



Comments of Clinical and Microbiological Experience with Daptomycin in Chronic Osteomyelitis Treatment



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Editorial

In the last decade, the use of daptomycin (alone or in combination) for the treatment of Chronic Osteomyelitis (CO) due to *Staphylococcus aureus* shows successful outcomes in the most complicated patients, and emerges as an option to be considered for elderly patients with several associated comorbidities.

The consideration for select daptomycin, a cyclic lipopeptide antibiotic drug, approved for complicated skin and soft tissue infections, right-sided infective endocarditis and bacteraemia due to *Staphylococcus aureus* [1], but not approved for use in bone infection; to treat a complex pathology like CO, comes from different factors like daptomycin's bactericidal activity against Gram-positive bacteria, including Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Vancomycin-Resistant Enterococci (VRE), a novel mechanism of action that kills Gram-positive bacteria by the disruption of multiple bacterial plasma membrane functions, without penetrating the cytoplasm [2]. Insertion of the lipophilic daptomycin tail into the bacterial cell membrane with oligomerization and channel formation causes rapid membrane depolarization and a potassium ion efflux. Arrest of DNA & RNA synthesis, toxin production, and protein synthesis follows, resulting in bacterial death without lysis of the cell wall, which gives a further advantage in diseases where inflammatory response associated counter antimicrobial use producing cell lysis [3-5], in addition, the in vitro potency of daptomycin has been demonstrated against Vancomycin resistant *S. aureus* (VRSA) and methicillin-resistant coagulase-negative staphylococci (MRCNS). The synergic effect for daptomycin that has been described in vitro with aminoglycosides (gentamicin), oxacillin, other betalactamics, macrolides and rifampicin, is very valuable to biofilm disease infections treatment, and this antibiofilm activity and reduction of the rifampicin resistance appearance makes a great value. Not antagonism interactions was observed with daptomycin use in

combination with several antimicrobial agents, only additive, synergistic effect or indifference were reported. Another relevant aspect is the partial anti-biofilm activity of daptomycin, combined or alone.

Daptomycin exhibits a dose-dependent post-antibiotic effect lasting from 1 to 6 hours against *E. faecalis* and *S. aureus* after exposure to concentrations ranging from 0.25 to 16mg/L (i.e., between one- and eightfold the MIC) [2,6-8]. Its 8-hours half-life, results in once-daily dosing gives a linear pharmacokinetics at doses up to 12mg/kg, with minimal drug accumulation.

Daptomycin distributes primarily in the plasma, with penetration to vascularized tissues. The drug is highly protein-bound (92%); excretion occurs primarily via the kidneys. Approximately 80% of the total dose, of which two-thirds is intact drug, is recovered in the urine. In patients with severe renal impairment (creatinine clearance <30mL/min), the dosing interval is increased from once daily to every 48 hours. Daptomycin's unique mechanism of action and its lack of metabolism by cytochrome p450 or other hepatic enzymes results in an absence of drug-drug interactions.

The most frequent side effect with daptomycin use is myopathy, but this mild myopathy was easily predicted and monitored by measuring serum creatine phosphokinase (CPK) concentration, and in the majority of cases, it was reversible upon the cessation of therapy [9]. Activity of daptomycin in bone infection were documented in real-life experience of several authors in retrospective studies [10-13], with clinical success and microbiological eradication of the bacteria. Another reasons to choose daptomycin (without approval for use in bone infection) is the nature of our patients, elderly people (65 or more years old), with huge comorbidities as high blood pressure (HBP), diabetes mellitus (DM), peripheral arterial occlusive disease and/or chronic venous insufficiency, liver and/or kidney function

impairment, the need of a prolonged treatment (6 or more weeks) using intravenous path without hospital admission (daptomycin regimens can be used as Outpatient Parenteral Antimicrobial Therapy -OPAT-), and considering the prior antimicrobial therapy (many patients previously received 3 or even 4 kinds of regimens without satisfactory outcomes), in the main of circumstances due to toxicity, microorganism resistance to antimicrobial drugs, biofilm-producer strains, poor bactericidal activity of the drug into the bone, low drug concentration in bone tissue, short time of treatment or failure in the switch among attack-phase drugs and consolidation-phase drugs.

Our experience working in a multidisciplinary healthcare group, where clinicians, surgeons, microbiology & clinical laboratory professionals interact day-by-day at the bedside (or next to the outpatient treatment room) of the patient, promotes more efficient outcomes. Our "know how" based on many years of management of very severe & complicated cases, and the concept of limb-salvation over the classical point-of-view of limb-amputation, increases our patients quality of life and gives us the possibility to give some advices or recommendations in order to improve management of bone infections.

One of the most complicated cases of chronic osteomyelitis is when the patient comes to the clinic after years of different treatments without a complete resolution of its problem, at this point, the "collateral damage" produced by the antimicrobial treatments, lead the selection of a multi-drug resistant microorganism, in many cases a biofilm-producer strain, in a bone with several architectural damage, in a patient with limitations to use some kind of therapeutic regimens (liver disease, kidney failure, concomitant treatments for cardiovascular and/or metabolic pathologies, and a long etcetera), rides us to try new options to improve the action of the antimicrobial drugs, for example, reduction of biofilm biomass & elimination of the devitalized bone, all with the surgeons help using new technology like the hydro scalpel, that not cause inflammation; metabolic control of hyperglycemia; increasing the blood flow using red globules morphology modifiers & anti-thrombotic agents, all of these with the final outcome of improve life quality of the patient and achieve the cure.

Our experience since 2009, with regimens contain daptomycin as main drug in the attack-phase of treatment of chronic osteomyelitis with curative intention, gave us great results, with a very few limited adverse events, even in patients whom received extremely-high doses (major than 10mg/Kg/IV/OD), for 4 to 6 weeks, and then was switched to oral agents for consolidation phase for 4 to 6 weeks [14]. The use of daptomycin as monotherapy is controversial, we don't recommend, but in some special and very particular cases, it was the only option against limb amputation [15]. The most effective combination of daptomycin at high dose is with rifampin (standard dose), reserved to biofilm-producer bacteria, for a time of 6 to 8 weeks, follow by a consolidation phase of 4 to 6 weeks of linezolid at standard dose plus a macrolide (azithromycin or clarithromycin) at standard dose, or a quinolone

(moxi or levofloxacin) plus a macrolide [16]. The close monitoring of evolution is the key for the clinical & microbiological successful outcome of the patient, it includes laboratory controls to check acute phase reactants variation (twice a week), radiological control (every 4 or 6 weeks) to ensure the stabilization of lesions and watch the apparition of new lesions, clinical control (once a week) and microbiological control when is possible (bone biopsy), with emphasis in cases with poor evolution.

In our clinical & microbiological experience, daptomycin has an excellent efficacy and safety profile, plus great pharmacokinetics & pharmacodynamics characteristics for use in OPAT, even for prolonged periods, in elderly patients with multiple comorbidities in order to eradicate bacteria (even biofilm-producers) and cure chronic osteomyelitis.

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