapy. Scientifically speaking, direct measurement of drug concentrations at the infection site is attaining consideration for targeted antimicrobial treatment of deep-seated infections, whenever collection of extracellular fluid is feasible and new techniques, such as microdialysis, can be carried out[22]. However, this is largely impractical in daily clinical practice. Hence, plasma concentrations are still used as surrogate markers of drug exposure in tissues, although they do not predict tissue concentration[11]. PK studies of bone penetration can provide important information, but they cannot replace large clinical effectiveness trials[17].

Antibiotic Treatment-Practical Aspects

Without adequate debridement, chronic osteomyelitis does not respond to antibiotic regimens, no matter what the antibiotic choice or the duration of therapy is. Only for some exceptions, antibiotic administration without surgery may eradicate infection in childhood osteomyelitis, spondylodiscitis, tuberculous osteomyelitis and in selected cases, diabetic toe osteomyelitis[23]. Experts usually recommend an intravenous (IV) therapy for two to four weeks followed by an oral course of medication for additional months or weeks [2,24]. In parenteral administration, bone penetration of antibiotic agents is undoubtedly favorable and serum bioavailability is per definition 100%[25]. On the other hand, parenteral medication should be limited as far as possible in order to save unnecessary costs, prevent catheter-related complications and to increase patient and nursing comfort. The estimated proportion of complications attributed to prolonged IV course range around 15%[2,9].

Total duration of antibiotic therapy: As a general principle today, the duration of antibiotic administration does not depend on the pathogen with few exceptions including tuberculosis, other mycobacteria such as in buruli ulcer, fungi, Q fever, nocardiosis or brucellosis, and pathogens for which the literature suggests long-lasting antibiotic treatments[9,26-30]. In practice, long postoperative oral treatment regimens are frequent, ranging from six to ten months or even up to two years[2]. There are no clinical studies or documented records indicating the superiority of the 4-6 months course over shorter durations[2-5]. Long periods of supplementary oral treatment ensued from cases of relapsing osteomyelitis in the 1970s, which may be less frequent today due to improved surgery and newly available antibiotics. Thus, total duration of antibiotic treatment, concomitant to surgery, can be probably limited to 6 weeks[2,8,31]. Moreover, Eyichukwu et al. reported successful treatment of chronic osteomyelitis after surgery and short-term sensitivity-based IV course of 2-3 days, followed by oral administration[32]. A Cochrane review has included five trials comparing oral vs. IV antibiotics for chronic osteomyelitis in adults. There was no statistically significant difference in the remission rate[5]. In a retrospective single-centre study, the duration of total post-debridement antibiotic treatment or the duration of its initial parenteral part was not found to be associated with the remission rate. One week of IV therapy achieved the same success of 2-3 weeks or more. Four weeks of total antibiotic treatment revealed the same outcome of 6 weeks or more than 12. Less than six weeks was shown to be equal to more than six weeks[2]. Haidar et al. listed small individual reports in animals and humans obtaining remission of osteomyelitis with antibiotic durations ranging from 1 to 4 weeks[3,9].

Choice of the Antimicrobial Agent-Practical Aspects

Antimicrobials base their action on the susceptibility of the isolated pathogen, bone penetration, tolerance issues, and oral bioavailability (Table 1). Single-agent antibiotic therapy is usually adequate.

Intravenous agents: The most frequently used antibiotic agents, the beta-lactam antibiotics, ubiquitously show low oral bioavailability and low intraosseous penetration[3]. Since the bone penetration of vancomycin is only about 15-30% of the serum concentration, minimal serum levels of 20-25 mg/mL are believed to treat bone infections the best. In continuous perfu-

Tablo 1. Antibiotic treatment of chronic implant-free osteomyelitis (concomitant to surgery if no surgical removal in toto; personal suggestions)

Parenteral treatment	**(Duration 0-2 weeks)**		
	Antibiotic	**Alternatives**	**Dosage**
Resistant staphylococci	Vancomycin	Teicoplanin	Vancomycin 2 x 15 mg/kg
		Daptomycin	Daptomycine 6-10 mg/kg/d
		Linezolid	Linezolid 2 x 600 mg/d
Susceptible Gram-positives	Cefuroxime	Penicillins	
Gram-negatives	Ceftriaxone	Ceftriaxone	
		Ceftazidime	
		Cefepime	
Anaerobes	Amoxicillin-clavulanate	Carbapenems	
Oral treatment	**(Duration 6-12 weeks)**		
Resistant staphylococci	Fusidic acid + rifampin	Ciprofloxacin + rifampin	Rifampin 600-1200 mg/d
		Levofloxacin + rifampin	Levofloxacin 2 x 500 mg/d
		Doxycyclin + rifampin	Doxycyclin 2 x 100 mg/d
		Minocyclin + rifampin	Minocyclin 2 x 100 mg/d
		Cotrimoxazole + rifampin	2 double-strength tablets
		Linezolid + rifampin	Linezolid 2 x 600 mg/d
Susceptible Gram-positives	Clindamycin	Ciprofloxacin + rifampin	
		Levofloxacin + rifampin	
		Cotrimoxazole + rifampin	
Gram-negatives	Ciprofloxacin	Cotrimoxazole	2 x 500 mg/d in combination, 2 x 750 mg in monotherapy.
		Levofloxacin	2 x 500 mg/d
Anaerobes	Metronidazole	Clindamycin	Clindamycine 3 x 600 mg/d Metronidazole 3 x 500 mg/d

sion, the changes in serum concentrations are much lower than in intermittent application[33]. However, continuous perfusion does not guarantee a better outcome in term of remission[34]. Daptomycin depolarizes membranes and yields a rapid, dose-dependent bactericidal effect. It is only available in parenteral form and administered once a day at a dose of 6-8 mg/kg, making it suitable for an outpatient treatment[35]. Clinicians should keep in mind that emergence of a daptomycin-resistant *S. aureus* isolate during treatment of initially daptomycin-susceptible MRSA osteomyelitis has been described[36]. Trials with higher doses up to 10 mg/kg are in progress to overcome this problem. Aminoglycosides are less active in synovial fluid or in bone[37]. Furthermore, staphylococcal small-colony variants, a hallmark of chronic pre-treated osteo-articular *S. aureus* infections, are generally resistant to aminoglycosides[37]. However, in desperate situations and in low-income countries, aminoglycosides might be an option.

Oral agents: Ideally, the oral agent should have bactericidal activity against slow-growing and biofilm-producing bacteria. Rifampin fulfills these criteria for staphylococci, although the classical indication for combined rifampin treatment is staphylococcal implant infection[38]. However, rifampin can also be used for implant-free osteomyelitis. Since rifampin usually leads to the rapid emergence of rifampin-resistant staphylococci during monotherapy, a panel of different antibiot-

ics have been used in combination including quinolones, co-trimoxazole, daptomycin, linezolid, fusidic acid, dalbavancin, minocycline, and clindamycin[11,38-41]. Doses of rifampin range from 1 x 600 mg, 2 x 450 mg or 2 x 600 mg and are used in routine practice around the world, although even 1 x 450 mg is considered sufficient[8].

Linezolid can be administered orally at a dose of 600 mg bid, due to its high bioavailability of 100%[42]. There are some adverse facts to consider when prescribing it for more than four weeks. Besides an expensive price, it is associated with reversible bone marrow suppression; e.g. thrombocytopenia. Optic neuropathy and non-reversible peripheral neuropathy have been reported in 2% to 4% of patients with prolonged administration[43]. A severe serotonin syndrome in co-medication with certain antidepressant drugs, such as monoamine-oxidase inhibitors, has been described[44].

Co-trimoxazole is an inexpensive folate antagonist[45]. However, one reason for failure in severe osteo-articular infections might be the amount of thymidine released from damaged host tissues and bacteria. Thymidine may decrease the anti-staphylococcal effects of trimethoprim and sulfa-methoxazole, the two compounds of co-trimoxazole. Hence, co-trimoxazole failure may well depend on the amount of tissue damage and bacteria burden[46].

Oral fusidic acid 500 mg tid has demonstrated efficacy in chronic osteomyelitis[47-49]. Most experts do not recommend monotherapy due to resistance development[50]. The duration of treatment until the outset of resistance is unknown and might be inconsistent. The antibiotic can be combined with rifampin[38,51]. Fusidic acid is available in several European countries.

For anaerobic, streptococcal and staphylococcal clindamycin-sensitive osteomyelitis, bacterial protein synthesis inhibition by clindamycin 600-900 mg tid is an option[41]. The clinical efficacy of clindamycin in bone infection can be clarified by its excellent penetration[41]. For many physicians, metronidazole is the drug of choice for anaerobic disease, as are quinolones for gram-negative infection[6,39,40]. *Pseudomonas aeruginosa* and other non-fermenting gram-negative rods may rapidly develop resistance in quinolone monotherapy. Therefore, a combination with another parenteral drug or prolonged IV treatment in pseudomonal osteomyelitis would be wise, but an adapted antibiotic treatment for this situation has not been studied so far[52]. The optimal oral dose of ciprofloxacin for bone and synovial infections is set at 750 mg bid[8,39]. Finally, in patients with multidrug-resistant pathogen requiring prolonged IV drug administration (i.e. when oral treatment is inefficient due to bacterial resistance), subcutaneous infusion of antimicrobials, such as teicoplanin or ertapenem, could be useful, but data remains sparse[53].

Local antibiotic-releasing delivery systems: Available systems release antibiotics locally at concentrations exceeding up to one thousand times those of the MIC for the most common pathogens without releasing in the systemic circulation[54]. However, time duration over which these antibiotics continue to be active is less certain. Whether local antibiotic delivery could be equivalent to systemic antibiotics is unknown. Few available data suggest an equivalent remission up to 78% in osteomyelitis cases treated with beads alone[55]. The major disadvantage of local beads is the presumed need for surgical removal[54].

Outcomes and Variables Associated with Treatment Failures

Recurrences of osteomyelitis have been reported after several decades[56]. Many experts advocate that if the bone is infected, it may remain infected throughout life. Therefore, it is suggested that "arrest" or "remission" are more appropriate possibilities. Generally, remission rates for osteomyelitis oscillate between 40% and 90%, with a peak of success around 80%[2,3,9,57,58]. High remission reports are often seen in short follow-up times[59].

Risks of recurrence: Not many epidemiological studies exist regarding association with recurrence risk of implant-free long bone osteomyelitis. In general, comparison of treatment modalities in osteomyelitis should be interpreted with precaution, since reports are not based on standardized treatment regimens of osteomyelitis episodes including variable definitions such as, bones, pathogens, host factors and different chronicity of drainage[2,13,14]. Inadequate debridement may be the most important reason for failure[58]. Staphylococcal small-colony variants are further considered as risks[24,37]. Previously infected bone must be considered a lifetime focus of diminished resistance, and thus former osteomyelitis should be considered a risk factor for a second episode by another pathogen at the same site due to altered bone surfaces[56]. Further reported variables associated with treatment

failure are smoking, older age, or duration of discharge before treatment[58,60]. It is an unresolved topic if the pathogen itself increases the likelihood of treatment failure in implant-free osteomyelitis. Sparse and heterogeneous data suggest that *P. aeruginosa* might be associated with more failures than *S. aureus*; however, confirmation is needed[52].

CONCLUSION

Chronic osteomyelitis is a multifaceted bacterial infection requiring surgery in concomitance to antibiotics for treatment. The duration and form of administration of antibiotic agents are based on expert opinion. The traditional recommendation of 6 to 12 weeks antibiotic therapy, of which at least the first 2-6 weeks are intravenously, is more and more challenging in favour of an oral antibiotic treatment with selected agents from the start. There is no evidence supporting that the total duration for more than 4 to 6 weeks improves outcome when compared to shorter regimens. In the future, duration of regimens with selected oral agents may even be shortened in adults, as research is already carried out for paediatric septic arthritis and (acute) osteomyelitis.

ACKNOWLEDGEMENTS

We thank the Orthopedic and Infectious Diseases Services of Geneva University Hospitals.

We are indebted to Dr. Elif Hakko and Dr. Mustafa Çıkırıkçıoğlu for editorial assistance.

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