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Review

Drug treatments for prosthetic joint infections in the era of multidrug resistance

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Abstract

Introduction: Despite many advances, the management of prosthetic joint infection is still a complex issue. Moreover, in recent years the problem of antimicrobial resistance has emerged as an important challenge.

Areas covered: We analysed recent advances in different aspects of prosthetic joint infections. The importance of biofilms needs to be considered for antibiotic selection because, when embedded in these structures, bacteria acquire resistant behaviour. Moreover, the presence of resistance mechanisms in some species of organisms increases the difficulty of management. In this sense, the growing importance of methicillin-resistant staphylococci, multidrug-resistant *Enterobacteriaceae* or *Pseudomonas aeruginosa* is of increasing concern. Together with these organisms, others with constitutive resistance against most antibiotics (like *Enterococcus* sp., mycobacteria or fungi) represent a similar problem for selection of therapy. Research into new materials that can be used as drug carriers opens a new field for management of these infections and will likely come to the front line in the coming years.

Expert opinion: Individualised therapies should carefully consider the aetiology, pathogenesis and antimicrobial susceptibility. Satisfactory clinical outcome could be further fostered by enhancing the multidisciplinary approach, with better collaboration in the antibiotic selection and the surgical management.

Keywords: Prosthetic Joint Infection, Treatment, Resistance, Multidrug-resistance, Biomaterial, Methicillin-resistant, Carbapenemase

Article Highlights:

*The management of prosthetic-joint infections is a complex process that must involve many different specialists, especially if a multidrug-resistant organism appears as the cause of the infection.

*The importance of the etiological diagnosis of the infection is increasing because the frequent isolation of microorganisms resistant to different antibiotics.

*The selection of proper antimicrobial therapy must take into consideration several issues (bone concentration, phenotypic resistance of the microorganism, bioavailability, experimental models, clinical experience, and many others).

*Surgery has a key role in the management of these patients and has important implications in antibiotic selection.

*The presence of a biofilm is the pivotal process in the pathogenesis of the infection, and is also of extreme importance regarding the selection of the optimal treatment of the patients.

*Future research is aimed mainly to the development of antibiofilm agents, new biomaterials or modifications of those currently used, and better antibiotic management for each patient and organism.

1-Introduction

Implant-associated infections represent a major challenge in every surgical department in this century. Surgical implantation of biomaterials has become the best approach to treat many current and devastating diseases with severe tissue damage that require reconstruction [1]. The inert surface of biomaterials is a privileged reservoir for any microbial inoculum that may be seeded during a surgical procedure, as it lies out of reach for any cellular or molecular defence mechanism. Independently of the implant, material or implant design [2], certain microorganisms have been isolated from explanted prostheses in chronically infected patients through many different methodologies, including sonication and molecular biology methods [3-6], thereby allowing us to determine the specific susceptibility of each microorganism. Despite advances in the diagnosis, many questions concerning patient management still remain. One extremely important issue is the increasing importance of multidrug resistance. This phenomenon has reached high worldwide importance, and the lack of new antibiotics increases the concerns regarding this issue [7-9]. In a previous review [10], some antibiotics with potential for use in prosthetic joint infection (PJI) were reviewed. However, since then, no new antibiotics have appeared, and a multidisciplinary approach is more necessary than ever to manage these infections and to contain menace of a return to the pre-antibiotic era. For this purpose we have reviewed the most important guidelines, as well as performed a PubMed research for the different organisms, and then evaluated the literature aiming to perform an opinion review.

2-The patient with a prosthetic joint infection: Need for a multidisciplinary approach.

Management of patients with PJI is challenging. This severe and difficult-to-treat infection can be life threatening and can cause substantial disability. In addition to functional issues, PJI can also create emotional problems [11], while the management of these infections has notable economic and social consequences.

Decision-making in PJI is usually complex and difficult to summarise, and most patients resist algorithmic categorisation [12]. There is sound evidence that work done by multidisciplinary teams improves health-care outcomes, and because the complex management of the PJI patients, a multidisciplinary management has also been proposed for PJI. It has been demonstrated that this approach optimises health care for PJI patients, offering them a good diagnostic strategy, the best available therapy, and optimised management of comorbidities, resulting in a better prognosis [13]. In another study, multidisciplinary management of PJI decreased hospital stay and readmission rates [14]. In a recently published prospective series of 125 patients with hip PJI managed by a multidisciplinary team, the mean Harris hip score improved from 38 (6 to 78.5) pre-operatively to 81.2 (33 to 98) post-operatively and the rate of successful control of infection was 96% at five years [13].

Multidisciplinary groups, often led by infectious-disease specialists and orthopaedic surgeons, can monitor antibiotic use and recommend prudent use of antimicrobials for better infection control. This team-based approach makes ambulatory care much more convenient for PJI patients, reducing the number of visits (these are patients with high

prevalence of disability and frequent pain) and precluding excessively long wait times before important clinical decisions are made. Other specialties should participate in health care of PJI patients [15],

orthopaedic surgeons, infectious disease physicians, plastic surgeons, expert microbiological, histopathological and radiological diagnostics, a service for administering intravenous antibiotics at home safely (OPAT), in-patient beds staffed by specialist nurses, physiotherapists, pharmacists, and multidisciplinary (combined) out-patient clinics. These units should be acknowledged and endorsed by hospital and clinic administrators and provided with the necessary resources to perform this activity that has so many advantages for patients and society.

3-Management of resistant organisms

3.1-Methicillin-Resistant *Staphylococcus* spp.

The main etiological agents isolated from PJIs are *Staphylococcus aureus* and *Staphylococcus epidermidis* [4, 16 17 18]. The isolation of methicillin-resistant *Staphylococcus* is very common in the case of coagulase-negative isolates [18] and uncommon for *S. aureus* isolates, although their relevance in health-care infections is rising [19]. The main problems in treating these infections arise when this resistance phenotype is associated with resistance to multiple antimicrobial agents, limiting the availability of therapeutic options [18].

Optimal antimicrobial therapy should include rifampin in combination with other drugs whenever the strains are susceptible [17]. This is due to the fact that rifampin has demonstrated excellent activity on susceptible staphylococci cells in stationary mode [20]. The use of combination regimens prevent the development of resistances due to the rifampin [17 18 21]. Also, studies such as Tang HJ *et al* [22] observed a poor inhibitory effect of rifampin for MRSA strains.

There are multiple options to use combinations regimens with rifampin, based on the results obtained from *in vitro* studies. One of the most successful combinations is with fluoroquinolones because of their good bioavailability, activity, and safety [23 17 24]. However, the best *in vitro* activity against quinolone-susceptible staphylococcihas been reported for ciprofloxacin when compared with other quinolones (moxifloxacin,

levofloxacin). The use of levofloxacin alone was unable to eliminate adherent staphylococci *in vitro* or *in vivo*, and as Murillo *et al* [25] observed for levofloxacin, high doses (750 to 1000 mg/day) are necessary after having been established that the efficacy of fluoroquinolones is concentration dependent. Currently, these high doses, which were approved and used for pneumonia or skin structure infection, have been recommended to treat orthopaedic prosthetic infections [26].

Antimicrobial therapy to treat MRSA and methicillin-resistant coagulase-negative strains is limited due to the fact that these strains are usually resistant to quinolones. For these reasons, an alternative antimicrobial combination with rifampin is necessary [27]. Cotrimoxazole has good bone biodisponibility and activity against MRSA, and therefore, it should be considered as a possible treatment in combination with rifampin [28 18]. The retrospective study developed by Nguyen et al, in which the efficacy of this combination was studied and compared against rifampin with linezolid, showed similar efficacy for both combinations when prolonged oral therapy had been used [29]. Vancomycin plus rifampin is another possible combination, which exhibits an *in vitro* synergistic effect against MRSA isolates with a high vancomycin MIC (2 _g/ml) [30], but this combination could easily induce high-level rifampin resistance (MIC_64 _g/ml) in biofilm MRSA isolates [22 31]. An alternative combination to Vancomycin plus rifampin is a three-drug treatment (vancomycin-fleroxacin-rifampin), which has been studied in an *in vivo* animal model by Chuard *et al* [24] with successful results, when compared with fleroxacin-rifampin regimens. Similar results have been obtained with Teicoplanin plus

rifampin, inducing high-level rifampin resistance (MIC_64 _g/ml) in biofilm MRSA isolates [22]

An alternative option to glycopeptides plus rifampin, in order to avoid the emergence of possible resistances, consists of vancomcyn or teicoplanin plus fosfomycin. This combination possesses antibacterial abilities against biofilm-embedded MRSA, with better results than combinations of rifampin, as shown in the study performed by Tang *et al* [32] in MRSA strains. In this study, combinations of glycopeptides plus fosfomycin showed a dramatically enhanced effect when compared with glycopeptides plus rifampin or glycopeptides alone.

Alternative drugs, such as minocycline, fusidic acid, fosfomycin and tigecycline, have been tested in combination with rifampin as possible options to rifampin plus quinolones in Staphylococcus strains [22, 32-33]. Minocycline plus rifampin has demonstrated in different studies a synergistic effect [33],[22, 34] ,decreasing the percentage of rifampin-resistant mutants in MRSA biofilm, as described for Tang *et al* [22]. Fusidic acid plus rifampin has demonstrated a synergistic effect and a decrease in the emergence of rifampin- resistant mutations. These characteristics allows this combination (Fusidic acid plus rifampin) to be considered an option to treat MRSA biofilm-related infections during long period [22] [32]. Similar results were obtained for fosfomycin plus rifampin and tigecycline plus rifampin, obtaining synergistic effects and a decrease in mutations. However, other alternative combinations with rifampin may be considered, such as fosmycin combined with minocycline, fusidic acid, and

tigecycline. Following the results obtained for Tang *et al* [32], fosfomycin employed at the recommended dose, in a combined treatment presents good antibacterial effect.

These results imply that the killing effects of fosfomycin, minocycline and tigecycline on biofilm-embedded MRSA are concentration- and dose-dependent, and as such, high doses should be used to prevent treatment failure and resistance [32].

Linezolid monotherapy exhibited excellent inhibitory effects against biofilm-embedded MRSA [22], combinations of rifampin plus linezolid have shown an increase in the antibacterial effect of linezolid in biofilm, and a synergic activity against eight MRSA isolates [22], [35], [34] being one of the alternative treatments in monotherapy [28]. There is abundant literature on the use of linezolid in monotherapy, showing high success rates [36] [37]. Its excellent bone and tissue penetration is one of the main reasons for this. *In vitro* studies have shown that the combinations of rifampin plus linezolid increase the antibacterial effect of linezolid in biofilm, and have synergic activity against eight MRSA isolates. [22], [35], [34]. This may be explained because of the strong penetration activity of rifampin against biofilm, being one of the reasons that caused the suggestion that this combination could be useful with the retention of implants [38] [39]. It is not well established the possible effect of rifampin in the clearance of linezolid, being a drug which metabolizes enzymes. *In vivo* studies such as Gandelman et al [40] showed that the combination is safe and well tolerated with only a small effect on the clearance of linezolid. One of the recommendations in the study carried out by Morata et al [36], when rifampin and linezolid are used in combination, was the monitoring of linezolid serum levels in order to control potential adverse effects. Gebhart et al [41] presented a case

report where the levels of linezolid decreased when this drug was used in combination with rifampin, confirming the need for monitoring the serum levels.

Other options for MRSA strains with a decreased susceptibility to vancomycin could be combinations of rifampin plus daptomycin. Daptomycin has a high bactericidal activity in the logarithmic growth and stationary phase, as shown in the study performed by John A-K *et al* in MRSA strains [42]. However, the study showed that none of the monotherapy regimens tested (vancomycin, linezolid, levofloxacin and daptomycin) cleared planktonic MRSA or erradicated adherent MRSA from the cages except rifampin monotherapy. The combinations daptomycin plus rifampin showed a better efficacy against adherent bacteria [42 33]. By contrast, the results obtained in this study for vancomycin and linezolid plus rifampin showed lower healing rate [42].

Recently, new lipoglycopetide antibacterial drugs with activity against Gram -positive have been commercialized, such as oritavancin, telavancin, and dalbavancin. Although with activity against skin and skin structure infections [43], there is no extended experience in PJIs and they are not included in the PJIs management. However, televancin has been successfully used in cases of osteomelitys, as described by Twilla et al [44], where they changed vancomycin by televancin. The results showed by Chan et al [45] in their study on the televancin biofilm activity seem to show that this drug may be considered as an alternative to treat infections by Gram-positive related to the development of biofilms.

Other new cephalosporin drugs with activity against MRSA are ceftobiprole and ceftaroline, which have activity in skin and skin structure infections. Although, there are no experiences in the treatment of PJIs for these new cepholosporins, they could be considered an alternative when non clinical response was obtained with the first-line and second-line treatments.

Tedizolid is another drug recently approved by the FDA, with activity against Gram-positive bacteria for treatment of skin and skin structure infections, but there are no studies and experience in PJI s [46]. It has some advantages over linezolid, such as having one daily intake versus one every 12h for linezolid.

3.2-*Enterococcus* spp.

The isolation of *Enterococcus* spp. from PJIs is not very common, and is only present in around 3% to 10% of cases [47] [26], The frequency of isolation in clinical samples is around 80-90% for *E. faecalis*, while 5-15% for *E. faecium*, an important point to understand the importance of possible resistances [48] There are studies such as Sandoe *et al* [49] in which *Enterococcus faecalis* and *Enterococcus faecium* are evaluated in order to register their ability to develop biofilms and the activity of different antibiotics (ampicillin, vancomycin and linezolid) in combination with gentamicin. The results obtained in their study concluded that high concentrations of ampicillin, vancomycin and linezolid are required to inhibit biofims *in vitro*, and the combination of these drugs with gentamicin may reduce the minimum biofilm inhibitory concentration. Following

the recommendations of IDSA guidelines for diagnosis and management of PJIs [28], the first-line treatment for penicillin-susceptible enterococci require bactericidal drugs such as penicillin G or ampicillin with optional combination with aminoglycoside. However, if there is an isolation of penicillin-resistant enterococci, or patients with penicillin allergy, the first-line should be vancomycin also with the optional combination with aminoglycoside [28].

Alternative experimental combinations of drugs have been studied in order to clarify the success of the combinations with aminoglycosides. Furustrand *et al* [50] in an *in vitro* and animal model (guinea pig) against *E. faecalis* detected an improvement of the activity by using daptomycin plus gentamicin, with a cure rate of 55%, compared with the activity of vancomycin plus gentamicin with a cure rate of 33%. Although the monotherapy regimens are not recommended due to possible emerging resistances, the cure rate observed for gentamicin alone was 50%. However, there are not enough *in vivo* studies to recommend the use of a combination systemic therapy of ² -lactams and vancomycin with amynoglucosides, as concluded by El Helou *et al* [51], due to the fact that prolonged antimicrobial therapy with these drugs may be harmful for the higher risk of nephrotoxicicty and ototoxicity. It is nevertheless important to remark that penicillin, ampicillin, and vancomycin are bacteriostatic antimicrobials against enterococci when used as single agents, but are bactericidal when used in a combination with an aminoglycoside. An alternative combination to ² -lactam-aminoglycoside is the combination ² -lactam- ² -lactam, such as the combination ampicillin-ceftriaxone. Ceftriaxone, together with an effective drug against enterococci such as ampicillin, presents a synergic effect and with lower toxicity than the combination with

gentamycin [48]. There is experience with this combination in treating endocarditis, but not in PJIs. [52]

Other antimicrobial combination therapies have been tested as possible alternatives for the treatment of enterococci PJIs. Oliva *et al* [53] showed in their *in vitro* and *in vivo* studies that the most efficient regimen for killing planktonic and adherent *E. faecalis* was the combination of fosfomycin and gentamicin when compared against combinations with vancomycin, daptomycin and rifampin. Also, they observed that the use of fosfomycin alone eradicated adherent *E. faecalis* in 42% of cases. However, due to the risk of emergence of fosfomycin resistance, fosfomycin is not recommended for monotherapy in clinical practice [53 54]. On the other hand, the authors saw no activity of rifampin against biofilm formation by enterococci, and activity against biofilms was only improved up to 8% in combination with vancomycin, to 17% with daptomycin, and to 25% with fosfomycin.

Currently, the emergence of vancomycin-resistance enterococci (VRE), most frequently E faecium which is usually present as multidrug- resistant, difficult the treatment of these patients [48] . In these cases, the recommended alternative drugs to vancomycin are linezolid or daptomycin [28]. *E faecalis* has a moderate susceptibility to ampicillin, leading to consider ampicillin as a reasonable choice in this VRE strains. In *E faecium* isolates with intermediate susceptibility to ampicillin (if the organism can be inhibited by 32 µg of ampicillin per ml), this drug should also be used. When ampicillin and vancomycin resistant strains are isolated, other drugs such as linezolid and daptomycin should be considered.

Novel combinations between daptomycin plus ceftriaxone have been studied in the *in vitro* models as an alternative antimicrobial therapy against VRE and daptomycin-non-susceptible enterococci. These combinations have shown an increase in the bactericidal effect, compared with daptomycin in monotherapy when daptomycin MIC was 4mg/l [55]. The combination increases the binding of daptomycin and other cationic peptides after ² -lactam exposure in MRSA and VRE . Another successful combination with daptomycin that has been studied in an *in vitro* model is its combination with ampicillin. [56]

3.3-Multidrug-Resistant *Enterobacteriaceae*

The isolation of gram-negative rods in PJIS represents around 30% of all cases [57]. One of the most common gram-negative rods isolated from PJIs is *Escherichia coli*, where the emergence of extended spectrum ² -lactamase (ESBL)- producing strains poses a health-care problem for reasons such as the possible plasmid transmission and other associated antimicrobial resistance, such as resistance to fluoroquinolones, aminoglycosides, and cotrimoxazole. For these reasons, alternative antimicrobial therapies are necessary. Fosfomycin, tigecycline, colistin and gentamicin have been studied in an *in vitro* animal model by Corvec *et al* [58] as possible antimicrobial therapies alone or in combination against ESBL-producing *E. coli* strains. In this study, the authors concluded that the combination that showed the highest antibiofilm activity against the ESBL-producing *E. coli* strain was fosfomycin plus colistin. It is important to remark that the results in this study showed that fosfomycin was the only single agent for which the eradication of *E. coli* from cages was achieved, suggesting fosfomycin as

a potential treatment for these strains. However, when fosfomycin was combined with colistin, the activity against both planktonic and biofilm bacteria was significantly improved [58].

Tigecycline does not seem to be effective as a single agent against gram-negative rods [59] [58]. However, a synergic effect with other drugs has been described, for example with colistin against MBL (VIM-1)- and ESBL (SHV-12)-producing *Klebsiella pneumoniae* [60]. Combinations of tigecycline plus amikacin showed synergy for 40-100% of *Enterobacter* spp., *Klebsiella pneumoniae, Proteus* spp. *and Stenotrophomonas maltophilia* isolates [59]. Currently the isolation of *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* is a significant health-care problem with limited therapeutic options due to the fact that these enzymes confer resistance to all ²-lactams, including carbapenems [61]. Recent studies for treatment of infections due to KPC producers suggested that antibiotic combinations have proved superior to monotherapy [62]. The *in vivo* animal model study developed by Michail *et al* [63] showed that among tigecycline combinations, the addition of rifampin improved tigecycline activity in the first place, followed also by the addition of gentamicin, while the combinations with colistin and meropenem even deteriorated tigecycline activity.

Two novel combinations of cepaholosporins with β-lactamase inhibitor have been recently approved by the FDA: ceftazidime/avibactam and ceftolozane/tazobactam. Both combinations in *in vitro* studies have shown activity against multiresistant *Enterobacteriaceae* such as KPC producers in the case of ceftazidime/avibactam [64]. Although these alternative new drugs could be considered a potential option to treat

multiresistant *Enterobacteriaceae* in PJIs, further experience and studies are necessary, due to the fact that the current indication is only set for complicated urinary tract infections and intra-abdominal infections.

3.4-*Pseudomonas aeruginosa*

Pseudomonas aeruginosa is another gram-negative species with a well-known ability to develop biofilms [65 66] that has been associated with PJIs (3-6%) [26]. A limited antibiotic therapy is available to treat PJI produced by this bacterium due to fact that there are very few drugs with activity against *P. aeruginosa,* and among them, only one oral antimicrobial treatment is available, ciprofloxacin. However, following the recommendations from IDSA guidelines [28], the use of a combination of two drugs may be considered, depending on the clinical characteristics of the patient. The first option as an antimicrobial therapy is cefepime or meropenem, and as alternative therapy ciprofloxacin or ceftazidime are also considered. The combinations of beta-lactams with aminoglycosides or ciprofloxacin should also be taken into consideration given the fact that the antibacterial effect from beta-lactams against biofilm cells could be affected by the low rate of cell growth, and a fast resistance could be developed in monotherapy [67]. However, fluoroquinolones show a greater antibiofilm activity [68], including activity against non-growing cells [69]. The use of combinations between beta-lactams and ciprofloxacin has been employed successfully in patients, as described Brouqui *et al* [70], where the combination of ceftazidime and ciprofloxacin was the option, while the study developed by Legout *et al* [71], where multiple isolates of *Pseudomonas spp.* were

obtained, also show the combination of ceftazidime with fluoroquinolones to be an effective treatment.

The novel drugs combinations ceftazidime/avibactam and ceftolozane/tazobactam, present *in vitro* activity against *P. aeruginosa* and may be considered a potential alternative in the management and treatment of PJIs caused by multidrug-resistant strains. [64]

3.5-*Mycobacterium* spp.

Mycobacteria are organisms that, although unusual, can be the cause of PJI [72-77] and, when these infections happen, they can be extremely difficult to treat because of the specific antimicrobial susceptibility of these organisms and the fact that they can produce biofilms that show high resistance against antibiotics [78-80]. PJI caused by *Mycobacterium tuberculosis* may be originated in local undetected disease or reactivation, by development of the disease after surgical treatment of these patients with a prosthesis [73, 75], or caused by haematogenous spread [72-75]. Of importance is the fact that, in some cases, the isolation of another organism may delay the diagnosis and treatment of tuberculosis [75]. Treatment of these cases does not differ from that of other forms of bone and joint tuberculosis. Implant removal has been recommended for these cases because of the difficulty of managing mycobacterial biofilms only with antituberculous drugs [73, 75]. The prolonged antibiotic regimens, from the 6 months to the recommended 9 months period, is the advised treatment for extrapulmonary tuberculosis (osteoarticular and PJIs) [81]. Each regimen has an initial phase in which the first line of antituberculous therapy consists of drugs during 2 months (isoniazid,

rifampin, ethambutol and pyrazinamide). If drug susceptibility test results show a fully susceptible bacterium, ethambutol need not be included, and a 2-drug therapy (isoniazid and pyrazinamid) may be performed until the end of the treatment. [81]

Although the problem of multidrug-resistant (MDR) tuberculosis (and extremely drug-resistant (XDR) tuberculosis,) is of enormous importance worldwide, the number of PJI caused by this organism is probably extremely low. Management of these infections probably must follow the current guidelines for the management of these diseases [82-83].

Among other mycobacteria involved in these cases, rapidly growing mycobacteria have been detected in several cases of PJI [76-77, 84]. These organisms have the ability to develop biofilm, both *in vitro* and in clinical samples [85], and have been described as causes of biomaterial-related infections in humans [86-87]. Management of these infections is due to the high resistance of mycobacterial biofilms to the different used antibiotics, [88-89]. Implant removal is mandatory in these cases in order to cure the patient, always associated to a combined therapy with at least two different *in vitro* susceptible antibiotics. However, suppressive therapy can be used in those cases where surgical removal of the implant cannot be performed [76].

3.6-*Candida* spp.

Not only bacteria have been associated with PJIs, but other microorganisms such as fungal species have also been isolated from these infections. The ability of *Candida* spp. to develop biofilms is one the main reasons why they are described as possible etiological agents of PJIs. Nevertheless, these pathogenic species represent a small

percentage of infections [26]. Following the IDSA guidelines, the antifungal options for oral antifungal therapies are limited, with one of these options being fluconazole (oral). This is the primary option in *Candida* osteoarticular infections, except for species with less susceptibility to fluconazole, such as *Candida krusei* or *C. glabrata*. Intravenous antifungal drugs are also available as a primary option, such as the lipid formulation of amphotericin B. There are alternative antifungal drugs, such as echinocandins, although as is the case with lipid formulation of amphotericin B, several weeks with an echinocandin should be followed by fluconazole therapy to end the treatment [90]. Kuiper *et al* [91], after reviewing 164 patients with hip and knee PJIs appearing in the literature, concluded that fluconazole and amphotericin B are the main choices to treat infections given their effective antifungal activity when employed in monotherapy [91].

3- Biofilms and their implications in future therapies

Arguably, one of the most important factors in the management of PJI is the concept of biofilm—a key factor in the pathogenesis of the disease. Despite biofilm is considered the most frequent form where microorganisms can be found in Nature [92], only over recent decades has their importance in human pathology been recognised. They are now considered the most important pathogenic factor in biomaterial-related infections [93-95].

One important issue surrounding the pathogenesis of orthopaedic infections is the concept of the "race for the surface" [16]. According to this theory, when an implant is placed in the patient, a race between cells and bacteria to colonise the implant surface starts. If cells win the race, the implant becomes integrated in the tissue and no infection develops. However, in rare cases, bacteria win the race and biofilm starts to be formed, with the subsequent development of infection. To fully understand this concept, bacterial adherence is the essential mechanism to study. This complex process can be divided in two (Figure 1) phases according to the forces implied in the process [96]. Once adhered, the organism begins to multiply and produce the extracellular matrix that surrounds them. Once the amount of bacteria (or other organisms) reaches a specific concentration, they communicate between them by using different molecules that integrate the *quorum sensing* system [97-98]. Once mature, the biofilm could have channels aimed at mobilising nutrients and debris inside it, while some specialised cells on the surface are released in order to colonise further territories. In the case of implanted biomaterials, this last step leads to the finding of bacteria in the surrounding tissues,

even as facultative intracellular organisms [99], and can be the cause of relapses even if the material is removed, if they were not removed too.

From a therapeutic point of view, the most important property of the biofilm is the increased resistance of sessile bacteria to most antibiotics, a phenomenon that has been studied *in vitro* revealing increases in the MICs higher than 1000 times [21]. This phenomenon can be due to different mechanisms [100-101].

Many studies have been performed to develop a specific "anti-biofilm" strategy that can help in overcoming this problem. Although biofilms are composed predominantly of water, other molecules, such as glycopeptides, DNA, and even lipids, can be found in its composition [80, 85, 102-109]. Dispersal agents that act against the structure of some of these components, like N-acetyl-cysteine [89, 110-118], DNAses [119-120] or even detergents like Tween 80 [89, 121-122] have been tested with variable efficacy, probably due to the fact that the molecules involved in the composition vary with the bacterial species. For example, polysaccharides are an important component of *P. aeruginosa* biofilm[108, 123], while mycolic acids are the most important component of mycobacterial biofilms [79-80].

Another approach involves the use of inhibitors of the *quorum sensing* system. Different molecules have been tested for this purpose like the RNA III-Inhibiting Peptide (RIP), tested in experimental models [124-125], or other molecules [97, 126]. As an example, Coenye *et al* [127] tested new molecules (i.e., baicalin hydrate, cinnamaldehyde, and hamamelitannin) against biofilms, and they found that the obtained *quorum sensing* inhibition increased the susceptibility of the organisms to different antibiotics. Despite the advances in this research, translation to clinical practice may not happen for quite

some time. Rifampin for staphylococci and probably other gram-positive bacteria, and fluoroquinolones against many gram-negative rods (and also staphylococci) are the most active antibiofilm antibiotics at the moment [10, 21, 128-133]. Further research is needed about the effect of antibiotics and antibiotic combinations on different biofilms, and, above all, proper standardisation is needed to evaluate the *in vitro* results [134].

5-Biomaterial development in the front line of *in situ* infection prevention and treatment.

This major therapeutic challenge can only be approached using a combination of surgical treatment and intense, specific antibiotic treatment, provided adequate in situ dosage is obtained. In this context, intensive research is under way to facilitate the in situ delivery of high antibiotic concentration, but also to impede the in situ colonisation of the pathogens that invariably contaminate the surgical implants.

Polymers have long been used as diffusers of antibiotics, and particularly polymethylmetacrylate (PMMA, or bone cement in use for cemented arthroplasties) was factory-mixed with gentamycin and used in primary and revision arthroplasties over three decades [135-138]. The long-term results confirm [139] that the rate of infection in these operations has decreased over the years due to different early innovations, including the use of antibiotics with cement. This successful local delivery strategy can spread the antibiotics to the surrounding bone and articular space. However, thermolabile antibiotics cannot be loaded in this polymer and require other vehicles due to the exothermic reaction of PMMA when curing (up to 80ºC). Thermostable aminoglycosides and polypeptides benefit from this biomaterial intraosseous distribution, although it is unclear how the release occurs in the surgical setting, what the dosage can be in the peri-implant tissue, and when this release ends, thus becoming a potentially colonisable polymeric implant[135, 140]. Whether this release has been sufficient to extinguish adhered microorganisms cannot be currently verified.

Bone substitutes and particularly bioceramics have emerged as potential antibiotic release systems [141-145]. Different formulations with different fixation mechanisms (adsorption, introduction in pores, etc) have been investigated and release curves have been explored by physical, chemical and biological methods to evidence the distribution, concentration and efficacy of the released antibiotic [142, 144-146]. Besides, the limited adherence of microorganisms to some experimental bioceramics [147-148] may orient these potential bone substitutes as implants to fill bone gaps in case of infected bone and deliver high dose of antibiotics to further treat the infection. Significant research remains to be completed about the amount and type of antibiotics to be loaded, the dose and timing after release, and many other important issues.

Metallic and polymeric implants currently used in joint and fracture reconstruction systematically suffer from bacterial adherence. Enhanced adherence has been associated with rough surfaces [149-150], but no component is spared of microorganism adherence when a reconstructive bone or joint is infected [2]. Besides treating the infection by removing the implant and systemically administering antibiotics, a potent research rationale is to generate implants with coatings that may limit bacterial adherence or even deliver antimicrobial agents that aid in infection healing while preventing implant colonisation [151-153]. Some new approaches focus on modifications of the implant surface structure, including the growth of nanocoatings that may difficult adherence (such as diamond-like coatings) or may expose compounds with well-known antimicrobial effect such as silver (Ag) in the surface, or even development of nanostructures (nanotubules or others) that may even release other substances such as loaded antibiotics [96, 154-160].

Abundant recent literature confirms the appeal of this genuine innovation with the aims of prevention, control or even healing these complex bone and joint implant related infections.

6-Conclusion

Management of PJI has always been a complex procedure that requires the involvement of different specialists, but at present, the menace of multidrug-resistant organisms increases the difficulties for such management. The fact that no new antibiotics are expected over the coming years [7-9] stresses the importance to optimise the management of currently available antibiotics among these patients. Moreover, recent research suggest that, at least in some cases, some monomicrobial infections may be polyclonal and have implications for antimicrobial susceptibility[161], a phenomenon with unknown implications in patient management. Despite the fact that data suggest that multidrug-resistant organisms have worse outcomes than susceptible organisms, the integration of knowledge about the infection pathogenesis, the comorbidities management, and the surgical approaches through the implantation of multidisciplinary teams (involving surgeons, microbiologists and infectious disease specialists) can improve these ominous tendency, leading to heal patients in a high percentage of cases [162-163].

7-Expert opinion

The importance of PJIs is expected to be increase over the coming years as the number of patients with prostheses is also expected to increase. It is also expected that the complexity of the management of these infections will increase because patients will have a growing number of comorbidities, and antibiotic therapy will need to take into account the interactions between antibiotics and all the pharmacotherapy that these patients receive for the treatment of underlying diseases [164-165]. Moreover, the increasing importance of antimicrobial resistance among the commonly found pathogens makes the best available antibiotic selection a problem that needs the combination of abilities in a multidisciplinary team.

The first step in this process is to establish a proper etiologic diagnosis of the infection. For this purpose, recent advances both in conventional and molecular diagnosis over the last decade have minimised the number of patients without etiological diagnosis [3, 5], and the evaluation of antimicrobial susceptibility of these pathogens can be performed. In this sense, recent data suggest the presence of multiple clones of the same species in many cases of theoretically monomicrobial infections, a fact that needs to be taken into account when antimicrobial susceptibility of the isolates is performed [161].

Once diagnosed, patient management is established according to the timing of infection. Early/acute infections can be managed with implant retention and proper antimicrobial therapy, while chronic/delayed cases need implant removal [3]. This is due to the most important individual factor for the management of the patient, which is the presence of biofilm, where bacteria become resistant to most antibiotics. Despite some advances in

this field, the possibility of eradicating biofilm without removing the implant is expected in the near future.

The presence of phenotypic antimicrobial resistance among the isolates is also of extreme importance. The presence of methicillin resistance among staphylococci is usually combined with multidrug resistance. In these cases, management of these cases needs to be individualised according to the results of susceptibility testing, but in most cases rifampin can be used. This antibiotic has a good antibiofilm activity, and an important effect of its use has been shown in patient outcomes [38]. However, this antibiotic needs to be combined with another one in order to prevent the rapid development of resistances. For this purpose, vancomycin has been commonly used, but other new antibiotics, such as linezolid or daptomycin, can be used and offer several advantages. For gram-negative organisms, fluoroquinolones have a similar role [166], but the recent menace of carbapenemase-producing multidrug-resistant *Enterobacteriaceae* limits their use. In these cases, antibiotics such as colistin, tigecycline, amikacin or others can be used, but individualisation of the therapy for these patients according to antimicrobial susceptibility testing results is mandatory. Other difficult-to-treat organisms (such as enterococci [167], *Pseudomonas aeruginosa*, mycobacteria or fungi) also require a detailed approach, because of the limited number of active antimicrobials.

The future may be problematic for the management of these infections, because no new antibiotics will be developed in the next years. However, new approaches are being researched and will likely be used in the near future. Local development of antibiotics using new biomaterials as carriers is a promising tool that can be also combined with the use of other substances such as anti-inflammatory drugs, anti-biofilm substances or

bone regeneration factors. This new approach could improve the management of these patients despite the increasing problem of antimicrobial resistance.

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Table 1: Different antibiotics used for the treatment of Prosthetic-Joint Infections

Antimicrobial agent	Spectrum activity against	Adverse reactions significant (>10%)	Posology	Drug distribution
Ampicillin	Gram-positive and Gram - negative bacteria	Erythema multiforme, exfoliative dermatitis, skin rash, urticaria* Diarrhea, enterocolitis, nausea* [168] [169]	Ampicillin sodium IV: 12 g /24 h continuously or in 6 divided doses [28]	Adequate concentrations in septic joint effusions. Persist sin fluid for long periods of time [170]
Amphotericin	Yeast and filamentous fungi	Nephrotoxicity Skin rash Anemia, leukopenia , thrombocytopenia Increased serum alkaline phosphatase, hyperbilirubinemia, increased serum ALT and. [171]	Lipid formulation of amphotericin B; 3–5 mg/kg daily [90]	The distribution achieved in bone is <1% of the total dose received. [172]
Ceftazidime	Gram -negative bacteria and *anti-Pseudomonas* activity	**5-10%:** Increased lactate dehydrogenase increased gamma-glutamyl transferase Eosinophilia Increased serum ALT and AST [173]	IV: 2 g / 8 h [174]	In bone samples the concentration was >1.8 µg/g [175] [176]
Cefepime	Gram -negative bacteria and *anti-Pseudomonas* activity	Positive direct Coombs test [177]	IV: 2 g /12 h [174]	Excellent diffusion in bone tissue [178]
Ciprofloxacin	Gram-positive and Gram - negative bacteria and *anti-Pseudomonas* activity	**1-10%:** Diarrhea, vomiting, abdominal pain, dyspepsia. Neurological signs and symptoms [179]	Oral:750 mg/12h IV: 400 mg /12 h [174]	Excellent bone and soft tissue concentrations are achieved for oral and i.v. [180]
Colistin	Gram –negative bacteria	Nephrotoxicity Neurotoxicity* [181]	IV: 2-3 MU/8h [169]	Very limited data available [182]
Cotrimoxazole	Gram-positive	Hematologic and	Oral:160- 800 mg	Intracellular

	and Gram - negative bacteria	oncologic:* Hepatic alterations* [183] [169]	Twice daily [174]	activity. [184] It penetrates in bacterial biofilm. [185] Similar level in serum and synovial fluid. [184]
Daptomycin	Gram-positive bacteria	Diarrhea, vomiting constipation Anemia [186]	Iv: 6 mg/kg / 24 h [174]**	Good penetration in synovial fluid and cancellous bone [187]
Echinocandin	Yeast and filamentous fungi	Overall are well tolerated<5% [188]	Anidulafungin: 200-mg loading dose, then 100 mg/day. Caspofungin: 70-mg loading dose, then 50 mg/day. Micafungin: 100 mg/day. [90]	Limited tissue penetration [188]
Ethambutol	First-line agent for treatment of all forms of tuberculosis	Retrobulbar neuritis [81]	40–90kg weight: 25mg/kg (maximun 2.000mg) during 2 months then 15mg/kg [189]	Good tissue distribution [190]
Fluconazole	Mainly for Yeast	Alkaline phosphatase increased, ALT and AST increased. Gastrointestinal [169] [191]	Oral: 400 mg (6 mg/kg) daily [90]	Good penetration into joint fluids. [192]
Fosfomycin	Gram-positive and Gram - negative bacteria	5-10% : Headache Diarrhea Vaginitis [193]	Oral: 1g/6h [169]	Achieves clinically relevant concentrations in bone. [194]
Fusidic acid	Gram-positive and Gram - negative bacteria	Gastrointestinal* Phlebitis* [169]	Oral: 1g/8-12h [169]	A good distribution throughout the body [195]
Gentamicin	Gram-positive and Gram -	Neurotoxicity, manifested by	IV: 5-7 mg/kg/daily	It penetrates well into synovial

	negative bacteria	ototoxicity*[169] Nephrotoxicity* [196]		fluid [197]
Isoniazid	First-line agent for treatment of all forms of tuberculosis	Asymptomatic elevation of aminotransferases [81]	<40kg weight: 5–7mg/kg 40–90kg weight: 300mg >90kg weight: 450mg [189]	It is widely distributed in body fluids and tissues [198]
Levofloxacin	Gram-positive and Gram - negative bacteria, and anti-Pseudomonas lower activity	5-10%: Headache Nausea [199]	Oral:750mg/24h [169]	Relative penetration into bone and soft tissue [200]
Linezolid	Gram-positive bacteria	Headache Diarrhea Decreased hemoglobin Thrombocytopenia Leukopenia [201]	Oral:600 mg /12 IV:600mg /12 h [174]	Excellent penetration into bone and infected tissues around joint prothesis [202]
Minocycline	Gram-positive and Gram - negative bacteria	Gastrointestinal Hearing loss, tinnitus mucous membrane pigmentation [169] [203]	Oral:100 mg /12h [174]	Good penetration into bone, and muscles. [204]
Moxifloxacin	Gram-positive and Gram - negative bacteria. Anaerobic bacteria.	**5-10%:** Gastrointestinal Headache [205]	400mg/24h [169]	Good penetration into skeletal muscle fluid, bone and subcutaneous tissue. [206]
Pyrazinamide	First-line agent for treatment of all forms of tuberculosis	>10%: Polyarthralgias [81]	40–90kg weight: 25–30mg/kg (maximum 2.500mg) [189]	The concentrations achieved into bone and skeletal muscle is less than in other tissues as lungs. [207]
Rifampin	A greater Gram-positive than	Dermatologic: Rash LFTs increased	<40kg weight: 10mg/kg	Excellent concentrations

	Gram –negative activity First-line agent for treatment of all forms of tuberculosis	[208]	40–90kg weight: 600mg (máximum 600mg) >90kg weight: 600mg [189]	are achieved into diseased and normal bone and in cancellous and cortical bone. [209]
Teicoplanin	Gram-positive bacteria	Allergic rashes* Nephrotoxicity* Leucopenia* [210]	IV: 6mg/kg/12h then 6mg/kg/24h [169]	Good concentrations of teicoplanin are achieved in the periosteum, bone marrow and trabecular bone. [210]
Tygecicline	Gram-positive and Gram - negative bacteria	Gastrointestinal: Nausea, vomiting and diarrhea [211]	IV: 100mg then 50 mg/12h [169]	Lower tygecicline levels are achieved in bone and synovial fluid than in serum. [212]
Vancomycin	Gram-positive bacteria	Hypotension accompanied by flushing Erythematous rash on face and upper body (red neck or red man syndrome) <1% :renal failure and Ototoxicity. [213]	IV: 15 mg/kg /12 h [174]	Adequate cancellous and cortical bone levels [214]

*Frequency not defined

**: Higher dosages (10 mg/Kg/24 h) have also claimed to be useful.

Figure 1: Steps in biofilm development: A: First part of adherence process (long distance forces). B: Second part of adherence process (short distance forces). C: Bacteria start to multiply and produce extracellular matrix (ECM). D: The amount to bacteria has reached enough number in order to starting the effective quorum sensing (QS) communication. E: Mature biofilm includes the metabolic differentiation of bacteria and the appearance of channels used for nutrient input and waste removal. F: In the final steps, some superficial bacteria detach from the biofilm in order to colonise new territories.