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Antibiotics Against Endocarditis – Past, Present and Future (Experimental Data)

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1. Introduction

"Bacterial infections are becoming increasingly resistant to existing antibiotics, and as the number of patients who have succumbed to these infections rises, the number of new antibiotics being developed continues to plummet." This extract from a letter addressed to President Barack Obama by the president of Infectious Diseases Society of America (IDSA) attests to the urgent need for new therapeutic options to fight multidrug-resistant (MDR) bacteria. Drug-resistant infections and related morbidity and mortality are on the rise in the United States and around the world. Despite the growing antibiotic resistance among Gram-positive and Gram-negative pathogens causing severe infections in hospital and community settings, the number of new antibacterial drugs approved for marketing in the United States continues to decrease. In addition to this worrying situation, only a few novel therapeutics for drug-resistant infections are in the drug development pipeline (Boucher et al., 2009; European Centre for Disease Prevention and Control, 2009). Reports of bacterial isolates resistant to almost all available antibiotics highlight the crucial need for new antibiotic therapies, especially for Gram-negative infections (Maltezou, 2009). Recently, IDSA and United States authorities have developed creative incentives to stimulate new antibacterial research and development (Infectious Diseases Society of America, 2010).

In vivo assessment is recognized as an essential link between in vitro data such as susceptibility testing and clinical studies. As indicated in 1999 in the introduction to the Handbook of Animal Models of Infection (Zak et al., 1999), it is hardly conceivable that a new antibiotic could move into clinical use without thorough verification of its antimicrobial efficacy in animal models of infection at an early stage. To facilitate the extrapolation of animal model data to humans, especially for determination of efficacy, animal models mimicking human disease are required. Pharmacokinetic (PK) and pharmacodynamic (PD) features of new antibacterial agents must be considered and differences between PK of antibiotics in animals and human should be limited using methods for obtaining human-like PK profiles in animals. Animal models mimicking human infections are considered discriminative models and are designed to assess the potent therapeutic effects of antibiotics against pathogens, and in some cases to extend or delimit the indications advisable for humans.

Animal models of endocarditis are used extensively to test the in vivo activities of new drugs or new regimens, and are particularly suitable for PK and PD analysis and optimization of therapeutic efficacy. Experimental endocarditis studies played a major role in the exploration and assessment of new antistaphylococcal drugs beginning with the oxazolidinone, linezolid, in the early 2000s, and were critical to the recent approval of the promising anti-MRSA cephalosporin ceftaroline by the United States Food and Drug Administration (FDA). The endocarditis model is referenced in approximately 100 PubMed publications, most of which are assessments of the in vivo activity of new therapeutic options against *Staphylococcus aureus* such as linezolid (Jacqueline et al., 2002), quinupristin-dalfopristin (Batard et al., 2002), moxifloxacin (Entenza et al., 2001), daptomycin (Sakoulas et al., 2003), tigecycline (Murphy et al., 2000; Jacqueline et al., 2011), ceftobiprole (Tattevin et al., 2010) and ceftaroline (Jacqueline et al., 2007). *Staphylococcus aureus* is the most common cause of endocarditis worldwide and methicillin-susceptible *Staphylococcus aureus* (MSSA) is detected in up to two-thirds of cases (Fowler et al., 2005). High rates of clinical failure have been reported with vancomycin therapy for MRSA endocarditis. The emergence of glycopeptide-intermediate *Staphylococcus aureus* (GISA) strains further highlights the need for new therapeutic options for treatment of infections by *S. aureus* strains that are resistant to methicillin and glycopeptides.

Ideally, clinicians should be able to use clinical trial data to support evidence-based medicine for the treatment of infectious diseases. However, difficulty in performing clinical trials in severe types of infection such as endocarditis has resulted in a lack of clinical information regarding use of new antibiotics in treating severe infections. Experimental animal models are one method used to assess the in vivo activity of new antimicrobials in the treatment of severe infections.

2. Experimental model of endocarditis: How to?

Although experimental rodent endocarditis models are sometimes used, white New Zealand female (weighing 2-2.5 kg) are most commonly used in experimental studies involving evaluation of antimicrobial agents. This model is based on the description by Garrison and Freedman in 1970 (Garrison & Freedman, 1970) modified by Durack and Beeson in 1972 (Durack & Beeson, 1972).

The rabbit model, as currently used, is based on the insertion of a polyethylene catheter via the right carotid artery into the left ventricle under general anaesthesia. The catheter is left in place throughout the experiment (until the euthanasia of the animal). After catherization for 24 hours, each animal is inoculated i.v. (using the marginal ear vein) with 1 mL of a bacterial suspension of the test pathogen. The inoculum is usually prepared from an overnight culture (broth), centrifuged and calibrated in saline to the appropriate dilution (range, 10^5 to 10^9 CFU/mL). Bacterial concentration of the inoculum (CFUs) is controlled by quantitative culture. Then, animals are randomly assigned to the different therapeutic regimens, including a control group (infected, no drug). The treatment is usually initiated 18 to 24 hours after bacterial challenge given that the time between i.v. inoculation of the bacteria and start of antimicrobial therapy is critical. As observed in other animal experimental models, this factor can influence the efficacy of tested drugs. Administration of antibiotics is widely realized by the intramuscular (thigh) or i.v. (marginal ear vein) routes. The animals are euthanized by using an i.v. bolus of thiopental at the beginning of the treatment period (controls) or at the end of therapeutic regimen (range, 1 to 5 days). Aortic

valve vegetations are excised; immediately placed on ice; and then weighed, homogenized in saline buffer, and plated on agar plates for surviving bacteria counts. Dilutions are used to eliminate potential carryover. Viable counts after 24 h to 48 h of incubation at 37°C are expressed as the mean ± standard deviation log_{10}CFU per gram of vegetation (most reliable judgement criteria). To determine whether antibiotic regimens could induce the selection of in vivo resistant variants, undiluted vegetation homogenates are spread on agar plates containing antibiotic at concentrations corresponding to two- and fourfold the MIC.

The experimental model of endocarditis has demonstrated to be highly valuable in assessing in vivo efficacy of antimicrobial agents by providing endpoints relevant in the evaluation of antibiotics (Lefort & Fantin, 1999):

- Surviving bacteria (expressed as number of CFU per gram of vegetation)
- Blood cultures (positive/negative)
- Ease of removing blood samples (PK assessment)
- Detection of the emergence of resistant variants during therapy
- Mortality
- Incidence of relapse after therapy discontinuation.

3. Linezolid, the first drug issued from the oxazolidinones, a novel class of synthetic antimicrobials

First marketed as oxazolidinone in the early 2000's, linezolid was approved by the United States FDA for the treatment of adults with nosocomial pneumonia, infections due to vancomycin-resistant *Enterococcus faecium*, complicated and uncomplicated skin and skin-structure infections, and community-acquired pneumonia (Zyvox [package insert], 2000). This new drug was considered a promising new option against MRSA in a context of increasing numbers of infections caused by resistant gram-positive bacteria and the emergence of MRSA strains with reduced susceptibility to glycopeptides (Hiramatsu et al., 1997).

3.1 *In vitro* antibacterial activity of linezolid alone and in combination with other antibacterial agents

Oxazolidinones are bacterial protein synthesis inhibitors: linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex (Aoki et al., 2002). This mechanism of action is specific to this class, and no cross-resistance with other antimicrobial agents has been observed. As with most protein synthesis inhibitors, linezolid displays nonbactericidal, time-dependent activity in vitro against staphylococci (Kaatz & Seo, 1996) (Figure 1). The bacteriostatic and time-dependent activity did not work in linezolid's favor for clinical use, especially for treatment of severe infections, where most clinicians are convinced that bactericidal drugs are required. Consequently, many studies examined the in vitro activity of linezolid in combination with partner drugs (Table 1), including vancomycin (Grohs et al., 2003; Jacqueline et al., 2003; Soriano et al., 2005; Sahuquillo Arce et al., 2006; Singh et al., 2009), gentamicin (Grohs et al., 2003; Jacqueline et al., 2003), rifampicin (Grohs et al., 2003; Jacqueline et al., 2003; Soriano et al., 2005; Sahuquillo Arce et al., 2006), carbapenems (Jacqueline, 2005, 2006), fosfomycin (Sahuquillo Arce et al., 2006), doxycycline (Sahuquillo Arce et al., 2006), ciprofloxacin (Grohs et al., 2003), levofloxacin (Soriano et al., 2005;

Sahuquillo Arce et al., 2006), and fusidic acid (Grohs et al., 2003). Although indifference is often observed for linezolid combinations against *S. aureus* (including methicillin-resistant strains), some cases of antagonism and synergism were reported and studied in vivo using the experimental model of endocarditis.
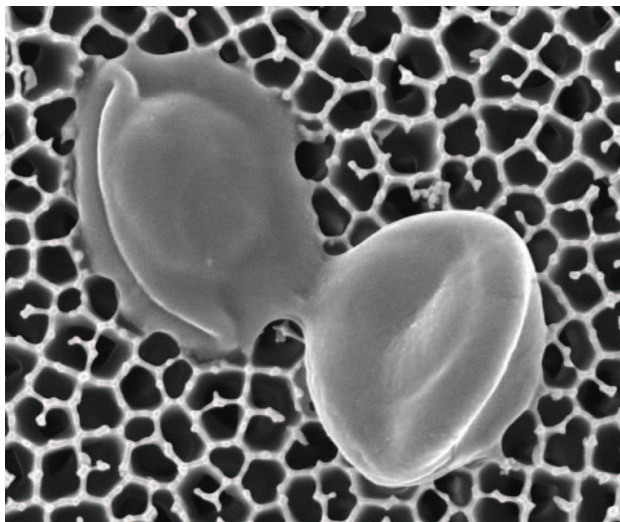

Fig. 1. Scanning electron micrographs of *S. aureus* exposed to linezolid (LNZ) at 8 times the minimum inhibitory concentration (MIC; magnification, ×50,000)

Partner drugs	Class of antibiotics	Interaction	Reference(s)
Vancomycin	Glycopeptides	Antagonism	Grohs et al., 2003; Jacqueline et al., 2003; Soriano et al., 2005; Sahuquillo Arce et al., 2006; Singh et al., 2009;
Gentamicin	Aminoglycosides	Antagonism (inhibition of the early bactericidal activity)	Grohs et al., 2003; Jacqueline et al., 2003
Rifampicin	Rifamycins	Indifference	Grohs et al., 2003; Jacqueline et al., 2003; Soriano et al., 2005; Sahuquillo Arce et al., 2006
Doxycycline	Tetracyclines	Addition	Sahuquillo Arce et al., 2006
Ciprofloxacin	Quinolones	Indifference or Antagonism	Grohs et al., 2003
Levofloxacin			Soriano et al., 2005; Sahuquillo Arce et al., 2006
Acid fusidic	-		Grohs et al., 2003
Fosfomycin	-	Synergy	Sahuquillo Arce et al., 2006
Imipenem	Carbapenems	Synergy	Jacqueline et al., 2005
Ertapenem			Jacqueline et al., 2006

Table 1. In vitro activity of linezolid in combination with partner drugs

3.2 *In vivo* antibacterial activity of linezolid alone and in combination in the experimental model of infective endocarditis

3.2.1 *In vivo* experimental assessment of linezolid activity: Bacteriostatic agent *in vivo*?

First reports of linezolid in vivo activity used oral administration (p.o.) of the drug. Given that linezolid can be administered intravenously (i.v.) or orally, and no dose adjustment is necessary when switching from the i.v. to the oral route of administration in humans (Zyvox [package insert], 2000). Infective endocarditis is considered to require maintenance of bactericidal levels of antibacterial agents for prolonged periods of time to result in eradication of the pathogen. For this reason, it was of special interest to assess the activity of the oxazolidinone in this model of endocarditis. Dailey et al investigated the activity of linezolid at three different p.o. dosages (25, 50, and 75 mg/kg) against MRSA in rabbits with experimental aortic-valve endocarditis (Dailey et al., 2001). After 5 days of treatment, linezolid displayed a stepwise decrease in the mean bacterial counts from the valve vegetation with a significant decrease for both 50 and 75 mg/kg. Showing a 4- to 5-log reduction in valvular bacterial counts, linezolid acted as a bactericidal drug in this study (Dailey et al., 2001).

Based on these results, the authors suggested that linezolid levels at or above the MIC in plasma combined with a minimum number of treatment days was required for the therapeutic efficacy of linezolid in this model. Further studies were then necessary to address the predictive pharmacokinetic and pharmacodynamic (PK/PD) parameters of linezolid.

The extrapolation of results obtained in animal experimental models to human therapy is always a difficult task. Owing to the very short spontaneous half-life of linezolid in rabbits (30 min; unpublished data) and to the difference in bioavailability of orally administered linezolid (approximately 30% bioavailability in rabbits compared to almost 100% in humans (Dailey et al., 2001)), the use of simulation of human pharmacokinetics was required to reach conclusions relevant to human applications. Simulation is particularly suitable for pharmacokinetic and pharmacodynamic analysis, and for the optimization of therapeutic efficacy. Computer-controlled simulation (Bugnon et al., 1998) of human kinetic profiles of linezolid in rabbits was used in the following study to improve the analysis (Jacqueline et al., 2002). The use of a computer-controlled pump allowing an adequate flow of antibiotics to be infused into rabbits enabled us to simulate the in vivo human pharmacokinetics of the antibiotics. The flow can be adjusted to a profile mathematically defined in time (Bugnon et al., 1998). Using this method, the serum linezolid levels obtained after administration of a dose simulating a 10-mg/kg dose in humans are shown in Figure 2. The corresponding mean peak concentration, area under the curve, and half-life were 11.9±1.1 mg/L, 76.3±5.9 mg.h/L, and 2.7±0.1 h, respectively, after administration of the first dose and 21.5±1.3 mg/L, 152.1±9.2 mg.h/L, and 3.4±0.7 h, respectively, at day 5. The increase of linezolid concentrations in plasma at day 5 compared to day 1 suggested drug accumulation as previously shown by Dailey (Dailey et al., 2001) using the same experimental model.

Using the computer-controlled simulation, linezolid significantly decreased the bacterial counts in aortic valve vegetations from rabbits, but failed to exhibit bactericidal activity, despite 5 days of treatment (Figure 3). The comparison with vancomycin administered as a

constant-rate intravenous infusion (to obtain a serum steady-state concentration of approximately 20 to 25 mg/L) was in favor of the glycopeptide with at least a 5-log_{10} colony-forming unit (CFU)/g of vegetation decrease (Figure 3). The oxazolidinone is a time-dependent antibiotic and for these drugs, the time above the MIC (T>MIC) is usually considered a critical parameter in the assessment of therapeutic efficacy (Carbon, 1990). In general, the maximal activity of continuous infusion was obtained at a steady-state concentration in serum equal to a multiple of the MIC, as previously demonstrated for ceftazidime (Cappelletty et al., 1995). To confirm this, continuous infusion of linezolid was used by Jacqueline et al (Jacqueline et al., 2002) to investigate whether it improves in vivo activity. A switch from intermittent dosing to continuous infusion (using the same total daily dose) improved the in vivo activity of linezolid against two strains of MRSA. By increasing the time above the MIC (T>MIC of 100%), linezolid continuous infusion achieved bactericidal activity in vivo with a >3-log_{10}-decrease as compared to the control animals (Figure 4).
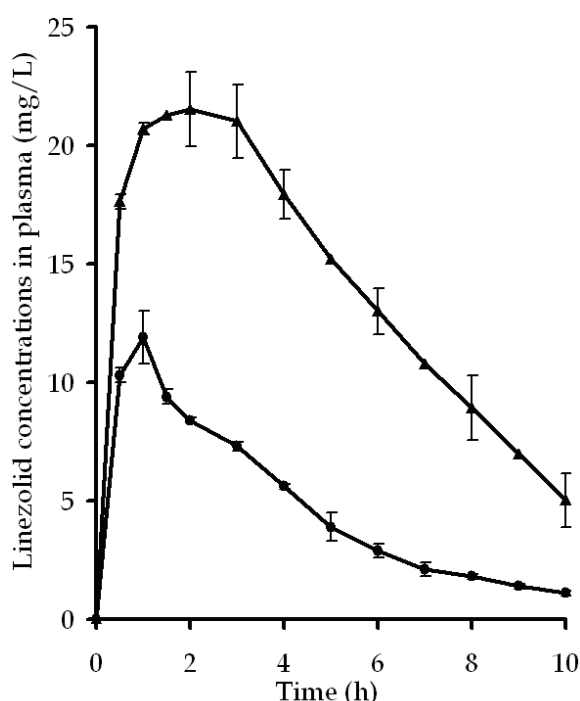

Fig. 2. Linezolid concentrations in plasma after simulation of a dose corresponding to a 10 mg/kg dose in humans (i.e., 600 mg). Circles, concentrations obtained after administration of the first dose; Triangles, concentrations obtained at day 5. Error bars represent standard deviations (adapted from Jacqueline et al., 2002)

Further studies are needed to investigate the potential clinical benefit of continuous infusion, which could be an appropriate alternative to the use of glycopeptides for the treatment of severe MRSA infections. Although no superiority of continuous infusion vs. intermittent dosing was demonstrated in a clinical study with critically ill septic patients (Adembri et al., 2008), Adembri et al showed that the continuous infusion modality has a theoretical advantage over intermittent infusion in the treatment of infection in these patients. Finally, there is a clear need for more powerful clinical trials to demonstrate the potent clinical benefit and the safety of this administration modality.
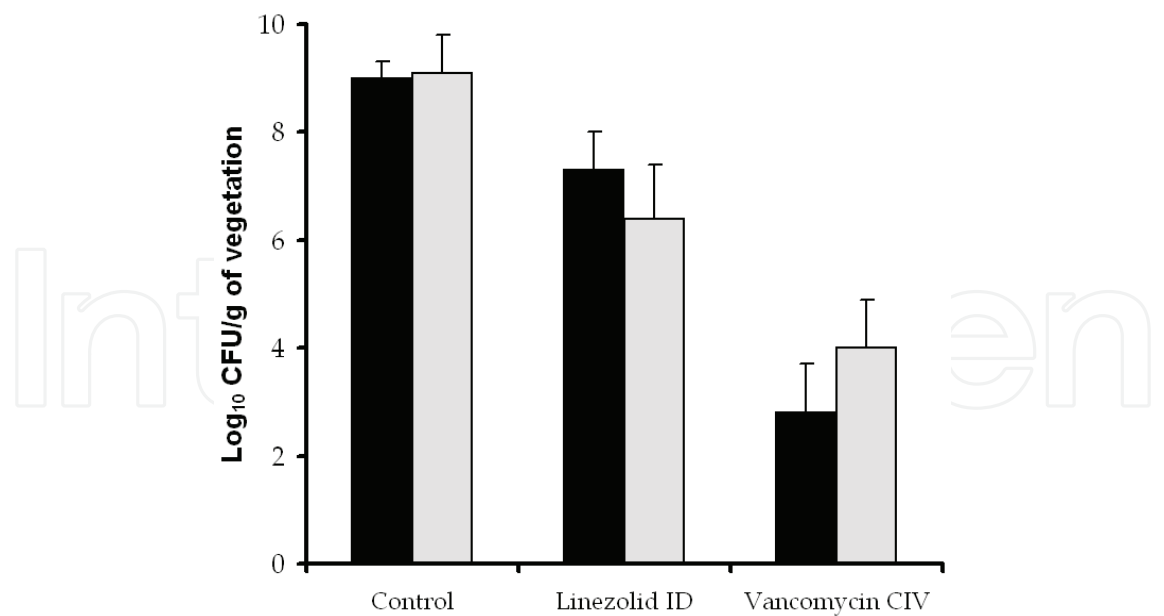
Fig. 3. In vivo activity of linezolid (human-equivalent of 600 mg q12hr, intermittent dosing, ID) and vancomycin (continuous infusion, CIV) against MRSA 1 (black) and MRSA 2 (grey) strains after a 5-day treatment. Error bars represent standard deviations (adapted from Jacqueline et al., 2002)
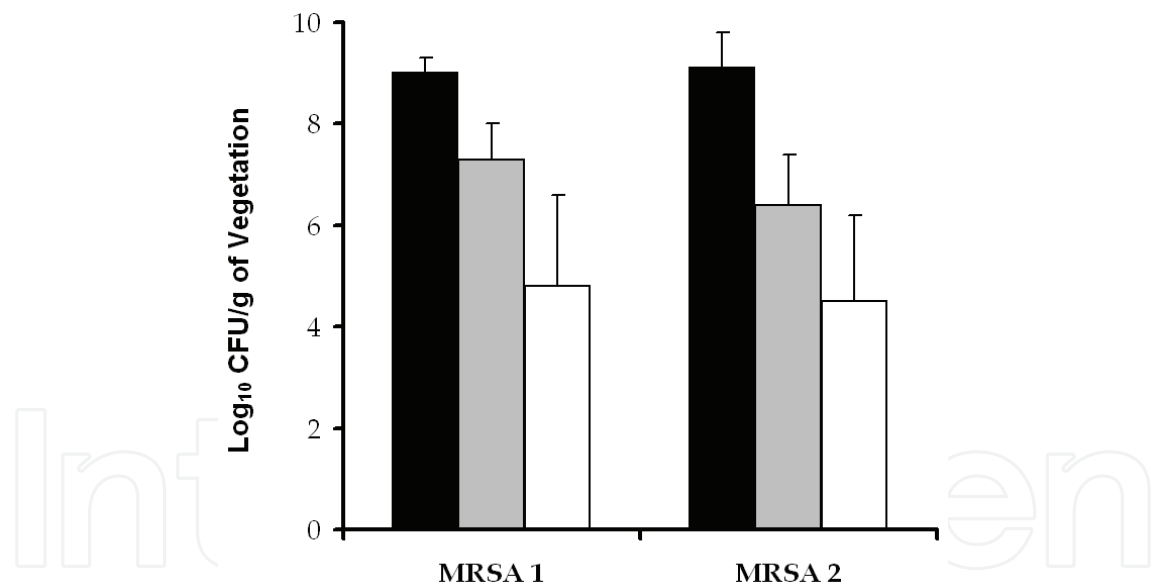

Fig. 4. Impact of the administration mode (intermittent dosing, ID vs. continuous infusion, CIV) on the in vivo activity of linezolid. Control animals (black); Linezolid ID (grey); Linezolid CIV (white). Error bars represent standard deviations (adapted from Jacqueline et al., 2002)

3.2.2 Improvement of the in vivo activity of linezolid by adding a partner drug: What is the good choice?

Infective endocarditis is considered to require bactericidal drugs to achieve clinical efficacy and/or microbiological eradication. Like most protein synthesis inhibitors, oxazolidinones

are bacteriostatic agents. Clinicians need to combine linezolid with another drug to (i) increase the bactericidal activity of therapy, (ii) prevent the emergence of drug-resistant subpopulations, and (iii) provide a complementary antibacterial spectrum. Moreover, the use of synergistic antibiotic combinations is appealing as a way to optimize therapy for infective endocarditis, especially when the causative pathogen is resistant (such as MRSA). Although in vitro interactions between linezolid and agents are well-documented (Table 1), the presence of in vitro synergism or antagonism and in vivo correlation or enhanced clinical outcome is not easy to highlight. In addition, the in vitro-in vivo correlation of either positive or negative interactions between two drugs can be difficult to assess and discrepancies occur.

3.2.2.1 Linezolid plus vancomycin

Although the combination of linezolid with vancomycin is not the most obvious choice, many papers have investigated the in vitro activity of this combination and have concluded they are antagonistic. Using the endocarditis model, Chiang et al have tested this association against an MRSA strain and they demonstrated that vancomycin alone was more effective than either linezolid alone or the combination of linezolid and vancomycin (Figure 5) (Chiang & Climo, 2003). This study is in line with in vitro reports (Grohs et al., 2003; Jacqueline et al., 2003) and the combination of linezolid plus vancomycin should be avoided in clinical practice.
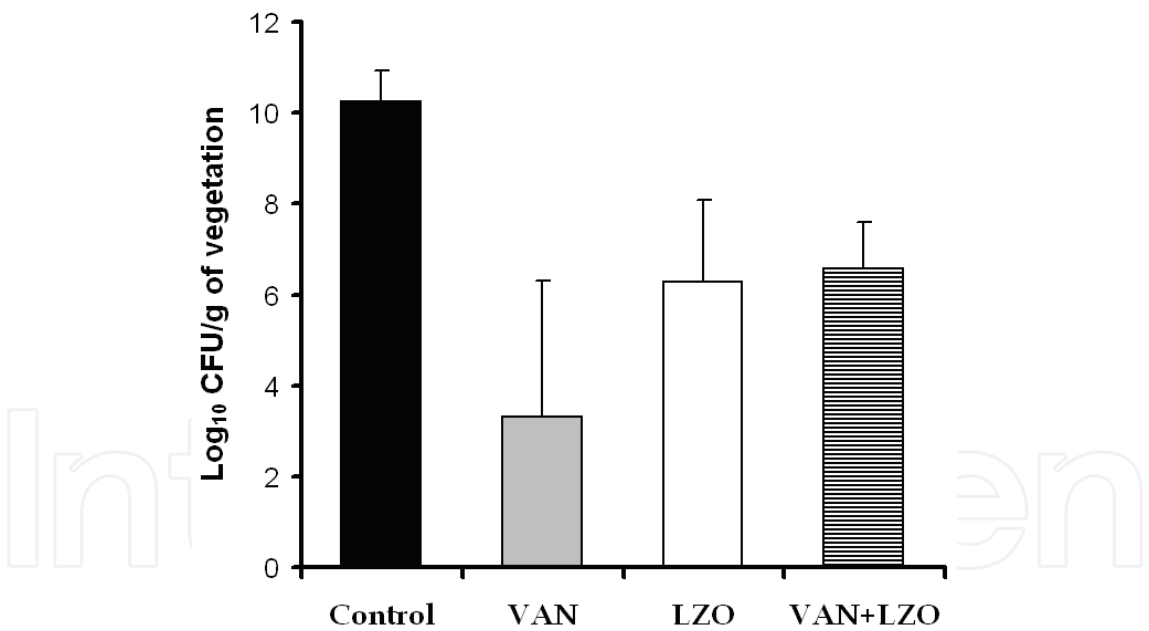

Fig. 5. Outcome of 5-day treatment of experimental MRSA endocarditis. (adapted from Chiang & Climo, 2003)

3.2.2.2 Linezolid plus gentamicin

Linezolid, when added to gentamicin, seemed to inhibit the early in vitro bactericidal activity of gentamicin, particularly over the first 6 h (Jacqueline et al., 2003). During this interval, inhibition of the bactericidal activity of gentamicin was dependent on the linezolid concentration. Aminoglycosides are bactericidal, concentration-dependent antibiotics that

act by creating fissures in the outer membrane of the bacterial cell (Gonzalez & Spencer, 1998). A combination of these agents with linezolid could be useful to increase the bactericidal activity of the therapy, especially during the first days of treatment.

Given that the presence of in vitro antagonism is not always correlated with in vivo failure, Jacqueline et al assessed the combination of linezolid plus gentamicin in the endocarditis model against two clinical strains of MRSA exhibiting MICs of 0.125 and 0.5 mg/L (Jacqueline et al., 2004). Using a human-like pharmacokinetic simulation for linezolid and gentamicin, the combination demonstrated a bactericidal activity against the two strains with a decrease of at least 4 $\log_{10}$ CFU/g of vegetation compared with controls. PK/PD aspects could probably explain the difference observed between the in vitro and in vivo activities. Contrary to constant concentrations in time-kill curves experiments, the concentrations of linezolid and gentamicin added to the vegetation changed over time. Although previous in vitro results suggest an antagonism, linezolid combined with gentamicin could be of clinical interest for the treatment of severe MRSA infections requiring combination antimicrobial therapy.

3.2.2.3 Linezolid plus rifampicin

Rifampicin is an RNA polymerase inhibitor that blocks bacterial transcription. Rifampicin is used clinically only as a part of combination regimens because development of resistance is rapid (Heep et al., 2000). In addition to its use against *Mycobacterium tuberculosis*, rifampicin is very useful in the management of bone and joint infections due to MRSA. Indifference was the main interaction observed in vitro between linezolid and rifampicin (Grohs et al., 2003; Jacqueline et al., 2003, Soriano et al., 2005; Sahuquillo Arce et al., 2006). The addition of linezolid prevented the selection of rifampicin resistant mutants after 24 h of incubation at 37°C. Consequently, a synergistic interaction can be considered by inhibition of the emergence of the resistance development.

By evaluating the bactericidal activity, synergy, and emergence of antimicrobial resistance, Dailey et al assessed the potent activity of linezolid plus rifampicin in the endocarditis model against a MSSA strain (rifampicin MIC<= 0.12 mg/L) (Dailey et al., 2003). After a 5-day treatment, the combination showed no in vivo antagonism between the drugs. As with in vitro tests, indifference was observed and the combination inhibited the emergence of rifampicin resistance. These data support a clinical interest in the treatment of infections due to *S. aureus*. A similar study was performed against an MRSA strain (rifampicin MIC= 2 mg/L) and indifference between linezolid and rifampicin was observed (Tsaganos et al., 2008). Moreover, this work demonstrated that (i) linezolid limited bacterial growth in the secondary foci of endocarditis, and (ii) that the combination favored the suppression of bacterial growth in the lung.

3.2.2.4 Linezolid plus carbapenems

Beta-lactam antibiotics act by inhibiting penicillin-binding proteins (PBPs) that are involved in peptidoglycan synthesis. Penicillin-binding protein 2A (PBP2A) is the protein responsible for the methicillin resistance mechanism in *S. aureus*. Methicillin resistance confers resistance to all the beta-lactams, including cephalosporins and carbapenems; however, many studies have reported a potent efficacy of imipenem against *S. aureus* when used in combination with other antimicrobial agents, including fosfomycin (Nakazawa et al., 2003), vancomycin

(Totsuka K et al., 1999; Benquan et al., 2002; Rochon-Edouard et al., 2000), and cephalosporins (Uete & Matsuo et al., 1995).

In vitro synergy between linezolid and carbapenems can be difficult to achieve; sub-inhibitory concentrations of the carbapenem must be used with linezolid to achieve synergy and higher concentrations can lead to an antagonism (Jacqueline, 2005, 2006). The infective endocarditis model was very useful to assess in vivo interaction. Continuous infusion of imipenem alone, the first carbapenem tested in this model, showed no activity against MRSA after 5 days of treatment (Jacqueline et al., 2005). The aim of using continuous imipenem infusion was to obtain an in vivo steady-state concentration that mimics the in vitro conditions so that synergy was observed as soon as possible (i.e., to achieve a target concentration of 1/32 the MIC for each strain). Using these conditions, linezolid plus imipenem exhibited bactericidal and synergistic activities against two MRSA strains, with at least a 4-$\log_{10}$ CFU/g decrease compared to the counts for the controls. Subsequent to that study, the carbapenem ertapenem was investigated in combination with linezolid using the same experimental model (Jacqueline et al., 2006). Ertapenem is a parenteral carbapenem antibiotic with a broad antibacterial spectrum and once-a-day dosing that is supported by clinical studies and an extended half-life (Zhanel et al., 2005). In this study, animals were randomly assigned to receive either no treatment (controls), a linezolid regimen mimicking the human dose of 10 mg/kg/12 h, an ertapenem regimen mimicking the human dose of 1 g/day, or a combination of both regimens. As previously observed with imipenem and confirming the in vitro data, linezolid and ertapenem exhibited a highly bactericidal and synergistic activity in vivo against three MRSA strains after 4 days of treatment (Figure 6). Due to the once-daily dosing of ertapenem and availability of an oral form for linezolid, this combination opens new therapeutic avenues in the field of severe Gram-positive bacterial infections, including an option for outpatient parenteral antimicrobial therapy.
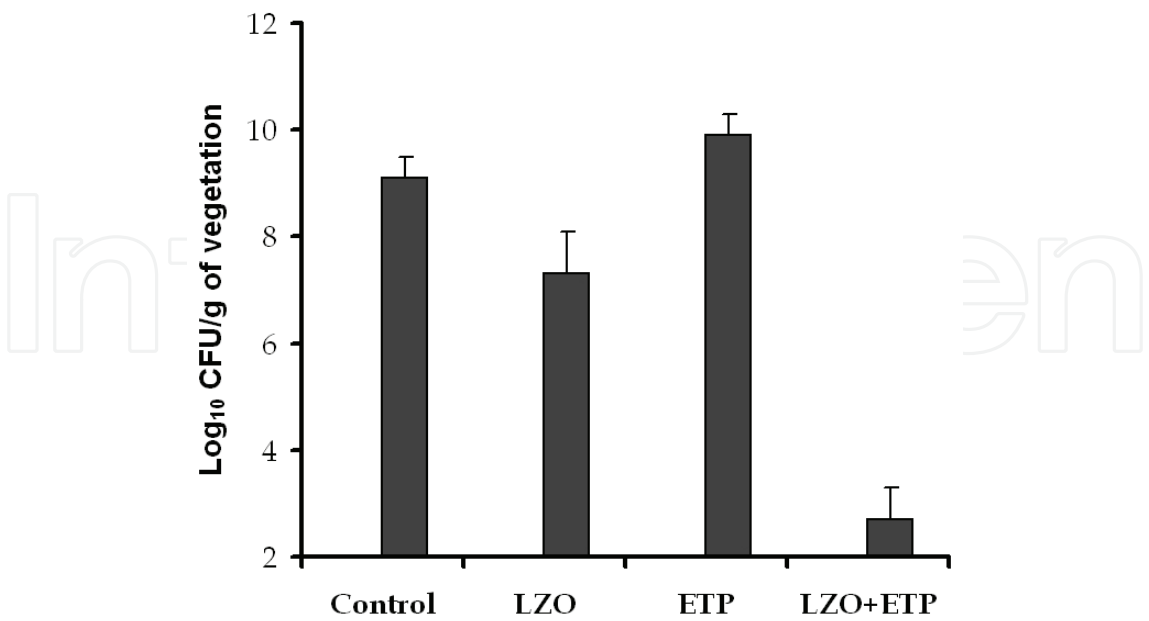

Fig. 6. In vivo synergy between linezolid (LZO) and ertapenem (ETP) against an MRSA strain in the endocarditis model. Error bars represent standard deviations (adapted from Jacqueline et al., 2006)

4. Quinupristin-dalfopristin: A therapeutic option for MRSA endocarditis?

Streptogramins inhibit protein synthesis by binding to the ribosomal 50S subunit, and the most frequent mechanism of quinupristin resistance encountered is target modification by methylation of an adenine residue in 23S rRNA (encoded by the *ermA*, *ermB*, or *ermC* gene). Constitutively expressed *erm* genes confer in vitro cross-resistance to macrolides, lincosamides, and streptogramin B. Quinupristin and dalfopristin are water-soluble injectable streptogramin B and streptogramin A antibiotics, respectively, whose combination in a 30:70 (wt/wt) ratio acts synergistically on Gram-positive bacteria (Bouanchaud, 1992). Despite in vitro susceptibility to quinupristin-dalfopristin, mutations in the L22 ribosomal protein are correlated with resistance to quinupristin in *S. aureus* (Bruni et al., 2000). The experimental model of infective endocarditis was used to address the efficacy of quinupristin-dalfopristin against susceptible and resistant *S. aureus* strains to quinupristin (but not quinupristin-dalfopristin). If quinupristin-dalfopristin remained active against quinupristin-susceptible MRSA after 4 days of treatment, a significant decrease of the activity was observed against a quinupristin-resistant strain. Nevertheless, the impact of the resistance on the activity of the combination can differ between studies (Batard et al., 2002; Pavie et al., 2002).

Combination with vancomycin improved the in vivo activity for susceptible and resistant strains (Pavie et al., 2002), but the benefit was less important against the resistant MRSA. Despite clinical interest in adding gentamicin (aminoglycosides) to quinupristin-dalfopristin, the combination showed no additive benefit against two MRSA strains (Batard et al., 2002). Although the lack of benefit may be due to the high efficacy of the monotherapies, these data did not argue for its use in clinical practice.

5. Daptomycin: Experimental evaluation of an old new drug

Daptomycin, previously called LY 146032, was first discovered in the 1980s by researchers at Eli Lilly, but an increase in creatine phosphokinase levels in serum in early clinical trials (probably related to skeletal muscle toxicity) led to initial abandonment of this promising compound (Tally & DeBruin, 2000).

Daptomycin is a novel lipopeptide antibiotic active against Gram-positive bacteria, including MRSA strains. It disrupts the bacterial cell membrane by forming transmembrane channels, and causes a calcium-dependent depolarization of the cellular membrane and inhibition of macromolecular synthesis leading to cell death (Silverman et al., 2003).

Daptomycin is a potential alternative to vancomycin for the treatment of severe MRSA infections, with benefits such as once-daily dosing, the lack of need for monitoring serum concentrations, and FDA approval for the treatment of right-sided endocarditis (Cubist, 2003). In vitro, the lipopeptide exerts its bactericidal action in a rapid (60 min) and concentration dependent way exhibiting more powerful activity than glycopeptides.

5.1 *In vivo* antibacterial activity of daptomycin: More bactericidal than glycopeptides?

The endocarditis model was used to assess the activity of daptomycin against MRSA and to confirm the highly bactericidal activity observed in vitro, especially in comparison with the

reference drug, vancomycin. Effectiveness against three MRSA strains, including one GISA strain (MU50), was tested using computer-controlled simulation to mimic the human dose of 6 mg/kg once daily (Jacqueline et al., 2011). After 4 days of treatment, daptomycin performed well against MSSA, MRSA, and GISA strains (daptomycin MIC= 0.5 mg/L) with a decrease of 5 $\log_{10}$ CFU/g (Figure 7).

More than 20 years ago, Kennedy & Chambers evaluated the potent in vivo activity of daptomycin, known at that time as a vancomycin-like lipopeptide, against *S. aureus* (Kennedy & Chambers, 1989). Vancomycin (25 mg/kg twice daily) was as effective as daptomycin (once-daily dose of 10 mg/kg) against both MSSA and MRSA strains in the endocarditis model. The next year Kaatz et al compared daptomycin (8 mg/kg q8hr) with the glycopeptides, vancomycin and teicoplanin (Kaatz et al., 1990). The conclusion of the study was interesting:

"We have established that, in the rabbit model and against the *S. aureus* test strains we used, daptomycin and teicoplanin-HD are as efficacious as vancomycin, but for certain strains of *S. aureus*, diminished susceptibility to both can develop during therapy" (Kaatz et al., 1990). Also at that time, the authors highlighted an important characteristic of daptomycin, its rapid propensity to select resistant variants during therapy. Despite high in vivo bactericidal activity, experimental models were not able to demonstrate that the rapid bactericidal activity of daptomycin observed in vitro was correlated with a better outcome in vivo than glycopeptides, vancomycin, or teicoplanin.
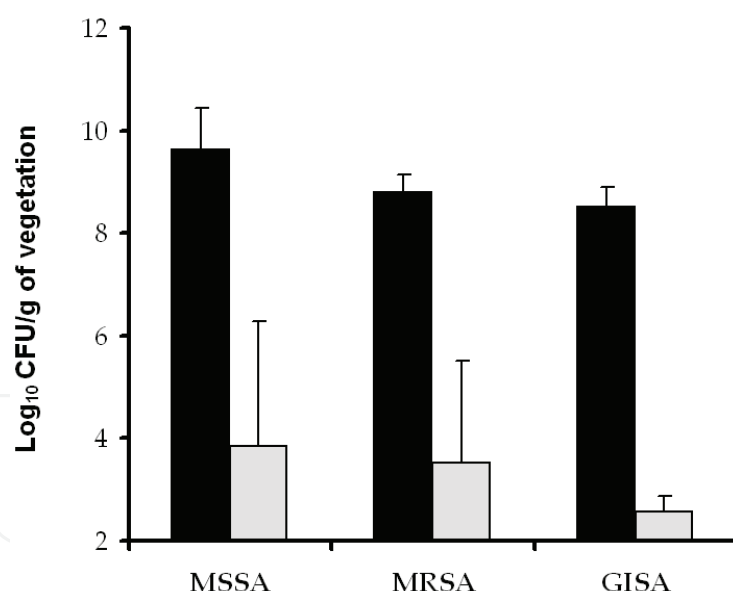

Fig. 7. In vivo activity of daptomycin (human-equivalent (HE) at 6 mg/kg/24 h) against MSSA, MRSA, and GISA strains after a 4-day treatment. Control animals (black); daptomycin-treated animals (grey). Error bars represent standard deviations (adapted from Jacqueline et al., 2011)

5.2 Emergence of daptomycin-resistance during therapy

The experimental endocarditis model is not considered an appropriate model for detection of the emergence of resistant variants. Nevertheless, emergence of daptomycin-resistant

variants was observed after only 4 days of therapy in a model using human-equivalent dosage (Jacqueline et al., 2011), as previously shown by Kaatz et al (Kaatz et al., 1990). This strongly suggests that combination therapy may be useful for daptomycin treatment of *S. aureus* infections. In the study by Jacqueline et al, the 6 mg/kg dosage regimen did not prevent the emergence of resistance in two animals (one in the MSSA group (8 animals) and one in the MRSA group (7 animals)) (Figure 8). Moreover, detection of resistant variants was correlated with a failure of daptomycin treatment in those animals. These data support the use of daptomycin dosages exceeding 6 mg/kg to increase bacterial killing and limit the risk of emergence of resistant variants during daptomycin therapy. Case reports have described safe and well tolerated daptomycin treatment at doses up to 12 mg/kg (Benvenuto et al., 2006; Cunha et al., 2006), but adequate dosing of daptomycin remains unresolved. A recent review about clinical utility of daptomycin in infective endocarditis specifies that adequate dosing of daptomycin for the treatment of left-sided or prosthetic valve S. aureus endocarditis should be ≥ 10 mg/kg/day (Cervera et al., 2011).
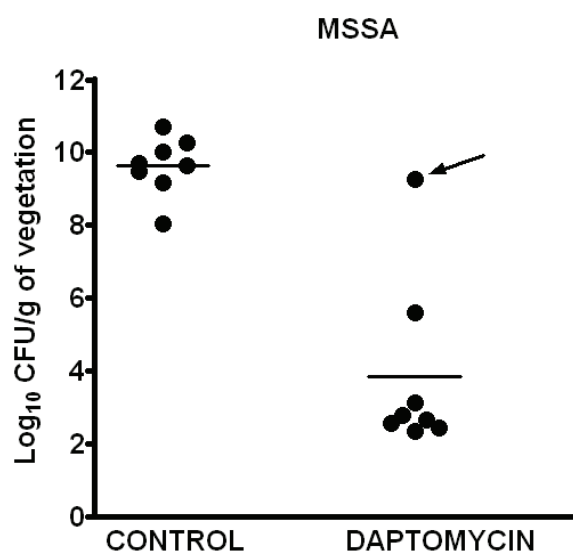

Fig. 8. Bacterial titers in vegetations infected by methicillin-susceptible *S. aureus* after 4 days of treatment with daptomycin (human-equivalent of 6 mg/kg once-daily). Arrows indicate animals with isolates exhibiting increased MICs to daptomycin (adapted from Jacqueline et al., 2011)

5.3 What partner drugs to use with daptomycin? An unresolved question

Faced with rapid emergence of daptomycin-resistant variants during therapy, clinicians should use a combination to limit the risk of resistance development. Rifampicin and gentamicin are often used in combination with antibacterial agents such as glycopeptides, beta-lactams, or linezolid. Two studies investigated the in vivo activity of daptomycin alone and in combination with rifampicin or gentamicin against different MRSA strains (LaPlante & Woodmansee, 2009; Miró et al., 2009). In experiments simulating human PK for all studied drugs, Miro et al demonstrated that daptomycin plus gentamicin was as effective as daptomycin alone (*P*=0.83). In addition, both were more active than daptomycin plus rifampicin (*P*<0.05) (Miró et al., 2009). Using an in vitro pharmacodynamic infection model with simulated endocardial vegetations, LaPlante & Woodmansee showed that daptomycin

monotherapy displayed better activity than daptomycin in combination with rifampicin or gentamicin (LaPlante & Woodmansee, 2009). These experimental data strongly show that the addition of gentamicin or rifampicin does not aid the in vivo activity of daptomycin. In vitro, Miro et al (Miro et al., 2009) showed a synergistic interaction between daptomycin and fosfomycin against MSSA and MRSA. Further in vivo and clinical studies are strongly needed to determine effective combinations for avoiding the emergence of resistance to daptomycin.

6. Tigecycline

Tigecycline is the first clinically-available member of a new class of broad-spectrum antibacterials, the glycylcyclines, which were specifically developed to overcome the two major mechanisms of tetracycline resistance (Zhanel et al., 2004). By binding to the 30S ribosomal subunit, tigecycline blocks the entry of aminoacyl-tRNA into the A site of the ribosome during translation (Slover et al., 2007). Like other protein synthesis inhibitors, the drug is bacteriostatic. Tigecycline is an obvious choice to treat MRSA endocarditis, however its potent in vitro activity against MRSA suggests that it should be used as a last resort.

Few studies have valuated the activity of tigecycline in experimental model of MRSA endocarditis. A study using a rat model of endocarditis showed a dose-effect relationship, with a >2-$\log_{10}$ decrease in bacterial counts with doses greater than 10 mg/kg/day for the course of treatment (Murphy et al., 2000). Using a computer-controlled simulation mimicking the human dose of 100 mg initially, followed by 50 mg twice daily, tigecycline demonstrated a significant and homogeneous activity against MSSA, MRSA, and GISA strains (Jacqueline et al., 2011). Nevertheless, the drug failed to exhibit a bactericidal effect versus the effect of the control treatment, despite 4 days of treatment (reduction, 2-$\log_{10}$ CFU/g compared with the controls) (Figure 9). This moderate activity could be improved
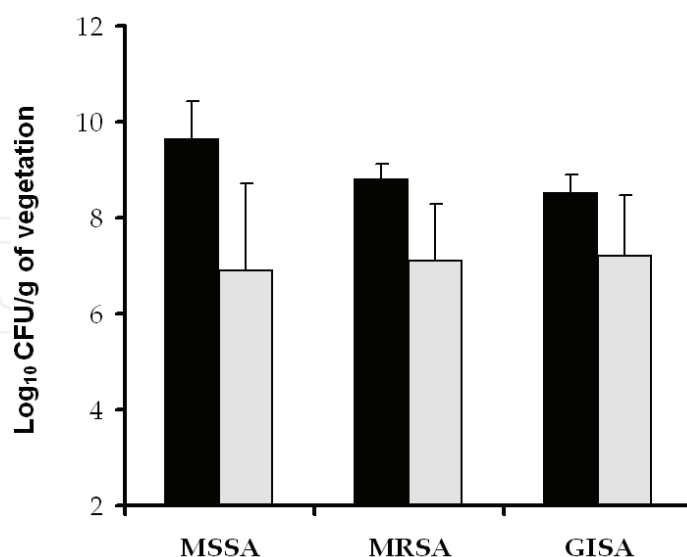

Fig. 9. In vivo outcome after a 4-day treatment of tigecycline (human-equivalent of 100 mg initially, followed by 50 mg twice daily) against MSSA, MRSA, and GISA strains. Control animals (black); tigecycline-treated animals (grey). Error bars represent standard deviations (adapted from Jacqueline et al., 2011)

by the use of a partner drug in combination with tigecycline. The addition of gentamicin significantly improved the killing activity of tigecycline in biofilm-forming *S. aureus* using an in vitro pharmacodynamic model (McConeghy KW & LaPlante, 2010). Finally, studies conducted in both animals and humans have demonstrated that tigecycline distributes widely into various tissues and body fluids (Rello, 2005), and peak serum concentrations do not exceed 1 mg/L, which may limit its utility in the treatment of bacteraemia and endocarditis (Paterson, 2006). The recommended dosage of tigecycline may be too low for the treatment of severe infections and assessment of higher doses in severe experimental animal models is needed.

7. Anti-MRSA cephalosporins exhibiting high affinity for PBP2A: A revolution?

PBPs catalyze transpeptidase or transglycosidase reactions, and are essential for the final stages of peptidoglycan synthesis (Spratt, 1977). β-lactam antibiotics, including penicillins and cephalosporins, inhibit PBPs. β-lactams are widely used because of their broad-spectrum activity and favorable safety profiles (Darville & Yamauchi, 1994). MRSA strains are not susceptible to the action of β-lactams because of the low affinity of β-lactams for PBP2a, an additional PBP encoded by the *mecA* gene and conferring methicillin resistance (Lim & Strynadka, 2002). Because β-lactam antibiotics are usually considered the most effective therapeutic option against *S. aureus* infections, researchers have sought to increase the affinity of β-lactams for the modified PBP2a. This is illustrated by the development of two cephalosporins, namely ceftobiprole and ceftaroline, which have potent antimicrobial activities against both Gram-positive (including MRSA) and Gram-negative bacteria. Ceftaroline binds to the four natural PBPs in *S. aureus*, but has maximum affinity for PBP2a (Villegas-Estrada et al., 2008). Because the marketing authorization for ceftobiprole was withdrawn in the United States and the European Union due to unfavorable assessments of the applications, ceftaroline is better studied.

7.1 Ceftaroline, a broad-spectrum cephalosporin active against MRSA

Ceftaroline is a novel broad-spectrum cephalosporin with potent activity against MRSA strains due to its strong affinity for *S. aureus* PBPs, including PBP2a, encoded by the methicillin resistance gene *mecA* (Lim & Strynadka, 2002). Ceftaroline acetate (PPI-0903) is an N-phosphono-water-soluble prodrug rapidly metabolized in vivo into the bioactive metabolite ceftaroline (PPI-0903 M). In vitro, bactericidal activity (≥ 3 $\log_{10}$ CFU/mL reductions) and time-dependent killing was observed for the cephalosporin from 4 times the MIC against an MRSA strain (Figure 10). Ceftaroline in vivo activity was assessed against two MRSA strains isolated from blood cultures (Jacqueline et al, 2007). The MRSA strain exhibited heterogeneous high-level methicillin resistance (methicillin MIC =128 mg/L), and the heterogeneous glycopeptide- intermediate *S. aureus* strain (hGISA) exhibited homogeneous resistance to methicillin (methicillin MIC >1,024 mg/L) and heterogeneous resistance to glycopeptides. Ceftaroline MICs/MBCs were 1/1 and 2/2 mg/L for the MRSA and hGISA strain, respectively. A human-like simulation was intended to provide apparent values of pharmacokinetic parameters close to those observed in healthy volunteers after a 1-h infusion of a 600-mg dose (approximately 10 mg/kg) of ceftaroline acetate: mean half-life
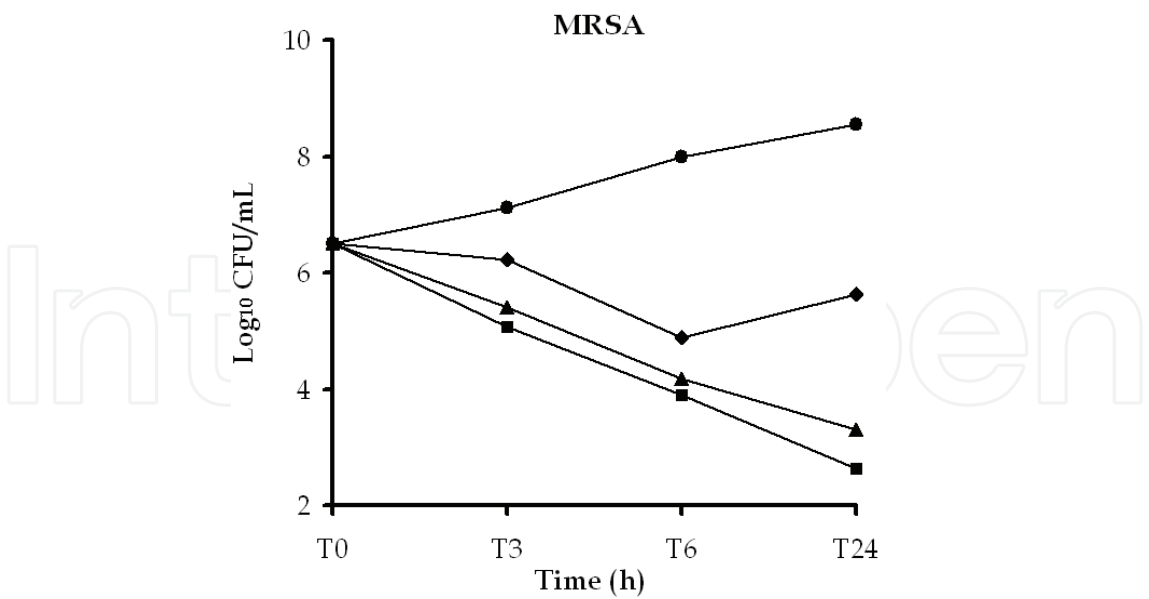
Fig. 10. In vitro activity of ceftaroline against methicillin-resistant *S. aureus*. Control (circles); ceftaroline at 1×MIC (diamonds); ceftaroline at 4×MIC (triangles), ceftaroline at 8×MIC (squares) (Author's unpublished data)

($t1/2$), 1.57 to 2.63 h; peak concentration (Cmax), 18.96 to 21.02 mg/L; and area under the curve (AUC), 56.08 mg.h/L (Cerexa, Inc., unpublished data). After simulation into the rabbit, the corresponding Cmax, AUC, and $t1/2$ values were 21.9±3.0 mg/L, 71.2 mg.h/L, and 2.4 h, respectively (Figure 11). Ceftaroline in vivo activity was assessed against two MRSA strains isolated from blood cultures (Jacqueline et al, 2007). The MRSA strain was a strain with heterogeneous high-level methicillin resistance (methicillin MIC =128 mg/liter), and
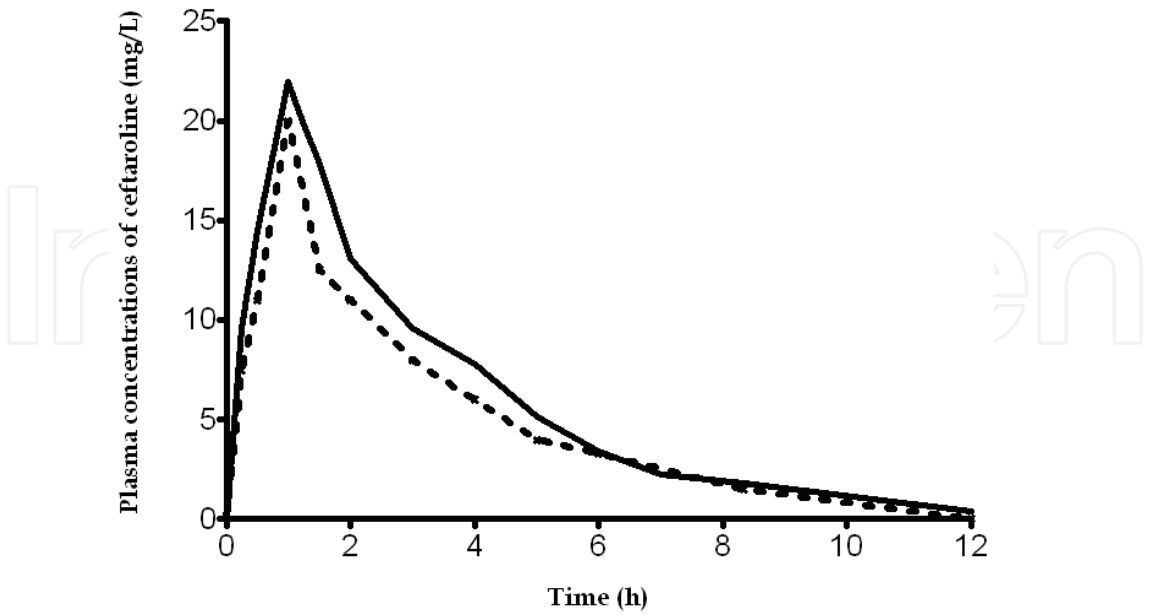

Fig. 11. Pharmacokinetics of ceftaroline in plasma after administration of a dose simulating a 600-mg dose in humans (dashed lines) and the corresponding human pharmacokinetics in animals (solid line) (adapted from Jacqueline et al., 2007)

the heterogeneous glycopeptide- intermediate *S. aureus* strain (hGISA) exhibited homogeneous resistance to methicillin (methicillin MIC >1,024 mg/liter) and heterogeneous resistance to glycopeptides.

Ceftaroline MICs/MBCs were 1/1 and 2/2 mg/L for the MRSA and hGISA strain, respectively. A human-like simulation was intended to provide apparent values of pharmacokinetic parameters close to those observed in healthy volunteers after a 1-h infusion of a 600-mg dose (ca. 10 mg/kg) of ceftaroline acetate: mean half-life ($t1/2$), 1.57 to 2.63 h; peak concentration (Cmax), 18.96 to 21.02 mg/liter; and area under the curve (AUC), 56.08 mg.h/liter (Cerexa, Inc., unpublished data). After simulation into the rabbit, the corresponding Cmax, AUC, and $t1/2$ values were 21.9±3.0 mg/liter, 71.2 mg.h/liter, and 2.4 h, respectively (Figure 11).

In this study, Jacqueline et al evaluated the in vivo activity of ceftaroline in comparison with vancomycin and linezolid, the two main therapeutic options available for the treatment of severe MRSA infections. In vivo outcome after a 4-day treatment is shown in Figure 12. Ceftaroline demonstrated excellent bactericidal and homogeneous activity against MRSA in the endocarditis model with at least a 6-$\log_{10}$ CFU/g decrease as compared to the control animals. In comparison, linezolid displayed moderate activity with a 2-$\log_{10}$ decrease. Vancomycin was as effective as ceftaroline against the MRSA strain (vancomycin MIC = 1 mg/L), but showed only bacteriostatic activity against the hGISA strain (vancomycin MIC = 4 mg/L). In addition, ceftaroline was able to sterilize 90% and 60% of the vegetations produced by the MRSA or hGISA strain, respectively, whereas vancomycin achieved sterilization of 67% and 0% of the vegetations, respectively.
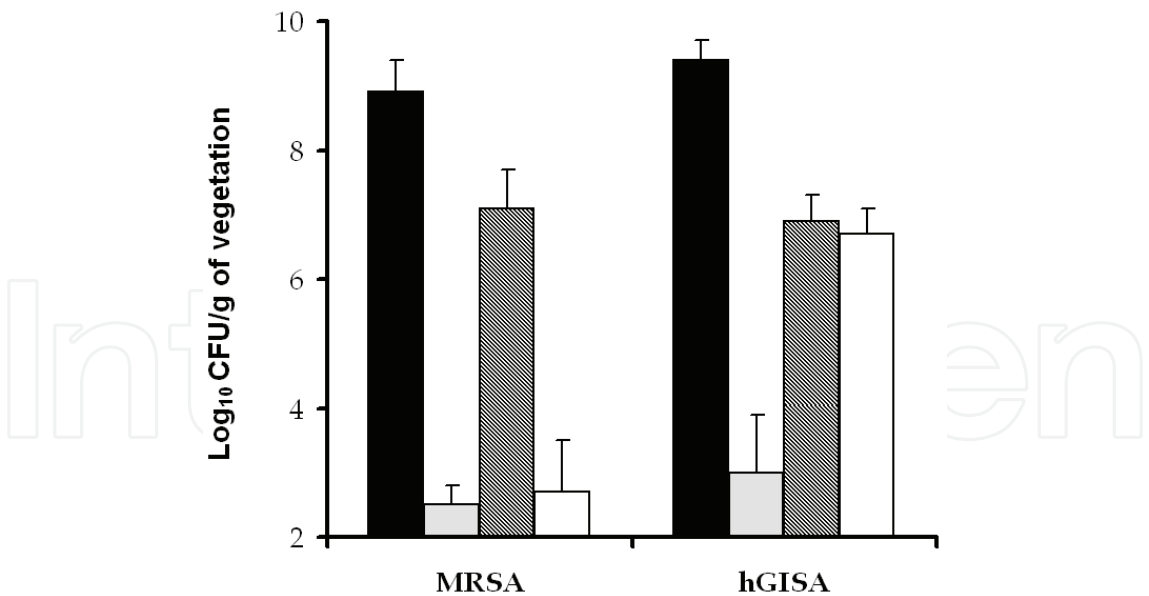

Fig. 12. Bacterial titers in vegetations infected by MRSA or hGISA strains after 4 days of treatment with ceftaroline (human-equivalent of 600 mg twice daily), linezolid (human-equivalent of 600 mg twice daily), and vancomycin (continuous infusion targeting a serum-steady state concentration of 25 mg/L). Control animals (black); ceftaroline-treated animals (grey), linezolid-treated animals (dashed lines), vancomycin-treated animals (white). Error bars represent standard deviations (adapted from Jacqueline et al., 2007)
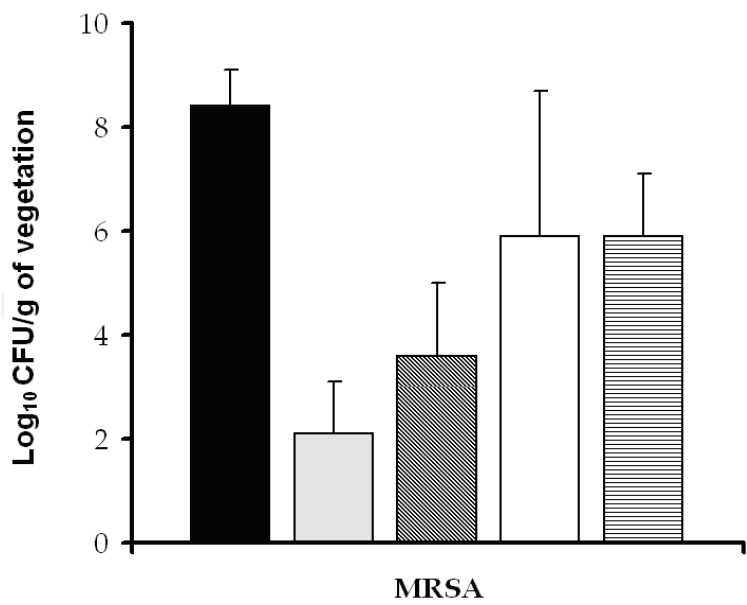
Fig. 13. Bacterial titers in vegetations infected by MRSA after 4 days of treatment with ceftobiprole medocaril (formerly BAL9141) (19 mg/kg of active drug [ceftobiprole] administered intramuscularly thrice daily), daptomycin (intravenous 18 mg/kg once daily), vancomycin (intravenous 30 mg/kg twice daily), and linezolid (75 mg/kg administered subcutaneously three times daily). Control animals (black); ceftaroline-treated animals (grey), linezolid-treated animals (dashed lines), vancomycin-treated animals (white). Error bars represent standard deviations (adapted from Tattevin et al., 2010)
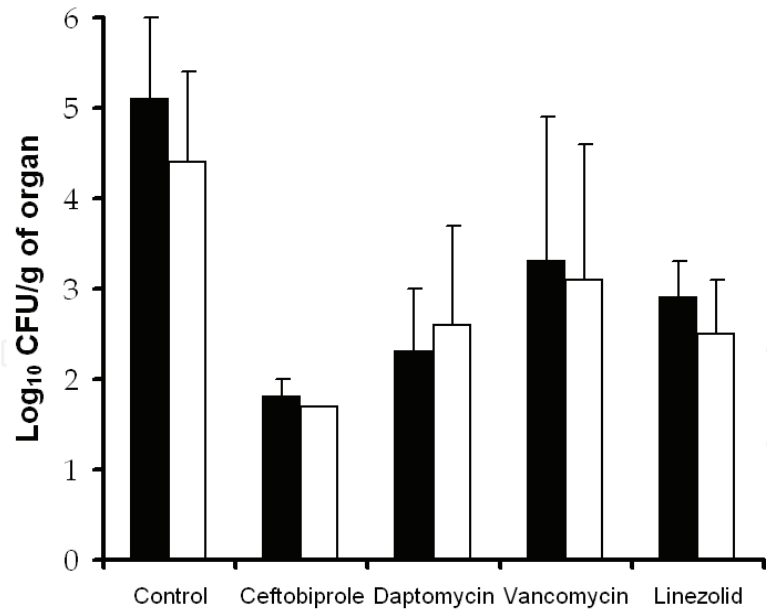

Fig. 14. Bacterial titers in spleens and kidneys after 4 days of treatment with ceftobiprole medocaril (formerly BAL9141) (19 mg/kg of active drug [ceftobiprole] administered intramuscularly thrice daily), daptomycin (intravenous 18 mg/kg once daily), vancomycin (intravenous 30 mg/kg twice daily), and linezolid (75 mg/kg administered subcutaneously three times daily). Spleen bacterial counts (black); Kidney bacterial counts (white). Error bars represent standard deviations (adapted from Tattevin et al., 2010)

Endocarditis studies evaluating the activity of ceftaroline are very limited. However, Tattevin et al have assessed the activity of ceftobiprole (formerly BAL9141), the other anti-MRSA cephalosporin with high affinity for PBP2a, against MRSA in comparison with vancomycin, linezolid, and daptomycin (Tattevin et al, 2010). Using experimental conditions similar to the conditions used by Jacqueline et al, they showed that the burdens of organisms in vegetations were significantly lower in ceftobiprole-treated rabbits than in rabbits treated with vancomycin, linezolid, or daptomycin (4-day treatment) (Figure 13). Moreover, the bacterial titers in spleens and in kidneys were significantly lower in ceftobiprole treated animals than in animals treated by linezolid or vancomycin (Figure 14). A study comparing ceftaroline and daptomycin, and using human-projected doses, demonstrated that both antimicrobial agents displayed highly bactericidal activity against *S. aureus* strains but ceftaroline achieved 100% sterilization of the vegetations infected by the MSSA, MRSA or GISA strains, whereas daptomycin sterilized 62%, 57% and 100% of the vegetations, respectively (Jacqueline et al., 2011).

7.2 Assessment of intramuscular administration of ceftaroline

Pathogens such as MRSA are becoming more virulent and are no longer confined to acute-care settings. There is a clinical need for new antibiotics that can be administered by intramuscular (IM) injection, facilitating outpatient antibiotic therapy for MRSA. The goals of the following experiments were to compare the pharmacokinetic parameters of ceftaroline after intravenous and IM administration and evaluate the in vivo activity of 3 different doses of ceftaroline against MRSA compared with teicoplanin as a positive control after IM administration by using an aortic valve endocarditis rabbit model (Jacqueline et al., 2010).

Six animals were divided into 2 groups, and a 20-mg/kg dose of the prodrug ceftaroline acetate was administered by IM injection into the right thigh or by a short intravenous infusion. Blood samples were obtained from the animals over 8 h (5, 10, 15, 30, and 45 min, and 1, 2, 4, and 8 h post-dose). Results suggest that ceftaroline has an excellent pharmacokinetic profile after IM administration. Bioavailability of IM administration exceeded 90% of intravenous infusion as calculated by AUC (Table 2). C_{max} was decreased with IM administration compared with intravenous infusion as ceftaroline was slowly released from the IM injection site. After IM administration of 5-, 20-, and 40-mg/kg doses, the C_{max} increased approximately in proportion to dose (5.18, 15.75, and 37.85 mg/L, respectively) and plasma half-life increased from 0.74 to 1.14 h (Figure 15). Compared with a short intravenous infusion, IM administration of ceftaroline resulted in longer plasma half-life and percentage of time that the concentration of ceftaroline remained above the MIC (%T>MIC), which is the most critical pharmacokinetic-pharmacodynamic parameter for efficacy (Table 2) (Andes & Craig, 2006).

Using the well-established rabbit endocarditis model, experimental endocarditis was induced with an inoculum of 10^8 CFU of a MRSA strain (ceftaroline MIC = 1 mg/L) with heterogeneous high-level methicillin resistance (methicillin MIC = 128 mg/L). Treatment was started 24 h after inoculation and antibiotics (ceftaroline and teicoplanin) were administered twice daily using the IM route for 4 days. Animals were randomly assigned to no treatment (controls), ceftaroline 40 mg/kg IM twice daily, ceftaroline 20 mg/kg IM twice daily, ceftaroline 5 mg/kg IM twice daily, or teicoplanin 20 mg/kg IM twice daily.

Pharmacokinetic parameter	Ceftaroline 20 mg/kg	
	IM administration	IV administration
C_{max} (mg/L)	16.1 ± 0.7	84.0 ± 7.5
T_{max} (minutes)	30	5
$t_{1/2}$ (hours)	0.9 ± 0.3	0.2 ± 0.00
AUC_{0-8h} (mg•h/L)	26.5 ± 2.9	29.2 ± 3.9
%T>MIC[a] (8-h period)	46.3 ± 2.0	22.5 ± 1.9
%T>MIC[a] (12-h period)	30.9 ± 1.3	15.0 ± 1.3

[a]Methicillin-resistant *Staphylococcus aureus* (MRSA) strain with ceftaroline MIC = 1 mg/L.
AUC = area under the concentration-time curve; C_{max} = peak concentration; T_{max} = time to peak concentration; $t_{1/2}$ = half-life; %T>MIC = time that drug levels in the serum remained above the MIC (Author's unpublished data).

Table 2. Pharmacokinetic parameters following single-dose intramuscular (IM) administration or short intravenous (IV) infusion of ceftaroline (mean ± SD)
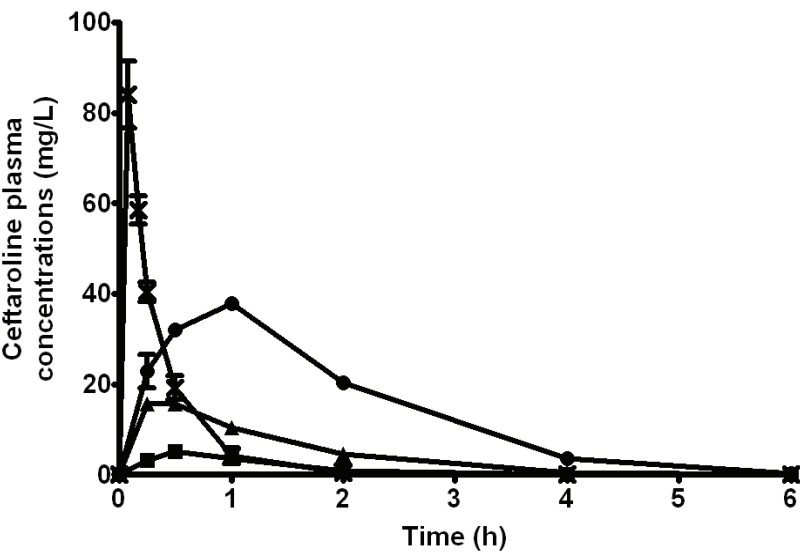

Fig. 15. Ceftaroline concentrations after intramuscular (IM) and intravenous (IV) administration in the rabbit (mean ± SD). ■ = 5-mg/kg IM dose; ▲ = 20-mg/kg IM dose; ● = 40-mg/kg IM dose; × = 20-mg/kg intravenous dose (Author's unpublished data)

The in vivo outcome after a 4-day treatment regimen and the rate of sterilization of the vegetations produced by the MRSA strain are shown in Table 3 (Jacqueline et al., 2010). A dose-dependent response was observed with sterilization rates for ceftaroline of 100%, 80%, and 33% for the 40-mg/kg, 20-mg/kg, and 5-mg/kg doses of ceftaroline, respectively. The difference between 20-mg/kg and 40-mg/kg doses was not statistically significant (*P*>0.05). In vivo bactericidal activity was consistent across all animals tested at the 40-mg/kg dose and for 9 of 10 animals at the 20-mg/kg dose of ceftaroline.

The %T>MICs attained with IM administration in this model were associated with bactericidal activity against MRSA (Tables 2 and 3). The efficacy of IM ceftaroline was similar to that achieved previously with intravenous ceftaroline administered in a regimen simulating the human dose (i.e., 600 mg twice daily) (Jacqueline et al., 2007). As expected, the positive control teicoplanin at 20 mg/kg IM displayed activity against the MRSA strain,

with a sterilization rate of 60%, and bacterial titers similar to those observed with vancomycin against the same MRSA strain (Jacqueline et al., 2007). Currently, teicoplanin is the only anti-MRSA drug approved as an IM injection; however, it is not available in the United States. Ceftaroline may be a valuable option for the IM treatment of MRSA infections. These findings are consistent with a favorable IM pharmacokinetic profile and strongly support the development of IM ceftaroline as a promising and effective therapeutic option for the treatment of severe MRSA infections.

Regimen	Mean ± SD $\log_{10}$ CFU/g of vegetation (no. of sterile veg./total no. of veg.) (%)
Controls	8.99 ± 0.47 (0/10) (0)
IM ceftaroline 40 mg/kg	2.45 ± 0.14 (10/10) (100)[a,b,c]
IM ceftaroline 20 mg/kg	3.14 ± 1.38 (8/10) (80)[a,d]
IM ceftaroline 5 mg/kg	5.26 ± 2.73 (3/9) (33)[a]
IM teicoplanin 20 mg/kg	3.07 ± 0.66 (6/10) (60)[a,d]

[a] $P<0.001$ vs controls; [b] $P<0.001$ vs IM ceftaroline 5-mg/kg regimen; Bonferroni's test after analysis of variance. [c] The titers for vegetations from all animals in the group were below the limit of detection. [d] $P<0.05$ vs IM ceftaroline 5-mg/kg regimen. IM = intramuscular.

Table 3. Bacterial titers in vegetations after 4 days of treatment with IM ceftaroline (5, 20, and 40 mg/kg) and IM teicoplanin (20 mg/kg) (adapted from Jacqueline et al., 2010)

8. Conclusions

Antimicrobial therapy is the cornerstone of the treatment of infective endocarditis. Although vancomycin still remains the standard treatment for severe MRSA infections, new therapeutic options are now available for the treatment of MRSA infective endocarditis. Introduction of linezolid, the first member of the oxazolidinone class, in the early 2000s, opened a new field of investigation that demonstrated that vancomycin was not the only solution against MRSA infections. Although linezolid was not the most effective option for endocarditis treatment, studies with the oxazolidinone demonstrated that experimental animal models are essential to (i) develop better understanding of the in vivo activity of a new drug, (ii) obtain important information not present in clinical trials.

Among the new recently available antimicrobial agents, experimental data strongly support daptomycin as an effective option in the treatment of MRSA endocarditis. The lipopeptide demonstrated homogeneous in vivo bactericidal activity against *S. aureus*, including methicillin-susceptible, methicillin-resistant, and glycopeptide-intermediate strains. Taking advantage of favourable drug pharmacokinetics (once-daily administration), daptomycin should be considered as a valuable alternative to vancomycin. Nevertheless, clinical use of daptomycin merit further investigation due to unresolved questions, such as adequate dosing, emergence of resistance during treatment, and appropriate combination therapy.

Ceftaroline fosamil (prodrug of the active metabolite) is a new, broad-spectrum cephalosporin recently approved in the USA for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. Data from both clinical trials (Corey et al., 2010; Wilcox et al., 2010; Rank et al., 2011) and animal studies

confirmed ceftaroline as a very promising new cephalosporin for the treatment of serious MRSA infections. Given its safety profile, bactericidal activity, and excellent activity against *S. aureus*, ceftaroline should play an important role in the treatment of MRSA infective endocarditis in the coming years.

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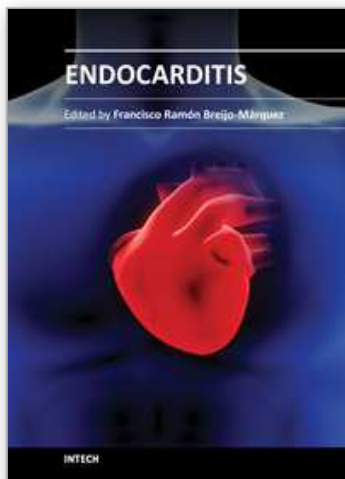
Endocarditis

Edited by Prof. Francisco Ramón Breijo-Márquez

Endocarditis is a disease that occurs as a result of the inflammation of the endocardium. It is an inflammatory process located in the inner lining of the cardiac chambers and native or prosthetic valves. It is characterized by colonization or invasion of the heart valve vegetations composed of platelets forming, fibrin and microcolonies of microorganisms, and occasionally of inflammatory cells. Other structures may also be affected, such as the interventricular septum, chordae tendineae, the mural endocardium or even intra-cardiac implants. The book covers, with scientific rigour, the most prevalent causes and current treatments of endocarditis, as well as the cases when the organs remote from the heart are affected by this disease.

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