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Daptomycin: a new treatment for insidious infections due to gram-positive pathogens

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Summary

Daptomycin, a new lipopeptide antibiotic, is highly bactericidal against the majority of Gram-positive human pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. Its mechanism of action is unique resulting in the destruction of the membrane potential without lysing the cell wall. The mechanism of action of daptomycin, its antibacterial spectrum, the development of resistance and pre- and clinical studies are discussed in this review.

Key word: daptomycin, gram-positive pathogens

Introduction

The treatment of infections due to Gram-positive cocci, especially *Staphylococcus aureus*, coagulase-negative staphylococci and enterococci represents an increasing challenge for clinicians in the hospital environment and in the outpatient setting. Based on a survey of the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE), which has monitored bloodstream infections in hospitals of the United States from 1995 to 1998, 60% of nosocomial bloodstream infections have been caused by Gram-positive pathogens [1]. Coagulase-negative staphylococcal strains caused about 32% of bloodstream infections, followed by *Staphylococcus aureus* with 25.7% and enterococci with 11.1%. In a study including 24 179 cases of bloodstream infections conducted by Wisplinghoff et al. [2] between 1995 and 2002, an increase of resistant isolates of all major Gram-positive strains was documented, jeopardising the use of standard antibiotics. This paper presents the actual epidemiological situation for the essential Gram-positive pathogens.

Methicillin-resistant *Staphylococcus aureus* (MRSA), which has been an exclusive nosocomial pathogen for decades [3], has begun to spread within the outpatient community. The National Nosocomial Infections Surveillance (NNIS) study reports a rate of 59.5% of MRSA among *Staphylococcus aureus* infections in ICU patients in the United States for the year 2004 [4]. Interestingly, only a few clones are spreading throughout the world and are responsible for the high resistant rates. Recently, Oliviera et al. [5] were able to identify five MRSA clones accounting for around 70% of the over 3000 MRSA isolates recovered in hospitals mainly in Southern and Eastern Europe, South America, and the USA. The common feature of MRSA strains is the presence of the *mecA* gene, encoding the low affinity penicillin-binding protein 2A conferring resistance against methicillin and other beta-lactam antibiotics. Furthermore, MRSA are resistant to other antibiotic classes, even to quinolones. Quinolone resistance has become a hallmark of nosocomial MRSA. For decades, vancomycin was the only effective treatment for severe MRSA infections. Since 1996 however, strains with an intermediate resistance to vancomycin (VISA: vancomycin-intermediate *Staphylococcus aureus*), with MICs between 8 and 16 mg/L have been reported from Japan [6, 7] and since 1997 from the United States [8]. VISA strains harbour a thickened cell wall, trapping vancomycin molecules and so preventing them from reaching their targets, the cell wall precursors on the outside of the plasma membrane [9]. More alarming are recent reports of vancomycin-resistant *Staphylococcus aureus* with an MIC of 64 mg/L [10, 11]. The mechanism of resistance is based on a transfer of a transposon containing a *vanA* gene originating from vancomycin-resistant enterococci.

For decades, MRSA has been the paradigm of a nosocomial microorganism, causing severe infections. More recently however, it is evident that MRSA can be acquired in the community as well. Community-acquired methicillin-resistant *Staphylococcus aureus* infections usually occur in otherwise healthy children and young adults and represent an increasing problem worldwide [12]. A typical landmark of these community-acquired

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strains is the presence of the Panton-Valentine leukocidin, a cytotoxin leading to the destruction of host leukocytes and causing tissue necrosis. In general, these strains are more susceptible to non-beta-lactam antibiotics (eg, tretracyclines, trimethoprim-sulfamethoxazole) than hospital-acquired MRSA.

Until 1989, resistance to vancomycin was non-existent in enterococci in the United States. However, a dramatic increase in vancomycin-resistant enterococci has occurred since 1990, primarily in ICUs. Nowadays, the rate of vancomycin-resistant enterococci has reached around 30%, based on a recent NNIS report [4]. Interestingly, the vast majority of resistant strains are *E. faecalis*. Wisplinghoff et al. reported resistance rates around 70% in US hospitals for the period from 2000 to 2002 [2]. Vancomycin-resistant enterococci are able to alter the structure of the vancomycin target (the cell wall precursors) by exchanging an amino acid of the peptide side-chain from D-alanine-D-alanine to D-alanine-D-lactate.

Streptococcus pneumoniae, a common colonising microorganism of the pharynx, has also become resistant to penicillin and other antibiotic classes. Resistance has been triggered by exposure to antibiotics especially used for infections of the upper respiratory tract. In the United States, penicillin-resistance of pneumococci reached 40% in adults in a recent survey [13].

Confronted with the ubiquitous increase of resistance rates of these major human pathogens against conventional antibiotics, there is a need to develop new antibiotics which are highly active against Gram-positive microorganisms. Among the candidates, daptomycin, a new lipopeptide, is one of the most promising compounds. Here we present its mechanisms of action, its antimicrobial spectrum and its effectiveness in Gram-positive infections.

Structure and mechanism of action

Daptomycin is a cyclic lipopeptide antibiotic produced by fermentation of *Streptomyces roseosporus* [14]. Usually *S roseosporus* produces a variety of lipopeptides with different long-chain fatty acid tails. Daptomycin, which contains a C_{10}-lipid side-chain, is produced by addition of decanoic acid to the growth medium during fermentation [15]. Daptomycin contains 13 aminoacids of which 10 form a cyclic frame linked by an ester bond between the terminal kynurenine and the hydroxyl group of threonine (fig. 1).

The predominantly acidic nature and the negative charge (3-) at neutral pH are responsible for the high solubility in aqueous solutions of this antibiotic. Its lipid tails and some hydrophobic amino acids warrant amphipathic properties.

The antibacterial activity of daptomycin is highly calcium-dependent. Its antibacterial efficacy is optimal in the presence of a Ca^{2+} concentration around 1.25 mM (50 mg/L) and negligible in absence of Ca^{2+} [16–18]. This crucial Ca^{2+} level corresponds to levels usually measured in human serum [19]. The calcium-induced changes in the daptomycin structure lead to a relative increase of the hydrophobic surface of 5% and promote daptomycin oligomerisation [20]. Although the mechanism of action of daptomycin has not been completely clarified, the main target is the bacterial plasma membrane. The most conceivable scenario is a multistep process as proposed by Silverman et al. [21]. In a first step, calcium binds daptomycin which itself is weakly bound to the cytoplasmatic membrane. This leads to conformational changes and insertion into the plasma membrane and subsequent oligomerisation of daptomycin. In a second step, this oligomerisation of daptomycin builds channels causing membrane leakage and outflow of intracellular potassium.

The bactericidal activity of daptomycin is based on the depolarisation of the membrane

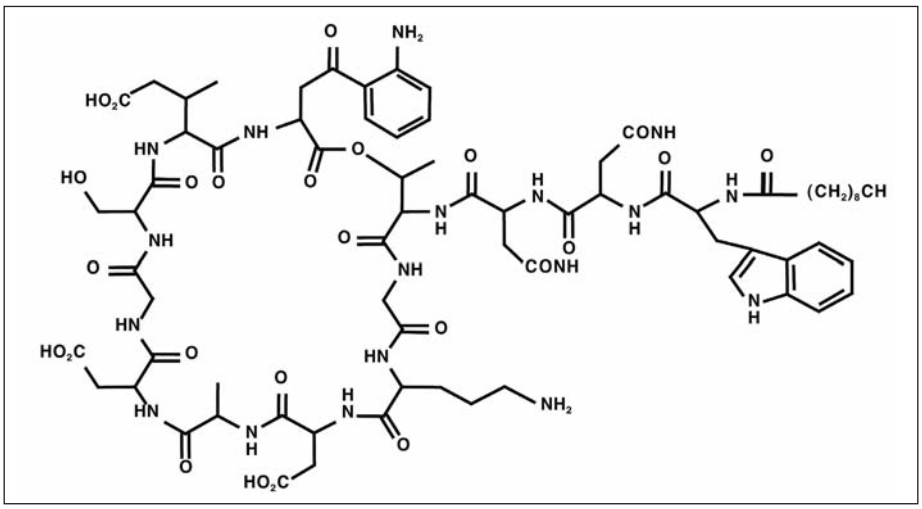

Figure 1
Structure of daptomycin.

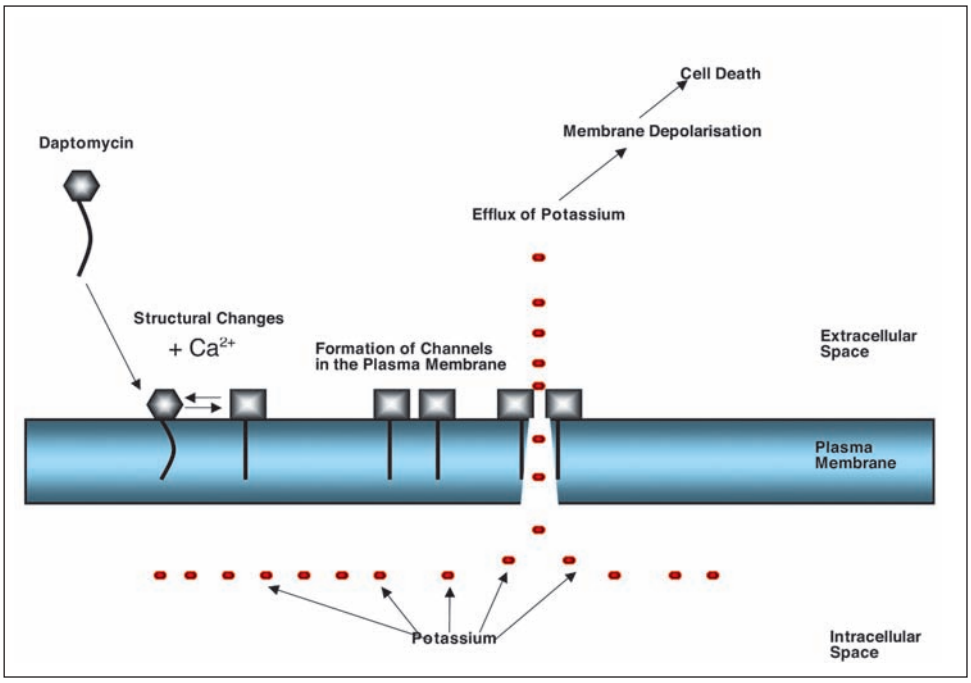

Figure 2

Scheme of the mechanism of action of daptomycin.

which leads to cell death. Jung et al. [20] proposed a more complex model and suggested that the bactericidal action of daptomycin is not solely due to the membrane depolarisation but that daptomycin also interacts with several bacterial components, such as cell wall, various enzymes, RNA and DNA, similarly to the multilevel mechanisms of action of antibacterial cationic peptides [22–25]. The mechanism of action of daptomycin is summarised in figure 2.

Antibacterial spectrum

Daptomycin is efficacious *in vitro* against a broad range of aerobic and anaerobic Gram-positive microorganisms, including multi-drug resistant strains [19, 26–35]. The MIC ranges, MIC_{50} and MIC_{90} for the different isolates are summarised in table 1. One of the most striking features of daptomycin is its activity against the most difficult to treat Gram-positive microorganisms, especially methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediate *S. aureus* (GISA) and vancomycin-resistant enterococci (VRE). For Staphylococcus species the MIC_{90} ranges lie around 0.5 mg/L. Enterococci (vancomycin-resistant strains included) are slightly less sensitive with MIC_{90} between 1 and 4 mg/L. In general, daptomycin has the highest activity against streptococci. Daptomycin is also effective *in vitro* against some anaerobic strains (eg, clostridium und propionibacterium species), against rare Gram-positive microorganisms, as corynebacterium, and some bacillus species. Daptomycin is also active against Listeria species with MIC around 2 mg/L. The MIC breakpoints have been determined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for staphylococci and streptococci (except for pneumococci) as follows: sensitivity: 1 mg/L and resistance >1 mg/L [36].

Daptomycin is not active against Gram-negative bacteria because of its inability to penetrate the outer membrane of these microorganisms [37, 38].

Resistance

In general, the widespread use of antibiotics represents a major risk for the development of resistance. The risk of bacterial resistance to daptomycin is much less pronounced than for conventional antibiotics due to its unique mechanism of action. Gram-positive microorganisms have a low potential for developing resistance against daptomycin *in vitro*. Resistant mutants do not emerge spontaneously and more than 20 passages in presence of daptomycin are needed to produce a small number of resistant isolates [39]. Many mutants showed significant growth defects and other mutants had lost their virulence. Recently, Kaatz et al. [40] demonstrated that *in vitro* development of daptomycin resistance in *S. aureus* correlated with the loss of an 81 kDa membrane protein. One conceivable explanation is that this protein interacts directly with daptomycin in the plasma mem-

Table 1
In vitro activity of daptomycin against gram-positive organisms

Species of Microorganism	N	MIC Range	MIC50	MIC90	Reference
Staphylococcus species					
S. *aureus*	3202	≤0.12–2	0.25	0.5	Streit JM. J. Antimicrob. Chemother. 2004;53:669–674
Coagulase-negative *Staphylococcus* spp.	838	≤0.12–2	0.25	0.5	
Enterococcus species					
E. faecalis (vancomycin-susceptible)	626	≤0.12–4	1	1	Streit JM. J. Antimicrob. Chemother. 2004;53:669–674
E. faecalis (vancomycin-resistant)	20	0.25–1	1	1	
E. faecium (vancomycin-susceptible)	97	≤0.12–8	2	4	
E. faecium (vancomycin-resistant)	55	0.25–4	2	4	
Streptococcus species					
viridans group streptococci	149	≤0.12–1	0.25	0.5	Streit JM. J. Antimicrob. Chemother. 2004;53:669–674
Other β-haemolytic streptococci (including Group A, B, C, Group F, Group G and *S. dysgalactiae*)	247	≤0.12–0.5	≤0.12	0.25	
Anaerobes					
Clostridium difficile	102	0.125–2	0.5	1	Tyrrell KL. Antimicrob Agents Chemother. 2006;50:2728–2731.
Clostridium perfringens	101	0.06–8	0.5	2	
Propionibacterium acnes	117	0.25–1	0.5	1	
Finegoldia magna	101	≤0.015–2	0.5	1	
Rare Gram-positives					
Corynebacterium species	21	≤0.03–8	≤0.03	1	Goldstein E. Antimicrob Agents Chemother. 2003;47:337–342
Bacillus species	10	≤0.12–8	1	2	Streit JM. J. Antimicrob. Chemother. 2004;53:669–674.
Listeria species	18	0.25–4	2	2	

brane. Friedman et al. [41] described in clinical daptomycin-resistant isolates point mutations in the *mprF* gene and nucleotide insertion in the *yycF* gene, encoding a lysylphosphatidylglycerol synthetase and a histidine kinase, respectively. In the clinical setting the emergence of daptomycin-resistance is low until now. In a prospective study including 120 patients treated with daptomycin for bacteraemia and endocarditis caused by *Staphylococcus aureus*, resistant isolates were documented in six cases (5%) with MICs increased during daptomycin treatment [42]. Following several years of experience under experimental settings however, development of resistance against daptomycin has been observed in clinical isolates of MRSA during daptomycin therapy [43–45]. A matter of increasing concern is the cross-resistance between vancomycin and daptomycin described in *Staphylococcus aureus*, although the strains were not exposed to daptomycin. The underlying mechanism is not clear but might be due to cell wall thickening of vancomycin-resistant strains, preventing daptomycin to reach the plasma membrane [9, 46, 47].

Pharmacodynamics

Once-daily dosing of daptomycin increases the antibacterial efficacy and minimises the side effects [48]. Daptomycin is effective in a dose-dependent manner with a long half-life around 8 hours and produces a post-antibiotic effect up to 6.8 hours [49]. Dosed once a day, daptomycin exhibits linear pharmacokinetics with minimal drug accumulation. Daptomycin is excreted primarily renally, with the majority of the drug remaining intact in the urine [48]. The penetration of daptomycin into the tissues varies from 9% into the lung [50, 51] to 68% into blister fluid [52]. Daptomycin penetrates only marginally (2%) into the cerebrospinal fluid of non-infected rabbits [53] but increases to 6% during pneumococcal meningitis [54]. Plasma clearance is low, due in part to high protein binding (87–94%) [55].

Clinical and experimental studies

Daptomycin is now approved by the FDA for the use in adults with complicated soft tissue and skin infections caused by *S. aureus*, streptococci and *E. faecalis* (vancomycin-susceptible strains only). In two international randomised phase III studies involving 1092 patients with complicated skin and skin-structure infections, daptomycin was not inferior to the comparators (penicillinase-resistant penicillins or vancomycin) with success rates of 83.4% and 84.2%, respectively. In the daptomycin group, 63% of the patients required only 4 to 7 days of therapy compared with 33% in the comparator regimen [56]. A recent review very carefully analysed the efficacy and safety of daptomycin in the treatment of bone and joint infections with cure rates about 81% [57].

Further two phase III studies were conducted to evaluate daptomycin in hospitalised patients with community acquired pneumonia (CAP). The objective of non-inferiority compared to ceftriaxone was not achieved [58, 59]. The cause of the failure of daptomycin in CAP was probably due to sequestration and inactivation of daptomycin by pulmonary surfactant [50].

Daptomycin is also FDA approved for bacteraemia and right sided endocarditis caused by MSSA or MRSA based on the data from an open-label randomised trial. Patients with *S. aureus* bacteremia with or without endocarditis were randomised as follows: 120 were treated with daptomycin (6 mg/kg) and 115 with a standard regimen (gentamicin plus either antistaphylococcal penicillin or vancomycin). In this study, daptomycin met the criterion of non-inferiority with a similarly successful outcome (44.2% for daptomycin versus 41.7% for the standard regimen). Most patients with persistent or relapsing infections had complicated bacteraemia associated with osteomyelitis or indwelling protheses. The adverse events were slightly but not significantly less frequent in the standard regimen group. However, in the standard regimen significantly higher renal impairment (18.1% *vs* 6.7% in the daptomycin group) was documented. Falagas et al. [60] recently published a systematic review of the literature underlining the effectiveness of daptomycin for the treatment of endocarditis with or without bacteraemia.

In the experimental rat endocarditis model daptomycin was very efficacious in the treatment of endocarditis due to susceptible and multi-resistant enterococci. Daptomycin was more efficacious than teicoplanin against the glycopeptide-susceptible strain and superior to all comparators against an ampicillin- and vancomycin-resistant strain [61].

The efficacy of daptomycin was also demonstrated against penicillin-resistant and penicillin- and quinolone-resistant pneumococci in the experimental rabbit meningitis model. Against both strains daptomycin was superior to the standard regimen based on a combination of vancomycin with ceftriaxone. Daptomycin managed to sterilise the CSFs of all animals within four hours [54].

In the same experimental model, daptomycin was superior to vancomycin against a methicillin-susceptible *S. aureus* [53]. Addition of rifampicin to daptomycin drastically improved its efficacy in staphylococcal meningitis (unpublished data). Combination of daptomycin with ceftriaxone, as potential empirical therapy, has also been successfully tested in this model (Abstract, 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 2006). The bactericidal but non-bacteriolytic property of daptomycin, which is a prerequisite for an ideal treatment for pneumococcal meningitis, has also been demonstrated in this model. Compared to ceftriaxone, a bacteriolytic antibiotic, daptomycin led to a minimal release of cell wall fragments, a major virulence factor of pneumococci during meningitis. At the end of daptomycin treatment no morphological alterations of the pneumococci could be detected by electronmicroscopy [62]. In the infant rat meningitis model, daptomycin produced significantly less cytokines (metalloprotease-9 and TNF-α) and cortical damage than ceftriaxone during pneumococcal meningitis [62, 63].

Conclusions

Daptomycin's unique mechanism of action, low propensity to induce resistance and highly bactericidal activity against major Gram-positive pathogens qualify daptomycin to play a major role in the treatment of infections caused by insidious Gram-positive pathogens. Its efficacy in the treatment of complicated skin infections is well established. Also promising data in the treatment of staphylococcal bacteraemia have been recently published and resulted in a second FDA indication. Its role in the treatment of bacterial meningitis, as monotherapy or combined with ceftriaxone is unclear, but the preliminary data obtained in the experimental rabbit model deserve further clinical investigation.

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