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Current Opinion in Pharmacology

# New antibiotics against gram-positives: present and future indications

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Gram-positive cocci are the most frequent aetiology of community and nosocomially bacterial acquired infections. The prevalence of multidrug-resistant gram-positive bacteria is increasing and is associated with high morbidity and mortality. New antibiotics will be available in the European market during the next months. This revision is focused on lipoglycopeptides, new cephalosporins active against methicillin-resistant *Staphylococcus aureus* (MRSA) and the new oxazolidinone, tedizolid. The purpose of this review is to describe their *in vitro* activity, pharmacokinetic and pharmacodynamic characteristics, and experience from clinical trials.

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**Current Opinion in Pharmacology** 2015, **24**:45–51

This review comes from a themed issue on **Anti-infectives**

Edited by **Federico Pea**

For a complete overview see the Issue and the Editorial

Available online 30th July 2015

http://dx.doi.org/10.1016/j.coph.2015.07.004



## Introduction

Gram-positive cocci are the most frequent aetiology of community and nosocomially bacterial acquired infections. Among others, *Streptococcus pneumoniae* is the leading cause of community-acquired pneumonia (CAP), *Staohylococcus aureus* of infectious endocarditis [1], *Staohylococcus epidermidis* of implant associated infections, and *Enterococcus* spp. are progressively growing as a nosocomial pathogens.

## Lipoglycopeptides

During the last years, three new semi-synthetic lipoglycopeptides have been developed, two derived from vancomycin (telavancin and oritavancin) and one from teicoplanin (dalbavancin). The main difference with classical glycopeptides is the presence of a lipid radical ('lipo'glycopeptides) that probably explains their major intrinsic activity [2–4]. The activity against gram-positive cocci is depicted in Table 1 [5–7].

## Telavancin

Telavancin has a $t_{1/2}$ of 7.5 h and a post-antibiotic effect against *S. aureus* of 1–4 h. The recommended dose is 10 mg/kg every 24 h (adjusted to total body weight) infused in 120 min that obtains a maximum serum concentration ($C_{max}$) of 70–80 mg/L. Since the protein binding is 93%, the predicted free serum concentration is $\geq$10 times the $MIC_{90}$ for the main microorganisms. The majority of the unmodified drug (69%) is eliminated by urine and a dose adjustment to 7.5 mg/kg every 24 h is recommended when creatinine clearance ($Cl_{cr}$) is 30–50 mL/min and 10 mg/kg every 48 h when it is <30 mL/min [5].

Telavancin efficacy has been compared with vancomycin 1 g every 12 h in two phase III, double blind randomized clinical trials (RCT) including 1867 patients with skin and soft tissue infections (SSTIs) that required parenteral therapy. *S. aureus* was the most common etiologic agent [8]. Clinical efficacy was similar, except in the subgroup of patients with advanced renal failure ($Cl_{cr}$ < 30 mL/min) in whom telavancin showed poorer efficacy (69% versus 89%, 95% CI: −40.7% to 5%, $P$ = 0.086) [5]. This finding suggests that the dose adjustment in this population needs to be revisited.

Telavancin has also been compared with 1 g every 12 h of vancomycin in 2 phase III, double blind RCT including 1503 patients with nosocomial pneumonia, 50% admitted in intensive care units and 30% associated with mechanical ventilation [9••]. The cure rate in the clinically evaluable population ($n$ = 654) was similar in both groups (82.4% versus 80.7%). In the subgroup of patients with monomicrobial infection due to *S. aureus*, telavancin was superior to vancomycin (84.2% versus 74.3%, difference: 9.9%, 95% CI: 0.7–19.1) and the difference was more evident when the MIC of vancomycin was $\geq$1 mg/L (87.1% versus 74.3%, difference: 12.5%, 95% CI: 0.5–23).

In all studies vancomycin dose was 1 g every 12 h and monitoring serum concentration was not mandatory while telavancin was adjusted to total body weight. The different dosing strategies could explain, at least in part, different cure rates but also the higher rate of gastrointestinal adverse events (nausea, vomiting, metallic taste) and nephrotoxity rate (16% versus 6%) among patients receiving telavancin. Currently, European regulatory agency decided to stop telavancin commercialization until having more data on its safety profile, particularly about renal toxicity.

**Table 1**

**Activity ($MIC_{90}$ in mg/L) of telavancin, dalbavancin and oritavancin against the main gram-positive cocci (from Refs. [5–7])**

| Microorganism | VCM | TLV[a] | ORV[a] | DLB[a] |
|---|---|---|---|---|
| Methicillin susceptible *S. aureus* | 1 | 0.5 | 0.06 | 0.06 |
| Methicillin resistant *S. aureus* | 1 | 0.25 | 0.06 | 0.06 |
| Methicillin susceptible coagulase-negative staphylococci | 2 | 0.5 | 0.06 | 0.06 |
| Methicillin resistant coagulase-negative staphylococci | 2 | 0.5 | 0.06 | 0.12 |
| Vancomycin susceptible *E. faecalis* | 2 | 1 | 0.03 | 0.06 |
| Vancomycin susceptible *E. faecium* | 1 | 0.25 | ≤0.008 | 0.12 |
| Vancomicina resistant *E. faecium* (Van A) | >16 | 8 | 0.12 | >4 |
| Vancomicina resistant *E. faecium* (Van B) | >16 | 2 | ≤0.008 | >1 |
| *S. pneumoniae* | 0.5 | 0.03 | ≤0.008 | 0.03 |

VCM, vancomycin; TLV, telavancin; DLB, dalbavancin; ORV, oritavancin.
[a] For staphylococci, EUCAST breakpoints for telavancin, oritavancin (only for *S. aureus*) and dalbavancin are: $S \leq 0.125$ mg/L and $R > 0.125$ mg/L. There are no breakpoints for enterococci.

## Oritavancin

The most relevant data is the potent activity against vancomycin resistant *Enterococcus* spp. (VRE) [6]. It is important to remark that *in vitro* activity performed before 2008 is not reliable since it was done without polysorbate-80 that avoids the adherence of oritavancin to plastic.

The most peculiar pharmacokinetic characteristic of oritavancin is represented by the three-compartimental pharmacokinetic behaviour with a rapid initial distribution ($\alpha$-$t_{1/2}$ of 2.29 h) followed by a slower secondary distribution phase ($\beta$-$t_{1/2}$ of 13.4 h) and a slow terminal elimination ($\gamma$-$t_{1/2}$ of 245 h) [10]. The administration of a single dose of 1200 mg, considering a protein binding of 90%, maintains a free serum concentration ≥0.25 mg/L (4-fold the $MIC_{90}$ for gram-positive cocci) for 7–10 days. Experimental models of *S. pneumoniae* and *S. aureus* infections support this dosage [11]. Oritavancin may achieve a high intracellular concentrations [12•] and acts against bacteria which are in stationary phase, which are embedded in biofilms [13,14] and against both extracellular and intracellular small colony variants (SCV) of *S. aureus* [15,16]. Although no recommendation for dosage adjustment in renal insufficiency has been made, the low urine concentrations observed at day 7 after single administration suggests that no adjustment is necessary.

Single dose of oritavancin (1200 mg) infused in 3–4 h has been compared with vancomycin (1 g every 12 h or 15 mg/kg every 12 h) in a double blind RCT (SOLO I) in SSTIs that included 954 cases. Clinical efficacy and adverse events were similar in both arms [17••].

## Dalbavancin

Although dalbavancin activity against staphylococci is similar to that of oritavancin, dalbavancin is not active against VRE [7]. The long $t_{1/2}$ (170–210 h) could justify one single dose for the treatment of SSTIs. However, a RCT evaluating a single dose of 1100 mg, 1000 mg followed by 500 mg one week after or a comparator showed a cure rate of 62%, 94% and 76%, respectively [18]. Using the best dose, dalbavancin was compare to vancomycin in two RCT (DISCOVER 1 and 2) in SSTIs. They demonstrated similar results in terms of efficacy and rate of adverse events [19••]. A phase 2, open-label RCT randomized patients with catheter-related bloodstream infections due to *S. aureus* or coagulase-negative staphylococci to dalbavancin ($n = 33$) at the dosage of 1000 mg followed by 500 mg one week later, or vancomycin ($n = 34$) at the dosage of 1 g every 12 h for 14 days. The success rate was significantly higher in the dalbavancin group (87% versus 50%, $P < 0.05$) [20,21]. An ongoing trial is evaluating the efficacy of dalbavancin in the treatment of SSTIs administered as one single dose of 1500 mg in comparison with that of two subsequent doses (1000 mg followed by 500 mg one week later). A theoretical advantage of this drug versus oritavancin for treating outpatients is that the infusion time is consistently shorter (30 min versus 3–4 h).

## New anti-MRSA cephalosporins: ceftobiprole and ceftaroline

Beta-lactams are the first choice for the treatment of methicillin-susceptible *S. aureus* (MSSA) infections since they obtain the highest cure rate in comparison to other alternatives, mainly vancomycin [22]. Ceftobiprole and ceftaroline are two new cephalosporins with high affinity for the penicillin binding protein (PBP) 2A of *S. aureus* and for the PBP2X/2A/2B of *S. pneumoniae* [23,24]. The *in vitro* activity of ceftobiprole and ceftaroline against the main gram-positives is shown in Table 2 [25–27].

## Ceftobiprole

Ceftobiprole is stable in front of class A, B and C beta-lactamases of MSSA and it does not show inoculum effect when tested against a relatively high inoculum ($10^7$ UFC/mL) [28,29•]. By contrast, it has been described that *S. aureus* strains with vancomycin MIC > 1 mg/L have more frequently high ceftobiprole MIC (≥2 mg/L) [30]. Ceftobiprole is a low water soluble molecule at physiological pH and for this reason is administered as a pro-drug