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# New Antibiotics in the Therapy of Osteomyelitis

## Osteomiyelit Tedavisinde Yeni Antibiyotikler

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## Abstract

Osteomyelitis is probably the oldest known infection in the history of life. It can develop secondary to local tissue disruption, ischemia and associated chronic wounds or via hematogenous infection. Although it has been known to the medical community for a long time, treatment remains challenging. Detection of the microbial agent remains crucial for the associated antibiotic therapy. Also, tissue specimens for culture and histology must be obtained. Several factors such as biofilm formation, resistance development and special virulence factors can impede the efficiency of the antibiotic treatment. In the last two decades, developments of antibiotic agents with available data in the field of osteomyelitis primarily include brilacidin, ceftaroline, ceftobiprole, dalbavancin, daptomycin, tedizolid, telavancin, tigecycline. Many of them are not on the market, or under study, or only found in selected countries. However, they are expected to become more accessible in coming years.
**Keywords:** Osteomyelitis, antibiotic therapy, new developments, hyperbaric oxygen, nemanoxacin

## Öz

Osteomiyelit büyük bir olasılıkla yaşam tarihindeki en eski tanımlanmış enfeksiyondur. Lokal doku zedelenmesine ikincil olarak, iskemi ve iskemiyle bağlantılı kronik yaralarla ya da kanda oluşan bir enfeksiyon yoluyla gelişebilir. Tıp dünyası tarafından uzun süredir bilinmesine rağmen, tedavisi zorlayıcıdır. İlgili antibiyotik tedavisi için mikrobiyal ajanın saptanması çok önemlidir. Bunun yanında, kültür ve histoloji için doku örnekleri de elde edilmelidir. Antibiyotik tedavisinin etkisini; biyofilm oluşumu, antibiyotiğe karşı direnç gelişimi veya spesifik virülans faktörleri zorlaştırabilmektedir. Son 20 yılda, osteomiyelit alanında geliştirilen başlıca antibiyotikler arasında brilasidin, seftarolin, seftobiprol, dalbavansin, daptomisin, tedizolid, telavansin ve tigesiklin sayılabilir. Geliştirilen pek çok antibiyotik ya henüz pazara sunulmamış, ya hala çalışmaları devam etmekte ya da sadece belli ülkelerde bulunmaktadır. Ancak önümüzdeki yıllarda bu antibiyotiklerin daha erişilebilir olması beklenmektedir.
**Anahtar Kelimeler:** Osteomiyelit, antibiyotik tedavisi, yenilikler, hiperbarik oksijen, nemanoxacin

## Introduction

Osteomyelitis is a disease that has been known for centuries and has been detected in fossils that deceased 275 million years ago[1], due to possibly the same pathogens as today. Nevertheless, its treatment is still under ongoing discussion. Almost four years ago, we published a review in this journal regarding the pharmaceutic properties of antimicrobial agents for chronic implant-free osteomyelitis in adults[2]. Today, we give new insights into the developments of osteomyelitis of the last two decades with an emphasis on recent years. Of note, this review excludes diabetic foot osteomyelitis, which is an epiphenomena of a more important underlying chronic disease[3], such as arterial insufficiency, patient's compliance, polyneuropathy, and polyneuropathic anatomical alterations. Thus, the treatment of diabetic foot osteomyelitis emphasizes the corrections of underlying problems and would be beyond the scope of this review. Likewise, our short review excludes pediatric osteomyelitis, preventive aspects of nosocomial

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osteomyelitis[4,5], established surgical techniques, sacral osteomyelitis in paraplegic patients[6], mandibular, vertebral, sickle-cell, mycobacterial, fungal, parasitic[7], and brucellar osteomyelitis, treatment of implant-associated infections[8], septic arthritis[9] or coverage problems of plastic surgery, for which all a broader literature is available.

Several classification schemes have been developed in the past to guide treatment. Following its etiology, osteomyelitis can be divided into three clinical entities[10]. Hematogenous osteomyelitis can also occur in adults and especially elderly patients, but affects mainly pediatric patients[10-12]. The most common form in adults is associated with local tissue disruption that can follow bone surgery or trauma[10,12]. A third type is associated with vascular insufficiency and consecutive wounds of the lower extremities[3]. Foot ulcers often develop in diabetic patients, where neuropathy and metabolic changes add up to the infection susceptibility due to ischemia[3,10]. Treatment of osteomyelitis can be purely medicamentous in some acute settings with absence of necrotic areas or abscess formation, but is mostly combined with surgical debridement in chronic cases[13,14]. Effectiveness of antibiotic therapy depends not only on its availability and concentration at the infection site, but also on susceptibility of the infectious agent. Overuse, misuse and easy availability of antibiotics in combination with the property of bacteria to evolve when subjected to selective pressure has lead to resistance. The latter is increasing worldwide and also affects Europe and certainly the countries around the Mediterranean sea[15-17]. Unfortunately, only few new substances have been approved for osteomyelitis treatment in the last years, but several are currently being investigated[13].

## Epidemiology

*Staphylococcus aureus* is the most common bacterium isolated from bone samples in pediatric osteomyelitis, and the incidence of *Kingella kingae* in little children is rising, probably due to better detection and diagnostic performances[11]. In adults, roughly half of osteomyelitis cases might be implant-associated[18]. Therefore, the antimicrobial spectrum differs from pediatric osteomyelitis[18], in adults being 33% related to *S. aureus* and 32% to coagulase-negative staphylococci. More rarely, other germs can be found depending on endemic bacteria and fungi can be associated with immune suppression[2]. In bedridden patients, pressure sores have a high incidence and can lead to osteomyelitis via direct infection of neighboring tissues[6]. They have a high risk of complications and recurrence. Interestingly, pathogens isolated in recurrence of osteomyelitis in the same bone are different from the initial microbiology in 86% of cases[19]. While hematogenous spread mostly leads to mono-bacterial infection, ulcer-related infection is usually polymicrobial. Table 1 gives an overview of possible pathogens of different population of osteomyelitis patients.

## Diagnosis of Osteomyelitis

### Laboratory Tests

As a general principle, the detection of pathogenic bacteria within bone samples remains the gold standard for the confirmation of clinical diagnosis of osteomyelitis. Histology is supplementary. Of note, the microbiological samples have to be done within clinically or radiologically infected bone. There are numerous studies advocating an acceptable concordance of repeated consecutive fistula samples with bone samples, indicating that if several fistula samples are the same, the underlying bone is likely to be infected with the same pathogen[20]. We validated this widespread attitude in France also for the subset of patients with (diabetic) toe osteomyelitis[21]. However, these specific attitudes are not accepted in the international community. While serum inflammation markers such as C-reactive protein (CRP)

**Table 1. Possible microorganisms of different osteomyelitis populations; (literature review and personal experience of the authors)**

| Population | Main pathogens* | Additional pathogens* |
|---|---|---|
| Infants | *Staphylococcus aureus* | *Kingella kingae* |
| Children | *Staphylococcus aureus* | |
| Adults in good health | *Staphylococcus aureus* | Streptococci |
| Adults, posttraumatic | *Staphylococcus aureus* | any pathogens |
| Adults, open fractures | Gram-negative pathogens, Streptococci | |
| Adults, jaw osteomyelitis | Oral streptococci | Oral streptococci |
| Adults, spondylodiscitis | *Staphylococcus aureus* | Any pathogens |
| Adults, sickle cell disease | *Salmonella* spp. | *Pseudomonas* spp. |
| Adults, transplant patients | *Staphylococcus aureus* | Streptococci |
| Adults, endemic regions | Tuberculosis | Brucellosis |
| Victim of natural disasters | Gram-negative pathogens | |

*Summary of the literature

and erythrocyte sedimentation rate can be useful especially during follow-up of osteomyelitis, values within the normal does not exclude the latter. Especially, in the presence of fistula, diabetic foot and absence of systemic signs of infection such as fever, redness, or heat, the CRP values might be negative. We are not aware of any cut-off level or negative predicting values to exclude underlying osteomyelitis. Procalcitonin levels have not proven useful for diabetic foot osteomyelitis[22] or skeletal infection in children[23]. The microbial culture and resistance testing of the responsible infectious agent remains crucial. Histological samples as well as up to 5 soft-tissue samples for culture should be obtained[10]. Antibiotic prophylaxis given at the induction of anesthesia does not interfere with intra-operative sampling cultures[1]. If image-guided needle biopsy is obtained, at least 2 mL of fluid should be aspirated to improve sensitivity[24]. Depending on endemic and patient-specific factors, rarer pathogens like mycobacteria and fungi should be searched for. It is important to incubate implant-related samples for up to three weeks, as slow-growing bacteria like *Propionibacterium acnes* can otherwise be missed[25]. Lastly, cultures and histological examination are adjuncts to a clinical suspicion, but, when negative, cannot exclude osteomyelitis[26].

## Radiologic Imaging

X-rays of bone lesions remain a minimum standard, but the sensitivity is low especially in early osteomyelitis[27]. Magnetic resonance imaging (MRI) is an excellent tool and provides additional information about soft tissues[26-29]. The sensitivity and specificity of FDG positron emission tomography-computed tomography (PET-CT) is superior to all other imaging methods, but its availability is limited in most parts of the world (Figure 1)[27]. On standard X-rays, the earliest visible changes include swelling of soft tissue, periostal thickening or elevation, and focal osteopenia. Before the radiographs show lytic changes, probably 50% to 75% of the bone matrix must be destroyed, which takes at least two weeks[27]. MRI is very sensitive and can show tissue edema and increased regional perfusion. However, these changes can last for a long time after surgery and distinction between fibrovascular scarring, "overuse syndromes", gout, neuropathic osteoarthropathy and reactive infection is often difficult. Thus, MRI lacks specificity, especially in the post-surgery setting or in diabetic foot alterations. Kaim et al.[30] reported a sensitivity, specificity, and accuracy of 100%, 69%, and 78% for MRI in chronic post-traumatic osteomyelitis. Today, CT scans are better for the visualization of sequestra and are less expensive than MRI.

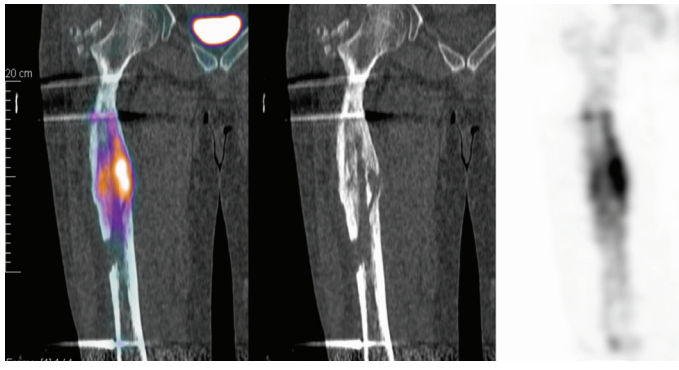


**Figure 1.** Chronic osteomyelitis in the right femur

**Left picture: Positron emission tomography-scan radio-tracer enhancement of a sequestrum (computed tomography scan: middle picture) and scintigraphic picture of that activity (right picture). Published with patient's consent*

In the future, the most specific and accurate radiological exam for osteomyelitis could become PET[31,32]. This performance was recently confirmed in another study with corresponding results of 100%, 76%, and 90%, respectively[33]. It is the most expensive radiological exam and lacks its established place in daily clinical life. To our best knowledge, there are no studies investigating the evolution of the metabolic signal post-surgery or during the antibiotic treatment of osteomyelitis. Scientific proof that PET permits to distinguish between physiologic remodeling and infection after a cut-off of 6 weeks post-surgery, has been studied only in the rabbit model[34]. Studying its quantitative signal during long lasting therapy in humans might become interesting, since it could help identifying patients for which a prolongation of therapy would not be necessary or it could detect zones of early collection for which a surgical re-intervention might become warranted. Scintigraphy has become less important harboring a low specificity for implant-associated infections[35]. Moreover, bone scintigraphy alone cannot distinguish between aseptic loosening and infection, and needs combination with a leukocyte-scintigraphy. Sensitivity, specificity and accuracy for a leucocyte-labeled scintigraphy are 63%, 97%, and 77% for implant-related osteomyelitis[36].

## Treatment of Osteomyelitis

### Surgical Treatment

Surgical treatment consists of radical debridement and lavage to diminish bacterial load and remove non-vital tissue. A relative wide resection with 5 mm clinical margins thereby diminishes recurrence[37]. Nevertheless, it should be as atraumatic as possible for adjacent soft-tissue covering[38]. Pulsed lavage irrigation has been shown to clear off bacteria more effectively than simple irrigation in animal studies[39]. To fill the remaining dead space, antibiotic-loaded polymethyl-methacrylate (PMMA) has been introduced almost 40 years ago[40]. The topical application allows very high local concentration without systemic side effects. Antibiotic-impregnated collagen fleece is widely used in clinical practice and shows higher release rates than PMMA, but shorter elution time[41]. Multiple other biodegradable substances have been developed during the last decades and are currently

under investigation[42,43]. Unfortunately, we are unaware of new developments regarding surgical techniques. As in the antiquity, the cornerstone of surgical management implicate amputation or at least the removal of all foci, especially sequestrate and fistulae, accompanied by intramedullar reaming or other techniques of intramedullar lavage[2].

## Antibiotic Treatment

The efficiency of antibiotic treatment is dependent on the complex interaction of the drug, the host and the microbial agent[44]. Theoretically, the concentration on the target site is crucial for antibiotic action. Not only type of administration and bioavailability, but also pharmacodynamic (PD) parameters have been taken into account when modeling treatment efficiency[44]. In a recent review published in this journal, our research group summarized the latest insights in the pharmacokinetic (PK) PK/PD aspects of antibiotics in the bone, which we would like to reference our previous review in this journal for the more interested reader[2]. Furthermore, microorganisms have developed mechanisms to inactivate antibiotic action, including resistance development and biofilm formation. In nature, 60-80% of bacteria are believed to exist in biofilms, where they are embedded in amorphous biomatrix[45,46]. The altered metabolism reduces susceptibility to antibiotics within hours[46]. Recent reports have shown that resistance developed during treatment in initially susceptible *S. aureus* can also be related to dynamic small colony variants. Some antibiotics like clindamycin, moxifloxacin and gentamicin can even induce the latter[47,48].

In *S. aureus* infection, the expression of Pantone-Valentine leukocidin (PVL) is a virulence factor. Most community-acquired methicillin-resistant *S. aureus* (MRSA) strains produce PVL[49]. Its production can be induced by certain microbial agents, penicillin-binding protein 1 has to been shown to trigger the latter. While oxacillin increased the release 2.5-fold, combination with clindamycin, rifampicin and linezolid prevented from this effect[49].

## Necessity of Parenteral Antibiotic Therapy?

In former times, experts usually recommended an intravenous (IV) therapy for 4 to 6 weeks[50] followed by an oral course of additional weeks or months. The belief for long periods of supplementary oral treatment evolved from cases of relapsing osteomyelitis in the 1970s which may be less frequent today due to improved surgical and antibiotic therapy. The rationale for a prolonged IV course was elevated serum concentrations. Today, the opinion has rather switched for IV treatment during the initial 2 weeks[51]. This initial two to six weeks of IV medication bases on experts' opinion rather than on clinical trials. Without doubt, bone penetration of antibiotic agents in parenteral administration is good and bioavailability per definition 100%[52]. At the same time, IV medication should be limited as far as possible 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 ranges around 15%[50]. Some antibiotics, such as ertapenem and ceftriaxone, could be administered via the subcutaneous route, but this route of administration is currently unlabelled. Prospective studies evaluating these points are urgently required.

## Local Antibiotic-releasing Delivery Systems

The ideal local antibiotic delivery system is lacking[53,54]. Antibiotic-containing cement is used for the treatment[53] and prophylaxis[53] of bone and prosthetic joint infections[54], but remains controversial in terms of additional benefit. Spacers for knee joint surgery may equally contain antibiotics[54]. All of these systems release antibiotics locally at concentrations exceeding up to one thousand times those of the minimum inhibitory concentrations (MICs) for the most common pathogens without releasing in the systemic circulation and without producing adverse effects[53]. However, the duration of time over which these antibiotics continue to be active and released is less certain. Moreover, the advantage appears minimal in two-stage procedures for arthroplasty infections[55]. Currently, there are few antibiotic-laden bone cement composites that have been approved by the Food and Drug Administration for clinical use: tobramycin, gentamicin, vancomycin, quinolones[53], cephalosporins[56], amphotericin B, and fluconazole[54]. Rifampin should not not be mixed with cement, since it may prolong the time to cement hardness by several hours. Gentamicin, the most frequently used antibiotic compound[57], may lead to development of small colony variants. Hand-mixing into cement is feasible to increase antibiotic dosage. The cement should be mixed first, and the antibiotics should then be added[54]. However, the addition of high doses of antibiotics (>4.5 g of powder) substantially weakens bone cement[54].

It is unknown if local antibiotic delivery could be equivalent to systemic administration of antibiotics. Few available data suggest an equivalent remission rates up to 78% in osteomyelitis patients treated with beads alone[57]. The major disadvantage of the PMMA beads is the presumed need for surgical removal, which usually takes place 3-4 weeks after their implantation[53]. Biodegradable implants are preferable to antibiotic-laden bone cement, because they do not require surgical removal. The PMMA is used in osteomyelitis to fill a bone gap, and facilitate the induction of a membrane (Masquelet) before bone grafting. Please note that some PMMA combine two antibiotics that could be synergic against the pathogen (gentamicin + vancomycin or gentamicin + clindamycin). Prospective studies are required to demonstrate that these new cements are better from a curative

and a preventive point of view (prevention of superinfection). Finally, new local agents are absorbable. For instance, colleagues in Oxford developed a gentamicin-loaded, calcium sulphate/hydroxyl-apatite biocomposite that is absorbable and proved to be effective in the treatment of chronic osteomyelitis[58].

## Duration of Treatment

The duration of antibiotic treatment for osteomyelitis has traditionally been several months with initial IV treatment. No concluding evidence regarding these questions exists so far. While data are very sparse that a regimen shorter than 4 weeks shows higher risk of failure[59], there is accumulating evidence that therapy longer than 6 weeks does not improve the outcome[60-63]. Even in periprosthetic joint infection with retained material, 8 weeks has been shown to be non-inferior to longer treatments[64,65]. When surgery cannot be performed (e.g. large infected area of the pelvis), antibiotics are only occasionally prescribed during one to several weeks upon clinical indication. This might be fever or increased purulent discharge. Importantly, the sinus tract should not be closed, because it represents the spontaneous drainage of a chronic infection.

## Recent Antibiotics in the Market and Scientific Evaluation

### Ceftaroline

This novel broad-spectrum cephalosporine is potent against MRSA[66]. It has been tested and approved safe and efficient in phase 3 studies for complicated skin and soft tissue infection and community-acquired pneumonia[66]. In a rabbit osteomyelitis model with MRSA it was superior to vancomycin[66]. Data for human osteomyelitis are numerous but anecdotal[67]. In these few reports and a recent review of roughly 180 osteomyelitis cases in the USA[67], ceftaroline reveals similar success rates to comparator drugs[67-69], but studies are clearly needed[69].

### Daptomycin

One of the recently studied agents for osteomyelitis is daptomycin, a cyclic lipopeptide. Its dosage regimen of q24h during 2 minutes makes it favorable for outpatient IV treatment.

The agent is currently on the market for treatment of Gram-positive infections, including complicated soft tissue infections, *S. aureus* bacteremia and right-sided infectious endocarditis. Clinical effectiveness for osteomyelitis with MRSA might be non-inferior[70-72], or even better than vancomycin[73] or other new agents like tigecycline, dalbavancin, linezolid and telavancin. High-dose daptomycin (up to 8 or 10 mg/kg/day) in combination with or without rifampicin was most effective in treatment of implant-associated MRSA infections[74]. In a large retrospective report including 638 cases, it was shown to be safe and effective in patients with osteomyelitis or orthopaedic implant-related infections[75].

### Telavancin

This lipoglycopeptide is a semisynthetic derivative of vancomycin[76]. It is approved in the USA for MRSA soft tissue infection[77]. In a rabbit osteomyelitis model with MRSA, telavancin shows lower MICs than linezolid and vancomycin, but similar efficacy[78]. In a case series of 4 patients with osteomyelitis all were treated successfully with telavancin and surgical intervention[79].

### Tigecycline

This glycylcycline, a semi-synthetic tetracycline, is administered IV and is approved for skin infections, abdominal infections and community-acquired pneumoinia[80].

Sometimes it is employed against resistant pathogens and resistant pathogens in osteoarticular infections[80]. In a rat osteomyelitis model due to MRSA, tigecycline revealed at least as efficacious as teicoplanin[81]. Side-effects are mainly gastro-intestinal. In one phase 3 trial for osteomyelitis and chronically infected diabetic ulcers, it was inferior to ertapenem with or without vancomycin[82] but a binational multicenter retrospective cohort study in France and Turkey underlined its potential as a salvage therapy with prolonged administration (mean follow up 54 weeks) in 36 patients with various multiresistant bone and joint infections[83]. Tigecycline might be probably used in combination therapy, especially in case of Gram-negative multi-resistant infections or combined infection with *Enterobacteriacae* and staphylococci[83].

## Promising Antibiotics in Development

Although the development of microbial resistance is not yet covered by respective effective antibiotic treatments, several new molecules are currently been studied in clinical trials for multi-resistant bacteria.

### Brilacidin

This defensin-mimetic non-peptidic molecule has bactericidal efficacy for Gram-positive and Gram-negative bacteria, even in non-replicative state[84]. Phase 2-studies have been completed and phase 3 studies are underway for acute bacterial skin and skin structure infections[85]. Topical administration for ophthalmologic infection has been studied[86]. No data for osteomyelitis is available nor are studies currently planned to our knowledge. Due to its potential action in biofilms, this drug could be interesting for the treatment of implant-related

infection.

## Ceftobiprole

It is the first broad-spectrum cephalosporin with bactericidal activity against MRSA and broad Gram-positive and -negative range. Its safety and non-inferiority to vancomycin has been shown for soft-tissue infections[87]. It was effective *in vivo* against PVL producing community-acquired MRSA osteomyelitis in rabbits[88]. Effectiveness for humans has only been shown in case-reports[89].

## Dalbavancin

The application interval of dalbavancin is even more advantageous as the above-mentioned daptomycin. It is usually administered 1/week IV, but a single-dose regimen is sufficient for complicated soft-tissue infection including MRSA[90]. Its action is bactericidal, the synthetic lipoglycopeptide blocking enzymes involved with polymerization and cross-linking of peptidoglycan[91]. It is approved and available on the market in the USA since 2014 and in Europe since 2015 for skin infections[91,92]. Minimum inhibitory concentrations for *S. aureus* isolated from diabetic foot ulcers and vancomycin-intermediate and heteroresistant types were measured *in vitro*, dalbavancin showed excellent activity and was superior to vancomycin[93]. Its distribution to bone and synovial fluid was measured in healthy subjects and shows concentrations superior to the MIC of *S. aureus* over 50 days[94,95].

## Debio 1450

This FabI inhibitor has been developed for soft-tissue infection and osteomyelitis. It is derived from the crystal structure of the active site of the enzyme and is staphylococcus-specific[96]. It is currently being tested in a phase 2 study for acute bacterial skin and skin structure infections [NCT02426918]; no data for osteomyelitis is available.

## Lefamulin

The semi-synthetic compound, a pleuromutilin-derivate inhibits bacterial protein synthesis by binding to the 50S ribosome. It was tested in a phase 2 trial for acute bacterial skin and skin-structure infections against vancomycin. It showed good efficiency against multi-resistant Gram-positive bacteria, including MRSA. It is expected to be available both parenterally and peroral. Studies are underway[97]; no large data for osteomyelitis is available.

## Nemonoxacin

Non-fluorinated quinolone with a broad spectrum against atypical pathogens, Gram-positive and Gram-negative microbes. It has been released in Taiwan for community-acquired pneumonia, but not yet for its other field of development, diabetic foot infection[98]. Clinical phase 2 and 3 trials have been registered and are underway, intermediate results are promising, but definitive results missing and the substance is not yet approved for the latter[99].

## Tedizolid

This oxazolidinone prodrug is converted to tedizolid *in vivo*. The molecule inhibits translation by binding to the bacterial 23S ribosome initiation complex[100]. Its spectrum covers Gram-positive pathogens, including linezolid-resistant *S. aureus*[101]. It has been shown to be efficient, safe and well-tolerated in phase 3 studies and a post-hoc analysis for Latino patients[101-103]. Its efficiency has been studied in rat foreign-body osteomyelitis, but no data for human osteomyelitis exists[104].

Finally, there are many other new agents already on the market in some countries or not, but which are powerful candidates for the future: delafloxacin, finafloxacin, zabofloxacin, eravacycline, omadacycline, ceftazidime/avibactam, ceftolozane/tazobactam, and others that still have to prove their non-inferiority to current regimens and which might become more interesting and valuable candidates in future reviews.

## Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy consumes very substantial resources[105]. It provides oxygen to promote collagen production, angiogenesis, osteogenesis, and healing in the ischemic or infected wound[106]. Animals receiving hyperbaric oxygen showed an acceleration in all phases of fracture repair[106]. Several authors have suggested that adjunctive hyperbaric oxygen therapy might be useful in the treatment of human chronic osteomyelitis, even if the results are not consistent though. The adjunctive role of hyperbaric oxygen in osteomyelitis is difficult to assess because of the multiple confounding variables of patient, surgery, organism, bone, and antibiotics. Today, although recognized for reimbursement by some insurers, the evidence base for hyperbaric oxygen therapy for diabetic foot care still remains weak[105].

## Conclusion

The majority of big pharmaceutical companies have exited the area of antibiotic development and focused on other, more rentable fields. Consequently, few new molecules for the treatment of osteomyelitis have been introduced to the market. In the surgical field, the development pipeline is even worse. Besides new substances for bone replacement and osteoneogenesis, practically little is different from the available knowledge several decades ago. Nevertheless, research is

still going on and recent developments of antibiotic agents in osteomyelitis include several promising molecules. While prospective randomized studies are available for some agents, they unfortunately still lack for others. Tigecycline could be a reserve antibiotic. Debio 1450 and lefamulin are potentially efficient for MRSA and studies for acute bacterial skin and skin-structure infection are underway, but no data is yet available for osteomyelitis. Nemonoxacin has been released in Taiwan for community-acquired pneumonia, clinical trials for its other field of development, diabetic foot infection, are underway. Ceftaroline, tedizolid and dalbavancin have been tested for osteomyelitis on animals, but clinical human studies are scarce. Ceftobiprole and telavancin were effective in animal studies and case-reports in humans. Daptomycin has been used in human osteomyelitis with very promising results.

For future developments, the results of the attended studies have to be included in clinical practice. Other interesting areas include the evaluation of absorbable antibiotic carriers for local therapy. Host-defense protein imitating drugs are ideal candidates for further research due to their low risk of development of resistance[107]. Raising economic pressure on medical treatment establishes the need for prolonged antibiotic therapy on an outpatient base. Even if modern treatment algorithms may cure the majority of acute and chronic bone infections, the risk of relapse or persisting disability is high. Finally, given that the prevalence of glucose-intolerance in Europe has risen to 22%[108] and treatment of post-traumatic osteomyelitis remains challenging, treatment of osteomyelitis will remain an important clinical issue.

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### Ethics

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### Authorship Contributions

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## References

1. Reisz RR, Scott DM, Pynn BR, Modesto SP. Osteomyelitis in a Paleozoic reptile: ancient evidence for bacterial infection and its evolutionary significance. Naturwissenschaften. 2011;98:551-5.
2. Deabate L, Pagani L, Uçkay I. Modern Antibiotic Treatment of Chronic Long Bone Infections in Adults-Theory, Evidence and Practice. Mediterr J Infect Microbes Antimicrob. 2014;3:9.
3. Uçkay I, Aragón-Sánchez J, Lew D, Lipsky BA. Diabetic foot infections: what have we learned in the last 30 years? Int J Infect Dis. 2015;40:81-91.
4. Uçkay I, Hoffmeyer P, Lew D, Pittet D. Prevention of surgical site infections in orthopaedic surgery and bone trauma: state-of-the-art update. J Hosp Infect. 2013;84:5-12.
5. Uçkay I, Sax H, Harbarth S, Bernard L, Pittet D. Multi-resistant infections in repatriated patients after natural disasters: lessons learned from the 2004 tsunami for hospital infection control. J Hosp Infect. 2008;68:1-8.
6. Jugun K, Richard JC, Lipsky BA, Kressmann B, Pittet-Cuenod B, Suvà D, Modarressi A, Uçkay I. Factors Associated With Treatment Failure of Infected Pressure Sores. Ann Surg. 2016;264:399-403.
7. Steinmetz S, Racloz G, Stern R, Dominguez D, Al-Mayahi M, Schibler M, Lew D, Hoffmeyer P, Uçkay I. Treatment challenges associated with bone echinococcosis. J Antimicrob Chemother. 2014;69:821-6.
8. Teterycz D, Ferry T, Lew D, Stern R, Assal M, Hoffmeyer P, Bernard L, Uçkay I. Outcome of orthopaedic implant infections due to different staphylococci. Int J Infect Dis. 2010;14:913-8.
9. Uçkay I, Tovmirzaeva L, Garbino J, Rohner P, Tahintzi P, Suvà D, Assal M, Hoffmeyer P, Bernard L, Lew D. Short parenteral antibiotic treatment for adult septic arthritis after successful drainage. Int J Infect Dis. 2013;17:199-205.
10. Lew DP, Waldvogel FA. Osteomyelitis. Lancet. 2004;364:369-79.
11. Cierny G, Mader JT. Adult chronic osteomyelitis. Orthopedics. 1984;7:1557-64.
12. Dunkel N, Pittet D, Tovmirzaeva L, Suvà D, Bernard L, Lew D, Hoffmeyer P, Uçkay I. Short duration of antibiotic prophylaxis in open fractures does not enhance risk of subsequent infection. Bone Joint J. 2013;95-B:831-7.
13. Uçkay I, Jugun K, Gamulin A, Wagener J, Hoffmeyer P, Lew D. Chronic osteomyelitis. Curr Infect Dis Rep. 2012;14:566-75.
14. Parsons B, Strauss E. Surgical management of chronic osteomyelitis. Am J Surg. 2004;188(Suppl 1A):57-66.
15. Fernandes P, Martens E. Antibiotics in late clinical development. Biochem Pharmacol. 2017;133:152-63.
16. van Duijn PJ, Dautzenberg MJ, Oostdijk EA. Recent trends in antibiotic resistance in European ICUs. Curr Opin Crit Care. 2011;17:658-65.
17. David MZ, Daum RS. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev. 2010;23:616-87.
18. Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis. J Bone Joint Surg Br. 2012;94:584-95.
19. Seaton RA, Malizos KN, Viale P, Gargalianos-Kakolyris P, Santantonio T, Petrelli E, Pathan R, Heep M, Chaves RL. Daptomycin use in patients with osteomyelitis: a preliminary report from the EU-CORE(SM) database. J Antimicrob Chemother. 2013;68:1642-9.
20. Bernard L, Uçkay I, Vuagnat A, Assal M, Stern R, Rohner P, Hoffmeyer P. Two consecutive deep sinus tract cultures predict the pathogen of osteomyelitis. Int J Infect Dis. 2010;14:390-3.
21. Bernard L, Assal M, Garzoni C, Uçkay I. Predicting the pathogen of diabetic toe osteomyelitis by two consecutive ulcer cultures with bone contact. Eur J Clin Microbiol Infect Dis. 2011;30:279-81.

22. Mutluoğlu M, Uzun G, İpcioğlu OM, Sildiroğlu O, Özcan Ö, Turhan V, Mutlu H, Yildiz S. Can procalcitonin predict bone infection in people with diabetes with infected foot ulcers? A pilot study. Diabet Res Clin Pract. 2011;94:53-6.

23. Faesch S, Cojocaru B, Hennequin C, Pannier S, Glorion C, Lacour B, Cheron G. Can procalcitonin measurement help the diagnosis of osteomyelitis and septic arthritis? A prospective trial. Ital J Pediatr. 2009;35:33.

24. Wu JS, Gorbachova T, Morrison WB, Haims AH. Imaging-guided bone biopsy for osteomyelitis: are there factors associated with positive or negative cultures? AJR Am Roentgenol. 2007;188:1529-34.

25. Butler-Wu SM, Burns EM, Pottinger PS, Magaret AS, Rakeman JL, Matsen FA, Cookson BT. Optimization of periprosthetic culture for diagnosis of *Propionibacterium acnes* prosthetic joint infection. J Clin Microb. 2011;49:2490-5.

26. Floyed RL, Steele RW. Culture-negative osteomyelitis. Pediatr Infect Dis J. 2003;22:731-6.

27. Pineda C, Espinosa R, Pena A. Radiographic imaging in osteomyelitis: the role of plain radiography, computed tomography, ultrasonography, magnetic resonance imaging, and scintigraphy. Semin Plast Surg. 2009;23:80-9.

28. Craigen MA, Watters J, Hackett JS. The changing epidemiology of osteomyelitis in children. J Bone Joint Surg Br. 1992;74:541-5.

29. Game FL, Jeffcoate WJ. Primarily non-surgical management of osteomyelitis of the foot in diabetes. Diabetologia. 2008;51:962-7.

30. Kaim A, Ledermann HP, Bongartz G, Messmer P, Muller-Brand J, Steinbrich W. Chronic post-traumatic osteomyelitis of the lower extremity: comparison of magnetic resonance imaging and combined bone scintigraphy/immunoscintigraphy with radiolabelled monoclonal antigranulocyte antibodies. Skeletal Radiol. 2000;29:378-86.

31. Termaat MF, Raijmakers PG, Scholten HJ, Bakker FC, Patka P, Haarman HJ. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. J Bone Joint Surg. 2005;87:2464-71.

32. van der Bruggen W, Bleeker-Rovers CP, Boerman OC, Gotthardt M, Oyen WJ. PET and SPECT in osteomyelitis and prosthetic bone and joint infections: a systematic review. Semin Nucl Med. 2010;40:3-15.

33. Nanni C, Errani C, Boriani L, Fantini L, Ambrosini V, Boschi S, Rubello D, Pettinato C, Mercuri M, Gasbarrini A, Fanti S. 68Ga-citrate PET/CT for evaluating patients with infections of the bone: preliminary results. J Nucl Med. 2010;51:1932-6.

34. Koort JK, Makinen TJ, Knuuti J, Jalava J, Aro HT. Comparative 18F-FDG PET of experimental *Staphylococcus aureus* osteomyelitis and normal bone healing. J Nucl Med. 2004;45:1406-11.

35. Smith SL, Wastie ML, Forster I. Radionuclide bone scintigraphy in the detection of significant complications after total knee joint replacement. Clin Radiol. 2001;56:221-4.

36. Sonmezoglu K, Sonmezoglu M, Halac M, Akgün I, Türkmen C, Onsel C, Kanmaz B, Solanki K, Britton KE, Uslu I. Usefulness of 99mTc-ciprofloxacin (infecton) scan in diagnosis of chronic orthopedic infections: comparative study with 99mTc-HMPAO leukocyte scintigraphy. J Nucl Med. 2001;42:567-74.

37. Simpson AH, Deakin M, Latham JM. Chronic osteomyelitis. The effect of the extent of surgical resection on infection-free survival. J Bone Joint Surg Br. 2001;83:403-7.

38. Tetsworth K, Cierny G. Osteomyelitis debridement techniques. Clin Orthop Rel Res. 1999;360:87-96.

39. Svoboda MS, Bice TG, Gooden HA, Brooks DE, Thomas DB, Wenke JC. Comparison of bulb syringe and pulsed lavage irrigation with use of a bioluminescent musculoskeletal wound model. J Bone Joint Surg Am. 2006;88:2167-74.

40. Koschmieder R, Ritzerfield W, Homeyer L. Addition of gentamicin to polymethyl methacrylate for therapy of infectious bone diseases. Experimental *in vivo* tests. Z Orthop Ihre Grenzgeb. 1975;113:147-9.

41. El-Husseiny M, Patel S, MacFarlane RJ, Haddad FS. Biodegradable antibiotic delivery systems. J Bone Joint Surg Br. 2011;93:151-7.

42. Gogia JS, Meehan JP, Di Cesare PE, Jamali AA. Local antibiotic therapy in osteomyelitis. Semin Plast Surg. 2009;23:100-7.

43. Cancienne JM, Burrus MT, Weiss DB, Yarboro SR. Applications of local antibiotics in orthopedic trauma. Orthop Clin North Am. 2015;46:495-510.

44. Mueller M, de la Pena A, Derendorf H. Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: kill curves versus MIC. Antimicrob Agents Chemother. 2004;48:369-77.

45. Peters G. Pathogenesis of *S. epidermidis* foreign body infections. Br J Clin Pract Suppl. 1988;57:62-5.

46. Uçkay I, Pittet D, Vaudaux P, Sax H, Lew D, Waldvogel F. Foreign body infections due to *Staphylococcus epidermidis*. Ann Med. 2009;41:109-19.

47. Monzon M, Oteiza C, Leiva J, Lamata M, Amorena B. Biofilm testing of *Staphylococcus epidermidis* clinical isolates: low performance of vancomycin in relation to other antibiotics. Diagn Microbiol Infect Dis. 2002;44:319-24.

48. Tuchscherr L, Kreis CA, Hoerr V, Flint L, Hachmeister M, Geraci J, Bremer-Streck S, Kiehntopf M, Medina E, Kribus M, Raschke M, Pletz M, Peters G, Löffler B. *Staphylococcus aureus* develops increased resistance to antibiotics by forming dynamic small colony variants during chronic osteomyelitis. J Antimicrobial Chemother. 2016;71:438-48.

49. Dumitrescu O, Badiou C, Bes M, Reverdy ME, Vandenesch F, Etienne J, Lina G. Effect of antibiotics, alone and in combination, on Panton-Valentine leukocidin production by a *Staphylococcus aureus* reference strain. Clin Microbiol Infect. 2008;14:384-8.

50. Matthews PC, Conlon CP, Berendt AR, Kayley J, Jefferies L, Atkins BL, Byren I. Outpatient parenteral antimicrobial therapy (OPAT): is it safe for selected patients to self-administer at home? A retrospective analysis of a large cohort over 13 years. J Antimicrob Chemother. 2007;60:356-62.

51. Lew D, Uçkay I. Infections in Skeletal Prostheses. In: Bennet & Brachman's Hospital Infections. William R Jarvis Lippincott, Williams & Wilkins 2007;5:39.

52. Smilack JD, Flittie WH, Williams TW Jr. Bone concentrations of antimicrobial agents after parenteral administration. Antimicrob Agents Chemother. 1976;9:169-71.

53. Kanellakopoulou K, Giamarellos-Bourboulis EJ. Carrier systems for the local delivery of antibiotics in bone infections. Drugs. 2000;59:1223-32.

54. Cui Q, Mihalko WM, Shields JS, Ries M, Saleh KJ. Antibiotic-impregnated cement spacers for the treatment of infection associated with total hip or knee arthroplasty. J Bone Joint Surg Am. 2007;89:871-82.

55. Duncan CP, Masri BA. The role of antibiotic-loaded cement in the treatment of an infection after a hip replacement. Instr Course Lect. 1995;44:305-13.

56. Alonge TO, Ogunlade SO, Omololu AB. The Belfast technique for the treatment of chronic osteomyelitis in a tropical teaching hospital. Int Orthop. 2003;27:125-8.

57. Walenkamp GH, Kleijn LL, de Leeuw M. Osteomyelitis treated with gentamicin-PMMA beads: 100 patients followed for 1-12 years. Acta Orthop Scand. 1998;69:518-22.

58. McNally MA, Ferguson JY, Lau AC, Diefenbeck M, Scarborough M, Ramsden AJ, Atkins BL. Single-stage treatment of chronic osteomyelitis with a new absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite. Bone Joint J. 2016;98:1289-96.

59. Gentry LO. Antibiotic therapy for osteomyelitis. Infect Dis J North Am. 1990;4:485-99.

60. Bernard L, Legout L, Zürcher-Pfund L, Stern R, Rohner P, Peter R, Assal M, Lew D, Hoffmeyer P, Uçkay I. Six weeks of antibiotic treatment is sufficient following surgery for septic arthroplasty. J Infect. 2010;61:125-32.

61. Bernard L, Dinh A, Ghout I, Simo D, Zeller V, Issartel B, Le Moing V, Belmatoug N, Lesprit P, Bru JP, Therby A, Bouhour D, Dénes E, Debard A, Chirouze C, Fèvre K, Dupon M, Aegerter P, Mulleman D; Duration of Treatment for Spondylodiscitis (DTS) study group. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. Lancet. 2015;385:875-82.

62. Lazzarini L, Lipsky BA, Mader JT. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? Int J Infect Dis. 2005;9:127-38.

63. Rod-Fleury T, Dunkel N, Assal M, Rohner P, Tahintzi P, Bernard L, Hoffmeyer P, Lew D, Uçkay I. Duration of post-surgical antibiotic therapy for adult chronic osteomyelitis: a single-centre experience. Int Orthop. 2011;35:1725-31.

64. Lora-Tamayo J, Euba G, Cobo J, Horcajada JP, Soriano A, Sandoval E, Pigrau C, Benito N, Falgueras L, Palomino J, Del Toro MD, Jover-Sáenz A, Iribarren JA, Sánchez-Somolinos M, Ramos A, Fernández-Sampedro M, Riera M, Baraia-Etxaburu JM, Ariza J; Prosthetic Joint Infection Group of the Spanish Network for Research in Infectious Diseases-REIPI. Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomised clinical trial. Int J Antibicrob Agents. 2016;48:310-6.

65. Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev. 2013:CD004439.

66. Jacqueline C, Amador G, Caillon J, Le Mabecque V, Batard E, Miegeville AF, Biek D, Ge Y, Potel G, Hamel A. Efficacy of the new cephalosporin ceftaroline in the treatment of experimental methicillin-resistant *Staphylococcus aureus* acute osteomyelitis. J Antimicrob Chemother. 2010;65:1749-52.

67. Britt RS, Evoy KE, Lee GC, Reveles KR, Sorensen KM, Jones X, Bollinger M, Frei CR. Early use of ceftaroline fosamil in the United States Veteran Health Care System. Drugs. 2017;77:1345-51.

68. Lalikian K, Parsiani R, Won R, Chang E, Turner RB. Ceftaroline for the treatment of osteomyelitis caused by methicillin-resistant *Staphylococcus aureus*: a case series. J Chemother. 2017;11:1-5.

69. Sanchez Eh, Mendes RE, Sader HS, Allison GM. *In vivo* emergence of ceftaroline resistance during therapy for MRSA vertebral osteomyelitis. J Antimicrob Chemother. 2016;71:1736-8.

70. Lalani T, Boucher HW, Cosgrove SE, Fowler VG, Kanafani ZA, Vigliani GA, Campion M, Abrutyn E, Levine DP, Price CS, Rehm SJ, Corey GR, Karchmer AW; S. aureus Endocarditis and Bacteraemia Study Group. Outcomes with daptomycin versus standard therapy for osteoarticular infections associated with *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother. 2008;61:177-82.

71. Seaton RA, Gonzalez-Ruiz A, Cleveland KO, Couch KA, Pathan R, Hamed K. Real-world daptomycin use across wide geographical regions: results from a pooled analysis of CORE and EU-CORE. Ann Clin Microbiol Antimicrob. 2016;15:15-8.

72. Liang SY, Khair HN, McDonald JR, Babcock HM, Marshall J. Daptomycin versus vancomycin for osteoarticular infections due to methicillin-resistant *Staphylococcus aureus* (MRSA): a nested case-control study. Eur J Clin Microbiol Infect Dis. 2014;33:659-64.

73. Moenster RP, Linneman TW, Finnegan PM, McDonald JR. Daptomycin compared to vancomycin for the treatment of osteomyelitis: a single-center, retrospective cohort study. Clin Ther. 2012;34:1521-7.

74. John AK, Baldoni D, Haschke M, Rentsch K, Schaerli P, Zimmerli W, Trampuz A. Efficacy of daptomycin in implant-associated infection due to methicillin-resistant *Staphylococcus aureus*: importance of combination with rifampin. Antimicrob Agent Chemother. 2009;53:2719-24.

75. Malizos K, Sarma J, Seaton RA, Militz M, Menichetti F, Riccio G, Gaudias J, Trostmann U, Pathan R, Hamed K. Daptomycin for the treatment of osteomyelitis and orthopaedic device infections: real-world clinical experience from a European registry. Eur J Clin Microbiol Infect Dis. 2016;35:111-8.

76. Higgins DL, Chang R, Debabov DV, Leung J, Wu T, Krause KM, Sandvik E, Hubbard JM, Kaniga K, Schmidt DE, Gao Q, Cass RT, Karr DE, Benton BM, Humphrey PP. Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant Staphylococcus aureus. Antimicrob Agent Chemother. 2005;49:1127-34.

77. Polyzos KA, Mavros MN, Vardakas KZ, Makris MC, Rafailidis PI, Falagas ME. Efficacy and safety of telavancin in clinical trials: a systematic review and meta-analysis. PLoS One. 2012;7:41870.

78. Yin LY, Calhoun JH, Thomas TS, Wirtz ED. Efficacy of telavancin in the treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis: studies with a rabbit model. J Antimicrob Chemother. 2008;63:357-60.

79. Twilla JD, Gelfand MS, Cleveland KO, Usery JB. Telavancin for the treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis. J Antimicrob Chemother 2011;66:2675-7.

80. Griffin AT, Harting JA, Christensen DM. Tigecycline in the management of osteomyelitis: a case series from the bone and joint infection (BAJIO) database. Diagn Microbiol Infect Dis. 2013;77:273-7.

81. Kandemir O, Oztuna V, Colak M, Akdag A, Camdeviren H. Comparison of the efficacy of tigecycline and teicoplanin in an experimental methicillin-resistant *Staphylococcus aureus* osteomyelitis model. J Chemother. 2008;20:53-7.

82. Lauf L, Ozsvar Z, Mitha I, Regöly-Merei J, Embil JM, Cooper A, Sabol MB, Castaing N, Dartois N, Yan J, Dukart G, Maroko R. Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. Diagn Microbiol Infect Dis. 2014;78:469-80.

83. Wach J, Dinh A, Dutronc H, Sipahi OR, Candevir A, Valour F, Zeller V, Lustig S, Laurent F, Chidiac C, Ferry T; Lyon BJI study group. Tigecycline-based prolonged salvage therapy in patients presenting with complex bone and joint infection. Med Mal Infect. 2017. pii: S0399-077X(16)30661-8.

84. McClain SL, Bohan JG, Stevens DL. Advances in the medical management of skin and soft tissue infections. BMJ. 2016;355:i6004.

85. Mensa B, Howell GL, Scott R, DeGrado WF. Comparative mechanistic studies of brilacidin, daptomycin, and the antimicrobial peptide LL16. Antimicrob Agents Chemother. 2014;58:5136-45.

86. Kowalski RP, Romanowski EG, Yates KA, Mah FS. An independent evaluation of a novel peptide mimetic, brilacidin (PMX30063), for ocular anti-infective. J Ocular Pharmacol Ther. 2016;32:23-7.

87. Deitchman A, de Jong D, Barbour AM, Derendorf H. Ceftobiprole medocaril (BAL-5788) for the treatment of complicated skin infections. Expert Rev Anti Infect Ther. 2016;14:997-1006.

88. Saleh-Mghir A, Dumitrescu O, Dinh A, Boutrad Y, Massias L, Martin É, Vandenesch F, Etienne J, Lina G, Crémieux AC. Ceftobiprole efficacy *in vitro* against Panton-Valentine leukocidin production and *in vivo* against community-associated methicillin-resistant *Staphylococcus aureus* osteomyelitis in rabbits. Antimicrob Agents Chemother. 2012;56:6291-7.

89. MacDonald A, Dow G. Ceftobiprole: First reported experience in osteomyelitis. Can J Infect Dis Med Microbiol. 2010;21:138-40.

90. Dunne MW, Puttagunta S, Giordano P, Krievins D, Zelasky M, Baldassarre J. A randomized clinical trial of single-dose versus weekly dalbavancin for treatment of acute bacterial skin and skin structure infection. Clin Infect Dis. 2016;62:545-51.

91. Citron DM, Tyrrell KL, Goldstein EJ. Comparative *in vitro* activities of dalbavancin and seven comparator agents against 41 *Staphylococcus* species cultured from osteomyelitis infections and 18 VISA and hVISA strains. Diagn Microbiol Infect Dis. 2014;79:438-40.

92. Ramdeen S, Boucher HW. Dalbavancin for the treatment of acute bacterial skin and skin structure infections. Expert Opin Pharmacother. 2015;16:2073-81.

93. Mendes RE, Castanheira M, Farrell DJ, Flamm RK, Sader HS, Jones RN. Update on dalbavancin activity tested against Gram-positive clinical isolates responsible for documented skin and skin-structure infections in US and European hospitals (2011-13). J Antimicrobial Chemother. 2015;71:276-8.

94. Dunne MW, Puttagunta S, Sprenger CR, Rubino C, Van Wart S, Baldassarre J. Extended-duration dosing and distribution of dalbavancin into bone and articular tissue. Antimicrob Agent Chemother. 2015;59:1849-55.

95. Barnea Y, Lerner A, Aizic A, Navon-Venezia S, Rachi E, Dunne MW, Puttagunta S, Carmeli Y. Efficacy of dalbavancin in the treatment of MRSA rat sternal osteomyelitis with mediastinitis. J Antimicrob Chemother. 2015;71:460-3.

96. Karlowsky JA, Kaplan N, Hafkin B, Hoban DJ, Zhanel GG. AFN-1252, a FabI inhibitor, demonstrates a *Staphylococcus*-specific spectrum of activity. Antimicrob Agent Chemother. 2009;53:3544-8.

97. Fellner C. Companies take aim at MRSA infections. PT. 2016;41:126-8.

98. Poole RM. Nemonoxacin: first global approval. Drugs. 2014;74:1445-53.

99. Kosinski MA, Lipsky BA. Current medical management of diabetic foot infections. Expert Rev Anti Infect Ther. 2010;8:1293-305.

100. Shaw KJ, Poppe S, Schaadt R, Brown-Driver V, Finn J, Pillar CM, Shinabarger D, Zurenko G. *In vitro* activity of TR-700, the antibacterial moiety of the prodrug TR-701, against linezolid-resistant strains. Antimicrob AgentS Chemother. 2008;52:4442-7.

101. Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA. 2013;309:559-69.

102. Ortiz-Covarrubias A, Fang E, Prokocimer PG, Flanagan SD, Zhu X, Cabré-Márquez JF, Tanaka T, Passarell J, Fiedler-Kelly J, Nannini EC. Efficacy, safety, tolerability and population pharmacokinetics of tedizolid, a novel antibiotic, in Latino patients with acute bacterial skin and skin structure infections. Braz J Infect Dis. 2016;20:184-92.

103. Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2014;14:696-705.

104. Park KH, Greenwood-Quaintance KE, Schuetz AN, Mandrekar JN, Patel R. Activity of tedizolid in methicillin-resistant *Staphylococcus* epidermidis experimental foreign body-associated osteomyelitis. Antimicrob Agents Chemother. 2017;61:1644-16.

105. Berendt AR. Counterpoint: hyperbaric oxygen for diabetic foot wounds is not effective. Clin Infect Dis. 2006;43:193-8.

106. Andel H, Felfernig M, Andel D, Blaicher W, Schramm W. Hyperbaric oxygen therapy in osteomyelitis. Anaesthesia. 1998;53(Suppl 2):68-9.

107. Scott RW, Tew GN. Mimics of host defense proteins; strategies for translation to therapeutic applications. Curr Top Clin Chem. 2017;17:576-89.

108. Eades CE, France EF, Evans JM. Prevalence of impaired glucose regulation in Europe: a meta-analysis. Eur J Public Health. 2016;26:699-706.