Daptomycin: A Review of Properties, Clinical Use, Drug Delivery and Resistance

C. Vilhena and A. Bettencourt*

Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL), Faculty of Pharmacy, University of Lisbon. Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal

Abstract: Daptomycin is a branched cyclic anionic lipopeptide antibiotic that was discovered in the early 1980's but got the FDA approval only in 2003. This novel pharmaceutical molecule has demonstrated great *in vitro* activity against a wide range of aerobic and anaerobic gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. Daptomycin has a unique mechanism of action, not completely understood, involving a calcium-dependent dissipation of membrane potential leading to the release of intracellular ions from the cell and bacteria death. This antibiotic has been already approved for the treatment of patients with complicated skin and skin structure infections, right-sided endocarditis and bacteraemia. Local delivery of daptomycin is an emerging area of study. Current *in vitro* studies show that daptomycin can be eluted from polymethylmethacrylate, calcium sulfate and chitosan films. Emerging cases of resistance to daptomycin have been reported, commonly occurring by spontaneous mutations, and have been associated with prolonged use, osteomyelitis, acute myeloid leukemia and leucocyte adhesion deficiency syndrome. This review examines the most recent literature evidences on daptomycin molecular structure, mechanism of action, bacterial spectrum, clinical uses, local delivery, toxicity and resistance.

Keywords: Cyclic lipopeptide antibiotic, daptomycin, drug local delivery, gram-positive infections, MRSA, resistance.

1. INTRODUCTION

The ongoing explosion of antibiotic-resistant infections in the hospital and more recently in the community threatens to seriously compromise our ability to treat serious infections [1, 2].

The microorganisms of special clinical attention and increasing resistance are gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), among others [3].

The Centers for Disease Control and Prevention (CDC) estimate that the number of people developing a serious MRSA infection in 2005 (in USA), was about 94,360. The number of people is also remarkable that died during hospital stays related to these serious MRSA infections, approximately 18,650 [4]. For many years, MRSA remained a problem restricted to hospitals, intensive care units and other health care medical facilities. This situation has now changed with astonishing rapidity across the globe with the emergence and spread of community-associated MRSA [1, 5].

Skin and soft tissue infections, bone and joint infections, endocarditis and bacteraemia [3] are among the relatively common gram-positive cause infections. The use of last resort antibiotics such as vancomycin is necessary for the treatment of MRSA systemic infections [6, 7]. However, increasing data suggest that vancomycin is losing its clinical and microbiological potency resulting in the increased use of novel antibiotics such as daptomycin [8-10]. This review describes the chemistry, mechanism of action, bacterial spectrum, clinical use, drug delivery, toxicity and resistance of this novel pharmaceutical molecule with bactericidal activity against gram-positive pathogens, including methicillin-resistant and glycopeptides-resistant gram-positive cocci.

2. HISTORY AND CHEMISTRY

Daptomycin is the first approved member of a new structural class of antibiotics - the cyclic lipopeptides. It is a semisynthetic antibiotic that was discovered in the early 1980s, at Eli Lilly and Company, by supplying decanoic acid to the growth media of *Streptomyces roseosporus* during fermentation [11, 12]. Daptomycin was initially developed in the late 1980s and early 1990s but was ultimately shelved due to concerns regarding adverse effects, particularly drug-induced myopathy [13]. Cubist Pharmaceuticals Inc. licensed worldwide rights from Eli Lilly and Company in 1997 [11]. After an intensive role of clinical trials, the U.S. Food and Drug Administration (FDA) approval was obtained in 2003.

Daptomycin contains a C10-lipid side-chain (Fig. **1**) and it is produced by a non-ribosomal peptide synthetase (NRPS) mechanism in *S. roseosporus* [12]. It is composed of thirteen D- and L- aminoacids of which tend to form a cyclic frame linked by an ester bond between the *C*-terminus of kynurenine and the hydroxyl group of threonine [14].

The high water solubility of daptomycin is due to its predominantly acidic nature and the negative charge (3^-) at neutral pH. Its lipid tails and some hydrophobic amino acids warrant amphipathic properties [15].

*Address correspondence to this author at the Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal; Tel: +351 217946400; Fax: +351 217946470; E-mail: asimao@ff.ul.pt

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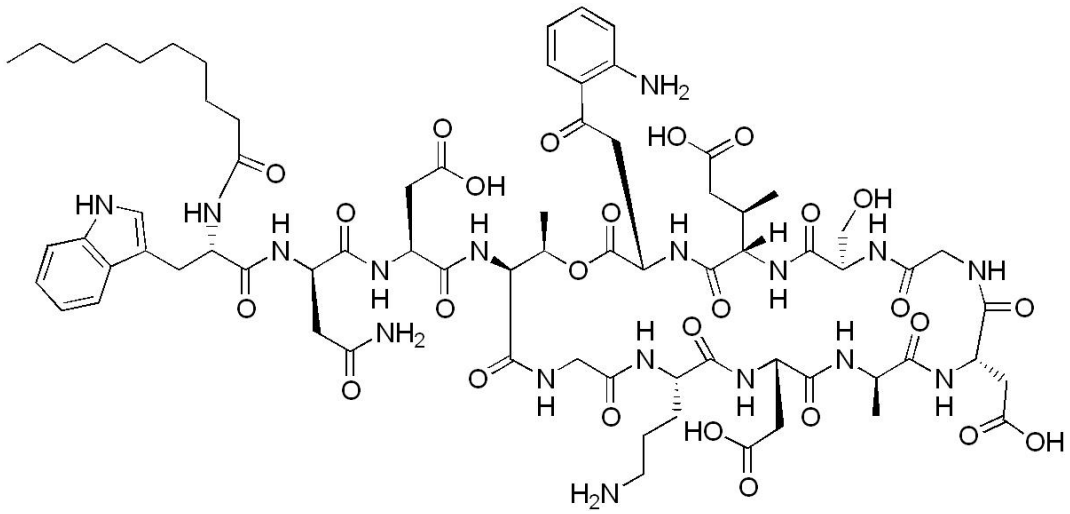

Fig. (1). Daptomycin molecular structure: IUPAC name: N-decanoyl-L-tryptophyl-D-asparaginyl-L-aspartyl-L- threonylglycyl-L-ornithyl-L -aspartyl-D-alanyl-L-aspartylglycyl-D-seryl-threo-3-methyl-L-glutamyl-3-anthraniloyl-L-alanine-lactone.

A current topic of interest is the generation of daptomycin derivatives. Recent efforts and advances in the generation of novel daptomycin derivatives by means of genetic engineering and chemoenzymatic approaches are recently highlighted and reviewed by Robbel and Marahiel [16].

3. PHARMACOLOGY

The pharmacology of daptomycin is well known. Some very good reviews on the subject have already been published [13, 15, 17-19]. Daptomycin has a rapid bactericidal activity and displays concentration-dependent killing. The drug has a significant post-antibiotic effect, with growth inhibition occurring up to 6 hours after exposure to the drug.

Daptomycin, administrated intravenously, has a once-daily dose. It exhibits linear pharmacokinetics with minimal drug accumulation [15]. Daptomycin distributes to all of the vascular tissues, in a small amount through the placenta, and does not cross the blood-brain barrier [20]. It is highly protein bound (≥ 90%) and does not interact with the P450 cytochrome, and consequently, there are no known cytochrome P450-mediated drug–drug interactions between daptomycin and other drugs [21, 22]. Renal excretion is the primary mode of elimination, with approximately 60% of the dose excreted unchanged in the urine. Some parameters of interest within the pharmacokinetic of this antibiotic are described in Table **1**.

As daptomycin is eliminated primarily by the kidney, a dosage modification is recommended for patients with creatinine clearance <30 mL/min, including those on hemodialysis or continuous ambulatory peritoneal dialysis [23]. Recently, Patel *et al.* [24] studied optimal daptomycin dosing in twelve adult patients receiving thrice-weekly hemodialysis (HD). It was concluded that administration of the daptomycin parent dose intra-HD or post-HD was optimal for the 48-h interdialytic period. For the 72-h interdialytic period, clinicians should consider increasing the dose by 50% to achieve more comparable area-under-the-curve (48-72) values.

Limited case reports concerns the dosage adjustment and safety of daptomycin in pregnant women.

Shea *et al.* [25] reported a successful daily treatment with daptomycin 260 mg (4 mg/kg) for 14 days, of a 27-week pregnant woman for pyelonephritis associated with vancomycin-resistant *Enterococcus faecium*. Recently, Stroup *et al.* [26] showed the safety use of daptomycin, consisting of a 6 mg/kg for 6 weeks therapy, of a 14-week pregnant patient for tricuspid valve endocarditis caused by *S. aureus*. Currently, in the absence of adequate and well-controlled trials in pregnant women, daptomycin should be used during pregnancy only if the potential benefit outweighs the possible risk.

Regarding the pediatric use of daptomycin, only relatively few studies have been published and limited data exist regarding dose guidance in patients under the age of 18 years [27-29].

Abdel-Rahman *et al.* [27] performed a pharmacokinetic analysis for single intravenous doses of daptomycin (8 or 10 mg/kg) in subjects aged 2 to 6 years, finding that both doses were well tolerated. Results from a multicenter open-label study with twenty-five children (12-17 years) lead the conclusion that the systemic drug exposure, after a single weight-adjusted daptomycin dose, is reduced in younger children compared with adolescents and adults, consequent to an apparent age-associated change in total plasma

Table 1. Pharmacokinetic Parameters of Daptomycin (Adapted from [21])

Antibiotic	Plasma concentration	Distribution Volume	Excretion	Elimination (%)	Protein Binding (%)
Daptomycin	9-10 mL/h/kg	0,1 L/kg	*Via* the kidneys	54%	92%

clearance [28]. In a very recent publication, Hussain *et al*. [29] reported the case of a neonate with MRSA bacteraemia successfully managed with daptomycin. It was found that dose requirements were substantially higher than those recommended for adults.

4. THE MECHANISM OF ACTION

The mode of action of daptomycin is a subject of continuing interest and despite a considerable number of research studies over the last 20 years, it has not been completely clarified [30-39].

Daptomycin exerts its rapid bactericidal effect by perturbing the bacterial cell membrane, a mode of action different from most other currently commercially available antibiotics [37]. First studies were conducted by Allen *et al*. [40] who reported that daptomycin inhibits the formation of precursor molecules utilized in peptidoglycan biosynthesis. Later it was suggested that another cell surface molecule, lipoteichoic acid, biosynthesis were the target site for daptomycin's mechanism of action [30-32]. However, more recent publications reported bactericidal activity against *Staphylococcus* and *Enterococcus* isolates even without the presence of lipoteichoic acid synthesis [33, 34].

Although, daptomycin´s mechanism of action is still not thoroughly elucidated, it is known that the main target is the bacterial plasma membrane of gram-positive bacteria and it is highly dependent on calcium ions [15]. Daptomycin antibacterial activity in the presence of magnesium cations was investigated by Ho *et al.* [41]. It was shown that the bioactivity was not completely abolished but minimum inhibitory concentrations (MICs) increased at least 32-fold.

A model for the bactericidal activity of daptomycin involving oligomerization of the antibiotic and disruption of the functional integrity of the cytoplasmatic membrane were proposed by Silverman *et al.* [33]. A clear correlation between dissipation of membrane potential and the bactericidal activity of daptomycin and the calcium-dependent release of potassium from daptomycin-exposed cells was demonstrated.

Jung *et al.* [35] proposed a more complex model and suggested that the bactericidal action of daptomycin is not solely due to the membrane depolarization but that daptomycin also interacts with several bacterial components, such as cell wall, various enzymes, RNA and DNA, similar to the multilevel mechanisms of action of antibacterial cationic peptides [15].

In recent years, novel methods for gaining insights into the mode of action of an antimicrobial agent have been developed as transcriptional profiling studies conducted by Muthaiyan *et al*. [39] to study the action of daptomycin on *S.aureus*. Results revealed that inhibition of peptidoglycan biosynthesis, either directly or indirectly, and membrane depolarization are parts of the mode of action of daptomycin. At present, the potential dual mode of action of daptomycin as revealed by transcriptional profiling studies is compatible with previous reports invoking both cell wall inhibition and membrane depolarization as modes of action of daptomycin [39].

5. ANTIBACTERIAL SPECTRUM

Daptomycin is active against a broad spectrum of aerobic and anaerobic gram-positive bacteria. It is not active against gram-negative pathogens because of its inability to penetrate the outer membrane of these microorganisms [15, 18]. One of the most striking features of daptomycin is its activeness against the most difficult to treat gram-positive micro-organisms, especially MRSA, glycopeptide-intermediate *S. aureus* (GISA) and VRE [15]. This antibiotic is also active against *Streptococcus pyogenes, S. agalactiae,* β-hemolytic Groups A, B, C and G.

Very interesting data on *in vitro* activity of daptomycin against European clinical isolates of gram-positive bacteria can be found in Hawkey [38]. Some remarkable results are the inhibition of all European and North America *S. aureus* strains at a daptomycin MIC of ≤ 1mg/L (100% susceptible).

Daptomycin is also a very promising agent in inhibiting organisms embedded in biofilm [42]. Stewart *et al.* [43] showed that fluorescently tagged daptomycin accessed the interior of *S. epidermidis* biofilm cell clusters within minutes. Structurally, biofilms are multi-layered cell clusters embedded in a matrix of extracellular polysaccharide (slime). Microorganisms growing in biofilms are signifi-cantly more resistant to killing because of much better protection against macrophages and antibiotics than their planktonic (free- living) counterparts [42, 44, 45].

Several *in vitro* studies [42, 43, 46-50], show that daptomycin alone or in combination with other antibiotics like rifampin [42, 49] is an important candidate for prevention and treatment of staphylococcal biofilm-related infections.

6. CLINICAL USE AND EXPERIMENTAL STUDIES

6.1. Daptomycin's Systemic Use

Daptomycin (brand name Cubicin®) is available only as an intravenous (IV) formulation. It is supplied as a lyophilized powder containing approximately 900 mg/g of daptomycin for a once-daily 30 min IV infusion.

Daptomycin was initially approved by the FDA, in 2003, for the nontopical treatment of complicated skin and skin structure infections (cSSSI) at a dose of 4 mg/kg of body weight per day administered IV [13]. Daptomycin´s approval was based on two randomized, multicenter, investigator-blinded trials comparing daptomycin to either vancomycin or a penicillinase-resistant penicillin (PRSP) in the treatment of cSSSI, including patients with wound infections, abscesses, diabetic and other ulcers [51, 52]. The outcome results demonstrated that clinical success occurred more rapidly with daptomycin than with comparable drugs.

In 2006, daptomycin was FDA approved as a once-daily therapy (6 mg/kg) for the treatment of *S. aureus* bloodstream infections (bacteraemia), including right-sided endocarditis caused by methicillin-susceptible *S. aureus* (MSSA) and MRSA based on the data from an open label randomized trial [15].

Ongoing clinical trials and experimental studies evaluate daptomycin's efficacy in the treatment of different pathologies as meningitis [53], ventriculitis [54], and peritoneal dialysis-associated peritonitis [55].

The use of daptomycin as a potential therapeutic option for patients with bone and joint infections such as MRSA osteomyelitis is also under investigation. Early clinical investigation of daptomycin in bone and joint infections unresponsive to antibiotics, such as vancomycin, has found a cure rate of approximately 80%, with a low incidence of adverse events and drug resistance [56]. Recently, complete reviews on this topic have been published [56, 57].

Considerable clinical experience with daptomycin in enterococcal infections is available in the form of published case reports, case series and the Cubicin Outcomes Registry and Experience (CORE®) database [58]. The most common enterococcal infections treated with daptomycin are: bacteraemia [59-61], infective endocarditis [62-64], skin and soft tissue infections (including surgical site infections) [51-65, 66] and bone and joint infections [67]. A small number of publications documenting the use of daptomycin for the treatment of other enterococcal infections have recently been appeared in the literature as for lower urinary tract infections [68] and peritonitis due to VRE [70, 71]. Recent review on the efficacy of daptomycin against enterococci in clinical settings was published by Canton *et al.* [72].

Daptomycin cannot be used to treat pneumonia and respiratory disease, due its inactivation in the presence of pulmonary surfactant [3, 73].

6.2. Daptomycin's Local Delivery

Daptomycin, due to its highly bactericidal activity against the majority of gram-positive human pathogens, including MRSA and VRE, is a good candidate for the application in systems for local drug delivery [74-76]. Local delivery of this antibiotic has potential, especially for musculoskeletal infections, due to resistant strains of bacteria. This is an emerging area of research, where few *in vitro* and *in vivo* animal model studies on daptomycin use in local drug delivery have been published [6, 74-82].

Published studies refer either to the incorporation of daptomycin in non biodegradable materials as polymethyl-methacrylate (PMMA) polymer [77-81] or in biodegradable ones [6, 74-76, 82]. The majority of papers published on the use of daptomycin in local drug delivery are preliminary studies. They refer to the description of daptomycin elution profile from the material matrix and to the evaluation of antibiotic antibacterial activity against *S. aureus*.

Kuechle *et al.* [78], McLaren *et al.* [79] and recently Weiss *et al.* [80] have shown that daptomycin maintained bioactivity after incorporation into different commonly used preparations of PMMA (cement and beads) and eluted into the surrounding medium.

A Mayo Clinic study evaluated the elution of daptomycin from PMMA in a continuous flow chamber designed to simulate *in vivo* conditions. It was shown that the antibiotic was released from PMMA *in vitro* at a rate similar to that of vancomycin [77]. Rouse *et al*. [81] demonstrated that daptomycin had similar activity and release from PMMA as vancomycin when used in a rat MRSA osteomyelitis model and suggested daptomycin may be a useful antibiotic for local treatment of resistant bacterial strains causing osteomyelitis.

The incorporation of daptomycin in degradable vehicles has been evaluated in bioceramics (calcium sulphate [74-76]) and in naturally occurring biopolymers as chitosan [6, 82].

Kanellakopoulou *et al.* [76] evaluated a synthetic crystallic semihydrate form of calcium sulfate as a biodegradable carrier for the *in vitro* elution of daptomycin. In this study, daptomycin was mixed directly with calcium sulphate powder. Elution lasted for 28 days. Daptomycin was incorporated within a calcium sulfate matrix in another two studies [74, 75]. Webb *et al.* [75] concluded that even at a low rate of elution, the drug amounts released, inhibited the growth of 10^4 colony-forming unit (CFU) of two different locally instilled isolates, one of *S. aureus* and another of *S. epidermidis.*

Daptomycin *in vitro* elution from a chitosan matrix was studied by Noel *et al.* [82] who found that daptomycin in the eluents inhibited the growth of *S. aureus*. Smith *et al.* [6] showed that a novel *in situ* loaded chitosan film has potential to absorb and deliver daptomycin at levels above *S. aureus* MIC for 72 hours.

Overall, on the basis of the research work, so far published studies suggest that daptomycin can be used in local delivery. It is a vital research area that warrants exploration. More studies are needed to evaluate the impact of daptomycin on the physical properties of materials [81], clarify antibiotic release profile, evaluate daptomycin elution *in vivo* and if local delivery of daptomycin demonstrates activity in the treatment of bone and joint infection.

7. TOXICITY

Daptomycin shows low occurrence of side effects comparable to other standard antibiotics [18]. The most frequently experienced potential side effects were gastrointestinal disturbances (ie, constipation, nausea and vomiting and diarrhea), reactions at the injection sites and headache [23]. All these effects were observed in frequencies similar to the comparator drugs (ie, 3%–6%) [83].

Although not frequent, the primary toxicity associated with daptomycin use is myopathy, manifested as muscle pain or weakness and associated with elevations in creatine phosphokinase (CPK). Such as, patients receiving daptomycin should be monitored for elevations in CPK and skeletal-muscle dysfunction namely development of muscle pain or weakness, particularly of the distal extremities [84]. Reviews on this subject report 1 case of severe myopathy after once-daily daptomycin administration [85] and 1 case of possible hepatotoxicity, ending after discontinuation of daptomycin [86].

On July 2010, FDA informed patients and healthcare professionals about the potential for developing eosinophilic pneumonia during treatment with daptomycin. Since 2007, the FDA has reviewed published case reports of daptomycin-associated eosinophilic pneumonia [87-90] and conducted a

review of post-marketing adverse event reports from the FDA's Adverse Event Reporting System (AERS). FDA's review identified 7 cases of eosinophilic pneumonia between 2004 and 2010 that were most likely associated with daptomycin.

8. RESISTANCE

Antibiotic resistance is a worldwide growing problem, requiring the development of novel agents to combat resistant organisms [1].

In the specific case of daptomycin, the risk of bacterial resistance is much less pronounced than for conventional antibiotics due to its unique mechanism of action and the fact that gram-positive microorganisms have a low potential for developing resistance [15]. The current susceptibility cut-off MIC of *S. aureus* isolates to daptomycin is set at 1mg/L and at 4 mg/L for *E. faecalis* and *E. faecium* [91].

Daptomycin has one characteristic that affects susceptibility testing. It requires free Ca^{2+} ions for activity *in vitro* and *in vivo*. Therefore, reliable *in vitro* susceptibility testing of daptomycin in clinical laboratories requires appropriate standardization of test media adjusted to a calcium content of 50 mg/L, otherwise resistant test may have falsely high MICs [92].

Clinical cases of emerging nonsusceptibility during daptomycin therapy were observed for *E. faecium* [93], methicillin-resistant *S. epidermidis*, methicillin-resistant *Streptococcus sanguis* [18], and MRSA [21, 94, 95], especially after prolonged drug exposure. Resistant mutants do not emerge spontaneously and more than 20 passages in the presence of daptomycin are needed to produce a small number of resistant isolates [96].

Although, a definitive mechanism of resistance to daptomycin has not yet been identified [1], recently it has been demonstrated that *in vitro* development of daptomycin resistance in *S. aureus* is correlated with the loss of an 81 kDa membrane protein [97]. Also it has been described in clinical daptomycin-resistance isolates point mutations in the *mpr*F gene and nucleotide insertion in the *yyc*F gene, encoding a lysylphosphatidylglycerol synthetase and a histidine kinase, respectively.

In the clinical setting, the emergence of daptomycin resistance is low until now. In an early study including 120 patients treated with daptomycin for bacteraemia and endocarditis caused by *S. aureus*, isolates with reduced susceptibility to daptomycin emerged in 6 patients with MICs increased during daptomycin treatment [84]. In the mentioned clinical study, daptomycin resistance developed in patients who had undrained abscess or retained hardware and therefore, it should be used cautiously on such population.

Based on the increase of MICs during therapy observed in some cases, it was concluded that daptomycin susceptibility should be monitored during therapy [98] and that dosing should be adequately high.

Special attention was raised by the clinical observation of reduced staphylococcal susceptibility to daptomycin after prior vancomycin treatment [99]. These findings may be explained by the shared target of vancomycin and daptomycin. Although, daptomycin and vancomycin have different mechanisms of action, both agents act on the bacterial cell wall [100] so the thickened cell wall may act as a physical barrier to penetration of the cell to both antibiotics [1]. This observation was confirmed by genetic investigations proving that the levels of proteins which form part of the bacterial response to the inhibition of peptidoglycan biosynthesis change similarly after exposure to either vancomycin or daptomycin [101]. Typical changes in the peptidoglycan composition occur in strains developing resistance to either vancomycin or daptomycin [102].

To date, most of the daptomycin-resistant isolates have been derived from severe ill patients with serious underlying conditions, often immunocompromised, and in many cases pre-treated with other antibiotics or receiving an inappropriate dose [38]. In the clinical setting, resistance has been associated with prolonged use [103], multiple co-morbidities [104], osteomyelitis [105], acute myeloid leukemia and leucocyte adhesion deficiency syndrome. The impact of resistance on the use of daptomycin is not great at the current level of experience with the drug. Close monitoring of resistance is essential to maintain the utility of daptomycin by reducing the likelihood of the emergence of resistant strains [98].

9. SUMMARY AND CONCLUSIONS

With the increasing numbers and types of resistant organisms, there is an increasing need for the development of new antimicrobial agents to treat gram-positive infections.

Daptomycin, a cyclic lipopeptide antimicrobial agent, shows a significant potency and spectrum against gram-positive species, including multidrug-resistant and strains, and may represent a reasonable therapeutic option for infections caused by these important pathogens. It is a semisynthetic antibiotic that exerts its rapid bactericidal effect by interaction with the cytoplasm bacterial membrane, a mode of action different from most other currently commercially available antibiotics. Daptomycin is indicated for cSSSIs, as well as bacteraemia and right-sided endocarditis caused by MRSA and MSSA strains. Though not approved, daptomycin might be considered also for systemic and local delivery use in joint infections and osteomyelitis. Preliminary experimental *in vitro* data obtained with different biodegradable and non-biodegradable carriers deserve further clinical investigation.

The rate of daptomycin adverse effects is comparable to other standard antibiotics. The most important adverse effect during daptomycin therapy is increased myopathies and the potential for developing eosinophilic pneumonia. Although, resistance to daptomycin is difficult to generate, recent data on emergence of resistance during therapy is a concern. Further studies on the subject are warranted.

In summary, daptomycin represents an important addition to the current panel of available antimicrobial agents with its novel mode of action, low occurrence of side effects, low resistance rates and high activity against key gram-positive pathogens, including resistant strains. Demand

for better knowledge will continue to drive intensive research into daptomycin´s derivatives, mechanism of action, clinical use, drug delivery, toxicity and resistance.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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