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The recent evolution of therapeutic weapons against resistant Gram-positive microorganisms

Running head: Management of multiresistant Gram-positive pathogens
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Abstract
Multiresistant Gram-positive cocci, including Staphylococcus aureus, the group of coagulase-negative staphylococci, Enterococcus faecalis and Enterococcus faecium, as well as Streptococcus pneumoniae and other streptococci, represent emerging pathogens. This issue is especially concerning in the setting of immunocompromised, hospitalized patients, in particular when surgery, invasive procedures, or prosthetic implants are carried out, patients are admitted in intensive care units, or underlying chronic disorders and immunodeficiency are of concern, and broad-spectrum antibiotics are widely used in the environment; moreover, a community spread of resistant Gram-positive cocci has been recognized during recent years. The spectrum of antimicrobials available for an effective management of these relevant infections is significantly threatened by the emerging of methicillin-resistant and more recently glycopeptide-resistant strains. The streptogramine association represented by quinupristin/dalfopristin, the oxazolidinone derivative linezolid, and the recently licensed daptomycin and tigecycline, together with a number of glycopeptides, fluoroquinolones, cephalosporins, and other experimental compounds, represent an effective response. It is due to the innovative mechanisms of action of these compounds, their maintained or enhanced activity against multiresistant pathogens, their effective pharmacokinetic/pharmacodynamic properties, their frequent possibility of synergistic activity with other compounds effective against Gram-positive pathogens, and a diffuse potential for a safe and easy administration, also to compromised patients. The main problems related to the epidemiology of multiresistant gram-positive infection, the potential clinical indications of all recently available compounds compared with the standard of care of treatment of resistant Gram-positive infections, and updated data on efficacy and tolerability of all these compounds, are updated and outlined on the ground of a review of recent literature evidences.

Key words: Enterococci, glycopeptides, Gram-positive organisms, novel antimicrobial agents, oxazolidinones, Pneumococci, resistance, Staphylococci, streptogramins

Introduction
Especially among nosocomial pathogens, since early eighties a significant reversal of tendency was observed, characterized by a predominance of Gram-positive over Gram-negative bacteria (which represented the most relevant concern in the two prior decades)1-4. The increased life expectancy of the general population, the extended survival of patients with underlying immunodeficiency and/or chronic disorders, the advances of surgical techniques and those of invasive diagnostic and therapeutic procedures and bone marrow and solid organ transplantation, the diffusion of prosthetic materials and other biocompatible materials, and the increased resort to endovascular catheters and devices, represent emerging risk factors for massive bacterial colonization, which turns into an increased risk of local and systemic infection. Moreover, the increased and prolonged administration of broad spectrum antimicrobial agents and their associations, and the wide employment of antifungal agents, all as therapeutic and/or prophylactic compounds in the immunocompromised to otherwise at risk host, extensively contribute to the re-emerging of Gram-positive pathogens, especially via a prolonged hospital admission. Among these microorganisms, both coagulase-positive and coagulase-negative Staphylococci and Enterococci are of particular concern in the hospital setting, because of their rising frequency, the severity of associated diseases, and the unpredictable spectrum of drug resistance5,9,10. This is also increasingly true in the pediatric population11,12,13.

On the other hand, in the community setting Pneumococci and other Streptococci remain the main respiratory pathogens, and their antibiotic resistance rate are progressively on the rise, although both macrolide- and beta-lactam resistant pathogens does not pose very striking problem in the majority of countries, until now2,4,8,12.

Finally, the progressive shortening of hospitalization favors the spread of hospital-acquired, nosocomial pathogens into the community, where there is increasing concern for the rising retrieval of microorganisms with a resistance pattern similar to that observed at the hospital, which may be responsible...
for an increasing failure of empiric therapeutic lines, when antimicrobial agents are administered before obtaining culture and in vitro resistance testing, or when cultures and sensitivity testing are not available or are still pending\textsuperscript{2,5,10,13}.

Together with the ever-evolving modification of multiple environmental conditions, the changing features of both host and its microbial flora, and the broadened spectrum of currently available anti-infective compounds (Table 1), other emerging features become prominent, related to the pathomorphism of clinical features of a number of infections caused by Gram-positive pathogens, often those which show an evident potential for the development and spread of antimicrobial resistance. While streptococcal scarlet fever, and post-streptococcal complications like rheumatic disease and acute glomerulonephritis virtually disappeared in the past two decades, a number of other disorders caused by highly pathogenic Streptococci gained increasing frequency and importance in the last decades, including severe cellulitides, necrotizing fascitiis, and toxic shock syndrome (TSS). When considering Staphylococci, the major pathogen \textit{Staphylococcus aureus} steadily ranks at the first place among the majority of nosocomial pathogens, and even in this case novel syndromes characterized by the predominant role of bacterial toxemia are progressively emerging: the so-called staphylococcal scalded skin syndrome (or SSSS) is the paradigmatic clinical picture. Moreover, severe staphylococcal skin and soft tissue lesions have been attributed to the action of the Panton-Valentine leukocidin\textsuperscript{10}. Remarkable levels of morbidity and mortality are also attributed to coagulase-negative cocci (i.e. \textit{Staphylococcus epidermidis} and related organisms), especially when vascular or bone-joint prosthetic devices, central vascular lines, ventilator-associated pneumonia, and parenteral nutrition are of concern. Until a couple of decades ago, the same coagulase-negative staphylococci were mostly considered as trivial contaminants, or part of the normal saprophytic human flora.

In the developed countries of the world, the rate of methicillin (oxacillin) resistance of \textit{Staphylococci} among hospitalized patients may overcome 20-25\% of cases, with an extremely elevated frequency registered in specialized intensive care units and bone marrow and solid organ transplant units\textsuperscript{1,4,5,8,13,14}. A relevant multicentre survey of nosocomial bacteremia carried out in 49 United States hospitals during a three-year period, allowed the authors to recognize a 64\% prevalence of Gram-positive pathogens, among over 10,000 identified microorganisms\textsuperscript{12}. When analyzing the frequency of single microorganisms, coagulase-negative \textit{Staphylococci} (32\%) preceded \textit{S. aureus} (16\%), and Enterococci as a whole (11\%). The overall level of methicillin resistance ranked around 29\% of isolated organisms, with peaks reaching 80\%, when coagulase-negative \textit{Staphylococci} were specifically considered\textsuperscript{13}. In a Spain nationwide \textit{S. aureus} prevalence study, an overall increase in resistance to most antimicrobials was detected, mainly to oxacillin (from a frequency ranging from 1.5\% and 32.5\% in the year 1986, to 31.2\%-61.3\% in the year 2002), although all isolates remained susceptible to available glycopeptides, quinupristin/dalfopristin and linezolid, and a surprisingly low resistance rate remained towards cotrimoxazole (0.5-2.1\%)\textsuperscript{15}. The same phenomenon has been observed at a large teaching Hospital in Taiwan, where the noticeable rise of methicillin-resistant \textit{Staphylococci} and vancomycin-resistant Enterococci paralleled the increased prescription of glycopeptides, broad-spectrum beta-lactams, carbapenems, and fluoroquinolones\textsuperscript{16}.

<table>
<thead>
<tr>
<th>Table 1. The classical factors which are known to act on the antimicrobial choice.</th>
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<tbody>
<tr>
<td><strong>Pathogenic microorganisms</strong></td>
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<tr>
<td>• emerging and re-emerging of different microbial organisms during time and in different settings</td>
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<tr>
<td>• development and transmission of resistance determinants due to the selective “pressure” exerted by the extensive use of broad-spectrum antimicrobial compounds in the general population and in the hospitalized patients, as well as in the environment</td>
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<tr>
<td><strong>Host features</strong></td>
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<tr>
<td>• increased mean age of patients, due to increased life expectancy</td>
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<td>• underlying immunodeficiency status and relevant co-morbidities</td>
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<td>• (multiple) concurrent disorders, and end-organ failure (i.e. kidney and liver failure)</td>
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<tr>
<td>• hospitalization, institutionalization</td>
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<tr>
<td>• invasive diagnostic and therapeutic procedures, intravascular lines</td>
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<tr>
<td>• major surgery, prosthetic implants and devices</td>
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<tr>
<td><strong>Environmental features</strong></td>
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<tr>
<td>• need of a permanent and repeated local microbiological monitoring, compared with national and international surveillance data</td>
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<tr>
<td>• study of patient’s colonization features (from a qualitative and a quantitative point of view), as predisposing conditions to invasive infection</td>
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<tr>
<td>• consideration of environmental reservoirs</td>
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<tr>
<td>• spread into the community of nosocomial pathogens (early patient’s discharge from Hospital, increase rely on Day-Hospital and Day-Surgery facilities, switch therapy of antimicrobials started at the hospital, and continued on outpatient basis)</td>
</tr>
<tr>
<td>• possibility of spread of resistant organisms from person to person in the community, too</td>
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<tr>
<td><strong>Antimicrobial agents</strong></td>
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<tr>
<td>• still represent the most prescribed drugs, on the whole (both inpatients and outpatients)</td>
</tr>
<tr>
<td>• progressive enlargement of the available pharmacological spectrum (over 110 molecules in the year 2006!)</td>
</tr>
<tr>
<td>• frequently inappropriate prescriptions (i.e. suspected viral infections, over-prescription in respiratory tract disorders, selection of broad-spectrum molecules in the frequent event of empiric prescription of antimicrobials)</td>
</tr>
<tr>
<td>• exaggerated use of broad spectrum molecules (distorted perception of the underlying concept, increase of resistances, false feeling of confidence, increased costs)</td>
</tr>
<tr>
<td>• modest diffusion and awareness of pharmacokinetic and farmacodynamic basis of single drugs and drug classes, and poor knowledge of drug-drug interactions</td>
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Among these microorganisms which share a predominant nosocomial isolation, the appearance of methicillin resistance is usually linked to an almost complete lack of \textit{in vitro} susceptibility to all beta-lactam antibiotics, but usually it extends to macrolides, lincosamides, and a large part of aminoglycosides and fluoroquinolones, also, therefore leading to a very striking reduction of remaining therapeutic options\textsuperscript{1,8,17}. Notwithstanding that the frequently concurrent pathophysiological conditions can also act unfavorably, by limiting both microbiological and clinical efficacy of an antimicrobial treatment \textit{in vivo} (Table 2), however the selection and spread of pharmacoresistant bacterial strains represents the main feature responsible for their severely reduced activity in current clinical practice.
The guidelines for empiric antimicrobial chemotherapy of the immunocompromised and/or neutropenic patient took into careful account of the etiological shift from Gram-negative towards Gram-positive organisms, which occurred during the last two decades, as reminded above. In fact, in the past decade the recommendations for empiric therapy of at-risk patients strongly pointed out the inclusion of drugs which are highly active against methicillin-resistant Gram-positive cocci, but concomitantly contributed to the appearance and further spread of mutant strains, which test either “intermediate” or even “resistant” to both available glycopeptides (vancomycin and teicoplanin), which represented the “gold-standard” reference molecules for the management of multiresistant Gram-positive cocci, until a few years ago. A relevant Italian survey referred to years 1997-1998, showed that Gram-positive microorganisms were responsible for slightly more than 50% of respiratory infection and septicemia identified in three different Italian intensive care units, with absolute predominance of *S. aureus* (29.2%), followed by coagulase-negative *Staphylococci* (9.5%), *Streptococcus pneumoniae* (4.1%), and *Enterococcus faecalis* (2.9%). Methicillin-resistance levels tested around 46% for *S. aureus*, but rose to 64% for coagulase-negative *Staphylococci*.

When evaluating the episodes of nosocomial sepsis, the international SCOPE study carried out in the year 1996 attributed the most elevated incidence to coagulase-negative *Staphylococci*, followed by *S. aureus* and *Enterococcus* spp., whose mortality rates proved 21%, 25%, and 32% of reported cases, respectively. *Enterococcus* spp. organisms showed an antibiotic susceptibility profile remarkably different between *E. faecalis* and *E. faecium*: this last pathogen was increasingly identified during recent years, in association with methicillin resistance levels often greater than 50% of tested strains. Concurrently, the incidence of methicillin resistance among coagulase-negative *Staphylococci* (with *S. epidermidis* as the leading organism) tested even greater in frequency (also over 60-80% in different clinical settings). Finally, an open debate is still ongoing regarding the role and frequency of staphylococcal strains which test “intermediate” to vancomycin and glycopeptides in general (the so-called “glycopeptide-intermediate *S. aureus*”, or GISA), which were early identified in Japan since ten years ago (year 1996). The incidence of this last phenomenon is estimated to be still contained, although it is more commonly recognized in countries where the frequent resort to glycopeptide administration supported a non-specific selective pressure. The spread of glycopeptide resistance may occur through different bacterial species especially in the gastrointestinal tract, which may act as a reservoir of genes conferring resistance to glycopeptides and concurrently to many other antimicrobial compounds.

### Quinupristin/dalfopristin: the streptogramin association

The streptogramin association quinupristin/dalfopristin is an antibiotic combination composed by two different molecules (in a 30%-70% proportion), which express a relevant synergistic activity against susceptible microbial pathogens, based on a double blockade of the peptidyl chain extension. Quinupristin/dalfopristin proves effective against a broad spectrum of Gram-positive organisms, even when they become resistant to methicillin and also glycopeptides. *Streptococci*, pneumococci, and especially coagulase-positive and coagulase-negative *Staphylococci, Clostridium* spp. and *Peptostreptococcus* spp., and *Enterococci*, with the partial exception of multiresistant strains of *E. faecalis* (whose susceptibility index is however around 30% of tested strains), represent the target microorganisms of this novel compound. The *in vitro* sensitivity spectrum of quinupristin/dalfopristin is also extended towards multiple relevant Gram-negative pathogens, including *Legionella pneumophila*, *Moraxella catarrhalis*, and *Mycoplasma pneumoniae*. The breakpoint values of quinupristin/dalfopristin recommended for *in vitro* microdilution techniques searching for minimum inhibitory concentrations (MIC) determination are ≤1 µg/mL for sensitive microorganisms, 2 µg/mL for moderately susceptible (or “intermediate”) organisms, and ≥4 µg/mL per isolates defined as resistant. Moreover, the development of acquired resistance against this streptogramin association is expected to represent a very rare event, as characterized by a frequency of mutations occurring in staphylococcal and enterococcal strains ranging from 10⁻⁵ and 10⁻¹¹, while a confirmed *in vivo* resistance accounts for around 2% of clinical episodes, and may rise to 8-20% in particular settings, where the incidence of vancomycin-resistant *Enterococci* is of elevated concern, or among some coagulase-negative multiresistant *Staphylococci*. However, this last microbiological resistance profile may be responsible for confirmed clinical failure. Because of its prolonged post-antibiotic effect (ranging from 2-6 hours for methicillin-resistant *S. aureus*, to over 18 hours for *Streptococcus pyogenes*), the quinupristin/dalfopristin association

<table>
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<tr>
<th>Table 2. Factors which variously contribute to the selection of empirical or selective antimicrobial chemotherapy, when resistant Gram-positive cocci may be of concern.</th>
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<tbody>
<tr>
<td>- Local epidemiology, hospital epidemiology</td>
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<tr>
<td>- Etiological diagnosis and in vitro antimicrobial susceptibility assays</td>
</tr>
<tr>
<td>- Patient’s conditions and eventual underlying disorders and support conditions</td>
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<tr>
<td>- Patient’s immune competence</td>
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<tr>
<td>- Predisposing conditions</td>
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<tr>
<td>- Appropriate prescription</td>
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<tr>
<td>- Spectrum of activity of prescribed antimicrobial agents, and their eventual association (to exploit additive or synergistic activity)</td>
</tr>
<tr>
<td>- Drug bioavailability, including drug disposition and diffusion, protein link, volume of distribution, tissue and intracellular penetration, pharmacokinetic and pharmacodynamic properties</td>
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<tr>
<td>- Serum and tissue half-life of selected compounds</td>
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<tr>
<td>- Expected or assessed antimicrobial resistance pattern</td>
</tr>
<tr>
<td>- Drug metabolism, post-antibiotic effects, elimination routes</td>
</tr>
<tr>
<td>- Peak levels, minimal inhibitory concentrations (MIC), minimal bactericidal concentrations (MBC), area under the curve (AUC), and related parameters</td>
</tr>
<tr>
<td>- Drug interactions (increased or reduced activity and toxicity), drug metabolism (active or inactive metabolites)</td>
</tr>
<tr>
<td>- Comprehensive duration of antimicrobial chemotherapy</td>
</tr>
<tr>
<td>- Comprehensive tolerability, and toxicity issues in otherwise healthy, or compromised subjects</td>
</tr>
<tr>
<td>- Patient’s compliance (also related to eventual concomitant pharmacological treatments)</td>
</tr>
<tr>
<td>- Crude and comprehensive costs of administration and delivery</td>
</tr>
<tr>
<td>- Comprehensive pharmacoeconomic issues</td>
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</table>
has a potent in vitro synergistic activity (often confirmed by in vivo experiences) with an elevated number of other antimicrobial drugs, including glycopeptides themselves, but also rifampicin and derivatives, ciprofloxacin and derivatives, ampicillin, and some cephalosporins, directed especially against meticillin-resistant Staphylococci. When considering E. faecalis strains testing resistant to vancomycin and teicoplanin, again glycopeptides, tetracyclines, and penicillins protected by beta-lactamase inhibitors, are expected to show a synergistic activity with quinupristin/dalfopristin\textsuperscript{7,17,23}.

Since the antimicrobial activity of quinupristin/dalfopristin is based on the synergistic action of both molecules, the pharmacokinetic and pharmacodynamic features of this fixed association are of striking importance: the rate of serum concentration of the two molecules is included in the range of antimicrobial activity of the quinupristin/dalfopristin association against the different susceptible microorganisms\textsuperscript{17,23}. The in vivo half-life of biologically active compounds is 2-3 hours for quinupristin, and around one hour for dalfopristin. Therefore, the area under the curve (AUC)/minimal inhibitory concentration (MIC) ratio remains above the MIC of the target pathogens (i.e. 1 µg/mL), while the plasmatic coverage is enforced by the prolonged post-antibiotic effect. The initial, current dosage (7.5 mg per Kg of body weight, every 8 hours or 12 hours), needs i.v. administration through extensive dilution in glucose solution, and preferably by a central venous catheter and an infusion duration of at least 60 minutes, in order to prevent local toxicity, which can occur when peripheral veins are used for long-term administration.

Given its in vitro spectrum of antimicrobial activity, the clinical indications for quinupristin/dalfopristin administration presently include all “difficult” Gram-positive lower airways infections, infections of skin and soft tissues, and especially vancomycin-resistant E. faecium disease (regardless of the interested body site), due to the difficulty to have an effective treatment of these severe pathologies determined by the increasing occurrence of multiresistant strains\textsuperscript{7,19,22}.

On the ground of the available clinical evidences reported by the international literature, severe infections of critically ill patient which deserve a quinupristin/dalfopristin treatment include those due to Gram-positive cocci testing in vitro resistant to glycopeptides, but also situations burdened by an elevated risk for multiresistant gram-positive agents, which failed to respond (clinically or microbiologically) to at least three days of a teicoplanin- or vancomycin-based antimicrobial chemotherapy. A combination treatment (including glycopeptides themselves, or rifampicin, aminoglycosides, cotrimoxazole), can be attempted on empiric basis or after in vitro susceptibility assays, in order to exploit the above-mentioned synergistic effects with quinupristin/dalfopristin\textsuperscript{7,17,20,23}. The therapeutic choice may prefer quinupristin/dalfopristin also when risk factors which make other combination poorly tolerated or difficult to be delivered, because of expected toxicity, intolerance, or underlying systemic disorders (such as diabetes mellitus, kidney failure, or myelotoxicity).

While quinupristin/dalfopristin dosage does not need adjustment until renal insufficiency becomes severe, a reduced daily dosage and strict monitoring of hepatic function are recommended when liver failure is of concern. Should an extensive end-organ liver disease is present, the administration of quinupristin/dalfopristin becomes contraindicated.

From a clinical-therapeutic point of view, during the pre-registration period the drug has been administered for the treatment of a high number of clinical episodes of severe diseases determined by multiresistant Gram-positive pathogens, often involving severely immunocompromised patients. Among disease localizations described in the earlier literature reports, we underline a wide spectrum of difficult-to-treat and life-threatening endocarditis, such as enterococcal endocarditis on a prosthetic valve\textsuperscript{26}, multiresistant S. epidermidis endocarditis\textsuperscript{27}, those due to multiresistant S. aureus occurring artificial valve and no chance of surgery, as well as E. faecium heart localization, where a combination with doxycyclin, rifampicin, and high-dose ampicillin was favorably used, and a demonstration of synergistic activity given\textsuperscript{28,29}. E. faecium is infrequently responsible for bone and joint infection, although a progressive increase of frequency has been noticed among patients undergoing replacement of infected prosthetic devices, where the role of coagulase-positive and coagulase-negative Staphylococci, and that of Enterococci, are mounting. Also in these events, an interesting case report demonstrated the efficacy of quinupristin/dalfopristin in an inveterate vertebral osteomyelitis caused by vancomycin-resistant bacterial pathogens\textsuperscript{30}. Given the low cerebrospinal fluid concentration obtained after quinupristin/dalfopristin administration\textsuperscript{31}, episodes of severe central nervous system infection caused by E. faecium (ventriculitis, ventricular drainage infection, meningitis, brain abscess), have been treated favorably after local drug administration (i.e. via intratecal or intraventricular route)\textsuperscript{31-33}, with a mean dosage of 2 mg, and in absence of significant untoward events; in one case of meningitis quinupristin/dalfopristin was concurrently administered i.v. at full dosage\textsuperscript{33}. Also in pediatric age, preliminary observations conducted on 11 overall children\textsuperscript{34,35}, underlined the microbiological and clinical efficacy and the safe profile of quinupristin/dalfopristin in the management of vancomycin-resistant intrabdominal E. faecium infection and septicemia, in patients who underwent bone marrow transplantation during treatment of hematological malignancies\textsuperscript{34}, and in other young patients with an underlying severe immunosuppression\textsuperscript{35}; the association with teicoplanin showed a synergistic effect also in these last episodes\textsuperscript{34}.

Relevant multicentre randomized trials, and an extensive spectrum of clinical experiences and case series treated with quinupristin/dalfopristin, confirmed the elevated efficacy of this novel streptogramin combination in the treatment of pneumonia and severe skin and soft tissue infection, as well as infected surgical wound infection frequently observed in hospital settings\textsuperscript{7,17,23,36-38}. Among randomized clinical trials, particular attention should be addressed to the comparison of quinupristin/dalfopristin with vancomycin in the management of gram-positive nosocomial pneumonia in critical care units\textsuperscript{36}, the comparison with cefazolin, oxacillin, and vancomycin in the therapy of skin-soft tissue infection\textsuperscript{17}, and the study especially devoted to E. faecium infections\textsuperscript{38}. The very favorable results obtained in these experiences hypothesized the use of quinupristin/dalfopristin in experimental protocols of eradication of methicillin-resistant staphylococcal colonization, and as an empiric choice for neoplastic patients with
febrile neutropenia. An underlying kidney failure followed by organ transplantation did not impair the effectiveness of this streptogramin combination in multivisceral and disseminated infections caused by multiresistant \textit{S. epidermidis} strains, sometimes in combination with chloramphenicol, and after failure of multiple therapeutic attempts carried out with glycopeptides\textsuperscript{39}. A more recent experience of the same research group, involving six patients who underwent hemodialysis (one submitted to renal transplantation, and four complicated be hepatic failure), confirmed the clinical efficacy and safety of quinupristin/dalfopristin even in patients with severe end-organ involvement, without need of drug dosage adjustment, and also determining the drug pharmacokinetic profile in these extreme conditions\textsuperscript{40}. However, especially when transplanted patients undergoing an immunosuppressive therapy are of concern, the need to proceed to a repeated monitoring of cyclosporin serum levels and dosage during quinupristin/ dalfopristin administration is confirmed, as already indicated in the early clinical experiences conducted with this streptogramine association\textsuperscript{41}.

As we can deduct from the results of the above-mentioned controlled studies, and the numerous, intriguing case reports and case series, quinupristin/dalfopristin appears to be an effective and well tolerated agent in the management of septicemia, heart-thoracic, intrabdominal, bone and joint, and skin and soft tissue infections caused by methicillin-resistant Staphylococci, also in combination with a glycopeptide, notwithstanding that the previous administration of the sole glycopeptide agent resulted not effective\textsuperscript{42-45}. The spectrum of activity of this dual streptogramin combination, since it remains restricted to gram-positive cocci, recommends the association with other antimicrobial agents with enlarged spectrum of action, when a polymicrobial infection is suspected, or a mixed flora containing Gram-positive and Gram-negative organisms is of concern\textsuperscript{7,17,23,44,46}. Finally, the hospital and environmental spread of pathogenic multiresistant Gram-positive cocci as a result of the selective pressure determined by the increased and prolonged administration of other broad- and narrow-spectrum antimicrobial agents, is probably responsible for the emerging of some streptococcal strains (i.e. \textit{Streptococcus mitis} and \textit{Streptococcus pneumoniae} in a broad surveillance study)\textsuperscript{47}, as well as some \textit{E. faecium} isolates\textsuperscript{48}, which became intrinsically resistant to streptogramins, regardless of the prior use of antibiotics belonging to the same of similar classes\textsuperscript{49}. In these last reports, the concomitant resistance to all available glycopeptides indicated the novel oxazolidinone linezolid as the only potentially effective alternative therapeutic choice\textsuperscript{23,42,43,46,48}.

The adverse events registered upon administration of quinupristin/dalfopristin include predominantly gastrointestinal tract disturbances (nausea, vomiting, and diarrhea), followed by hyperbilirubinemia, cutaneous rash, and diffuse arthromyalgia\textsuperscript{7,17,43}. These last signs and symptoms seem to be more frequent among hepatopathic and organ transplanted patients, and those treated with cyclosporin, although the mechanism of action of these adverse events still remains under investigation\textsuperscript{49}. The administration of quinupristin/dalfopristin in hospital setting, and through central i.v. lines and appropriate fluid dilution, significantly reduces the risk of local thrombophlebitis. Notwithstanding the practical difficulties related to drug administration, in an United States pilot study a quinupristin/dalfopristin treatment has been administered to 37 patients suffering from osteomyelitis, bacteremia, abscess and cellulitis due to \textit{E. faecium}, \textit{S. aureus}, and coagulase-negative Staphylococci, all in outpatient setting, as a prosecution or completion of treatment schedules initiated at the hospital, relying on peripherally-inserted central catheters, or tunneled catheters: 16 subjects out of 37 (43.2\%) showed mild-to-moderate local intolerance, during or after i.v. drug infusion\textsuperscript{50}. From a metabolic point of view, both quinupristin and dalfopristin are modified by the liver into different main derivatives, which contribute to its antimicrobial action, thanks to their intrinsic activities, and the maintained synergistic activity between themselves and the administered molecules\textsuperscript{7,17,23}. Since the metabolism is principally carried out by the hepatic cytochrome system P450, pharmacological interactions with all drugs which interact with the same detoxification system are expected: in particular, quinidine, lidocaine, nifedipine, terfenadine, astemizole, cisaprid, disopiramide, and midazolam, as well as drugs which might prompt a QT interval prolongation (antiarrhythmics, neuroleptics, antidepressive drugs, antiinflammatory compounds, fluoroquinolones, azole antifungals, and macrolides). A careful monitoring of serum levels (when possible) or clinical effect of these last drugs, and special clinical attention delivered to possible adverse events, and eventual need of dosage adjustment, are therefore warranted for patients who require a continued administration of the above-mentioned drugs, concurrently with that of quinupristin/dalfopristin\textsuperscript{7,17,17}. In the event of critically ill or transplanted patients, preliminary demonstrations of possible interactions of quinupristin/dalfopristin and cyclosporin have been reported, so that serum cyclosporin levels and drug dosage adjustments deserve careful attention\textsuperscript{17,40}.

\textbf{Linezolid: the oxazolidinone derivative}

Linezolid represents the first representative of a novel class of oxazolidinone derivatives, which encompasses an effective activity spectrum which covers all the most important Gram-positive organisms, including those resistant to methicillin and glycopeptides. The oxazolidinones have a unique mode of action, which inhibits the start of bacterial protein synthesis by preventing the formation of the ternary complex at 70S ribosomal subunit\textsuperscript{5}, by an apparent double blockade of both the 50S and the 30S bacterial ribosomal subunits. The particular mechanisms of action of linezolid, which includes a blockade of ribosomal assemblation which occurs before the initiation of bacterial protein synthesis\textsuperscript{6}, makes very improbable the emerging of cross resistance with other molecules. However, this phenomenon has been anecdotally reported until now, especially after long-term and low-dosage courses, and appears to be extremely rare among Staphylococci\textsuperscript{51}, although linezolid-resistant Enterococci have been occasionally reported in intensive care units\textsuperscript{52}.

From a pharmacokinetic point of view, linezolid is protein-bound for around 30\%, and favorably penetrates into a broad variety of tissues, such as fat, bone, muscle, cerebrospinal fluid and wound sites, beyond the known, elevated penetration into the lungs and the entire respiratory tract\textsuperscript{46}. The drug metabolism is not affected by the cytochrome P450 pathway, so that drug-drug interactions at this setting are not expected. On the other hand, urine concentrations is low (around 30\% of plasma levels).
I.v. formulation requires slow (30-120 minutes) infusion. Being formulated for both the i.v. and the oral route, linezolid retains a 100% bioavailability even after oral administration3,46,53, and regardless of meals, therefore making it easier to exploit the oral administration for switching therapies and early discharge from the hospital of patients who can be effectively followed on outpatient or Day-Hospital basis, and also to start therapy with oral route, whenever possible. These aspects have multiple favorable consequences, when comprehensive morbidity and mortality rates, overall length of hospitalization, and increased medical expenses are considered, even when compared with the proportionally elevated crude costs of linezolid therapy53. A European study54 considered 227 patients with serious Gram-positive infections, treated with linezolid compared with teicoplanin, and assessed hospital resource use and overall treatment costs. The enrolled patients were randomized according to a 50%-50% ratio to receive either linezolid or teicoplanin (initially by i.v. route, but with the possibility to shift to the oral administration as soon as possible), or teicoplanin (initially by i.v. administration, potentially followed by i.m. route)54. The mean i.v. treatment duration was 3.2-day shorter in the linezolid group (6.3 versus 9.5 days), tending to lead to a reduction of overall hospitalization costs, when comparing the novel oxazolidinone linezolid even against the most expensive glycopeptide teicoplanin53,54.

After expanded-access programs which included seriously ill patients suffering from multidrug-resistant, Gram-positive infections in situations also including bacteremia (46% of 796 cases), endocarditis, and line-related infection55 at its first approval in the United States, linezolid was initially registered for the treatment of both community-acquired and nosocomial pneumonia, uncomplicated and complicated skin and soft tissue infections (including diabetic foot infections and surgical site infection), and infectious caused by methicillin- and vancomycin-resistant Staphylococci and Enterococci, and penicillin- and macrolide-resistant Streptococci and Pneumococci, including episodes complicated by bacteremia53. Since ribosomal mutations have been detected that produce resistance against linezolid, longitudinal surveillance surveys remain needed to strictly monitor this phenomenon. The 2003 annual appraisal of potency and spectrum (ZAAPS) program compared MIC results of linezolid with 13-15 comparator agents in over 8,000 isolates56, and confirmed a maintained 99.93% linezolid susceptibility rate of tested Gram-positive organisms. The recently published continuation of this study until 200457 confirmed this figure on 20,158 overall tested isolates, pointing out that 99.5% of isolated S. aureus organisms had a MIC<sub>90</sub> value of linezolid ranging from 0.5 to 2 mg/L, with only one isolate tested at 4 mg/L.<sup>57</sup>

In particular, when considering complicated skin and soft tissue infections, a randomized, open study has been conducted on 1,200 hospitalized patients with ascertained or suspected methicillin-resistant staphylooccal isolates58. The most common disorders were represented by severe cellulitis (46%), cutaneous abscess (26%), and surgical wound infection (11%). In the intention-to-treat comparison between linezolid (given at 600 mg i.v. twice daily) and vancomycin (at 1 g i.v. twice daily), the cure rate was 92.2% versus 88.5% respectively (p=0.057), while involved pathogens included methicillin-resistant Staphylococci in 42% of cases, followed by methicillin-sensitive Staphylococci (29%), and coagulase-negative Staphylococci (8%)58. When considering methicillin-resistant staphylococcal infections only, a greater percentage of success rate was obtained with linezolid over vancomycin (88.6% versus 66.9% respectively; p<.001), paralleling the better bacteriological success rate of linezolid over vancomycin (p<.001)58. In a subset of the above-mentioned study including surgical site infections presumably due to methicillin-resistant Staphylococci58, although the clinical cure rate proved similar, linezolid obtained a greater bacteriological eradication rate (p<.008), and a higher rate of microbiological cure (p<.003)58. In an open study of complicated staphylococcal skin and soft tissue infections, oral linezolid and i.v. vancomycin were compared at the same dosage regimens for 7-21 days, and a higher clinical response was obtained with linezolid (p<.02), associated with a lower rate of failure requiring also surgical amputation (p<.02)58.

Pneumonia was assessed in two large, multicentre, randomized, double-blind trials conducted on 1,019 patient on the whole, affected by a nosocomial pneumonia presumably due to Gram-positive organisms. In these studies, an empirical linezolid treatment tested comparable to a vancomycin one, from an efficacy and safety point of view<sup>56,57</sup>. In a subgroup which included 123 patients with a confirmed hospital-acquired methicillin-resistant staphylooccal pneumonia, a greater survival rate (84% versus 62%; p=0.02), and clinical cure (62% versus 21%; p<.001) were achieved with linezolid, compared with vancomycin. In another study<sup>58</sup> which compared the efficacy of linezolid and teicoplanin in 430 patients with ascertained or presumed Gram-positive infections, linezolid proved as effective as teicoplanin in patients suffering from pneumonia (96% versus 93%), but infections complicated by bacteremia had a greater response rate when linezolid was administered (88.5% versus 56.7%; p<.001)<sup>59</sup>. The increasing recognition of the clinical potential of linezolid led to the inclusion of this novel agent in the treatment guidelines of the American Thoracic Society and those of the Infectious Disease Society of America, as empirical, initial choice for patients with a suspected nosocomial pneumonia caused by methicillin-resistant Staphylococci, or where the global prevalence of these organisms is elevated<sup>60,63</sup>. Smaller patient series and anecdotal case reports of linezolid use in other relevant infectious processes are increasing day by day. The excellent tissue penetration makes this oxazolidinone drug extremely promising for the approach to difficult-to-treat endocarditis with or without bacteremia<sup>64</sup>, central nervous system infections<sup>65,66</sup>, and bone and joint infections<sup>67</sup>, caused by resistant Gram-positive cocci. Moreover, pediatric experiences are increasing<sup>10,46</sup>.}

A combination therapy of linezolid with other antimicrobial compounds is indicated when the co-existence of Gram-negative pathogens is ascertained or suspected. Moreover, a very interesting activity of linezolid has been demonstrated both in vitro and in vivo against susceptible and especially multi-drug resistant Mycobacterium tuberculosis<sup>68-70</sup>, and a synergistic activity may be exploited with a broad spectrum of fluoroquinolones<sup>71</sup>, although the clinical significance of those associations needs to be clinically confirmed.
Interestingly, a recent study also pointed out a significant reduction of acute-phase proinflammatory cytokines from human peripheral mononuclear cells when linezolid was administered, thus confirming an immunomodulating response to linezolid use.

From a tolerability point of view, within the maximum allowed treatment duration of 28 days, linezolid showed a favorable safety profile, as showed in a very extensive methananalysis of 2,046 adult patients enrolled in seven different comparative, controlled studies. The 85% of reported adverse events was mild-to-moderate in intensity: the most common clinical events were diarrhea (4.0% to 5.3%), nausea (3.3% to 3.5%), and headache (1.9% to 2.7%), while the most common laboratory disturbances included anemia and thrombocytopenia. During the post-marketing surveillance, sparse cases of peripheral neuritis (also including optical neuritis), and lactic acidosis were anecdotally reported, especially when linezolid treatment was extended beyond four weeks. Also myelotoxic effects (whose pathogenesis still remains unknown) were associated with prolonged treatment durations, although some reports showed a somewhat earlier appearance. However, the risk of clinically significant thrombocytopenia as assessed on 686 patients with nosocomial pneumonia treated with linezolid for at least five days was limited to 6.4% (compared with 7.7% observed in the comparative vancomycin group). When chronic or acute kidney insufficiency or hemolysis or hemofiltration are of concern, no correction of linezolid dosage is needed, as opposed to the limitations occurring when vancomycin or teicoplanin are administered. Therefore, the selection of linezolid appears indicated when a co-existing renal insufficiency may hamper the use of glycopeptides and other drugs with an increased renal toxicity. Finally, the well know activity exerted by linezolid on the inhibition of monoamine oxidase may prompt potential adverse drug-drug interactions with a broad range of antidepressant medications, which has to be taken in careful account when facing patients who receive complex, multiple pharmacological treatments.

Although the efficacy and safety of linezolid have been well demonstrated in severe, high-risk infections where multiresistant Gram-positive cocci are involved, and multiple pharmacoeconomic appraisals show that the availability of a bioequivalent oral formulation and a rapid shift to an oral route of administration may effectively centerbalance the more elevated crude costs compared with older glycopeptides like vancomycin, however further controlled clinical trials are strongly needed to expand the indications of this promising antibiotic, and to check carefully its tolerability in more extensive patient populations and baseline conditions (i.e. extreme life ages, comorbidity including diabetes mellitus, drug-drug interactions, and so on). A ponderate prescription limited to selected cases of serious, resistant Gram-positive infections, associated with improved standards of control and monitoring of nosocomial infections, are expected to add significantly to the long-term planning of effective guidelines of prescription, and large-scale resource allocation, in the optimization process of the management of multiresistant Gram-positive infections in critical settings.

**The lipopeptide daptomycin**

The novel lipopeptide antibiotic daptomycin is a cyclic amino acid compound of particular interest, also due to its unique mechanism of action, encompassing a rapid concentration-dependent killing and an effective bactericidal activity, mainly exerted by its lipophilic tail, which inserts itself into the cytoplasmic membrane of Gram-positive pathogens, and disrupts it through a depolarization process, which is responsible of a bactericidal activity faster than comparators belonging to glycopeptides, oxazolidinones, and streptogramins, and is also corroborated by an appreciable post-antibiotic effect.

Since the spectrum of activity of daptomycin is extended to include key Gram-positive pathogens (regardless of their resistance status to other compounds, and including all glycopeptide-resistant staphylococci and enterococci, and multiresistant pneumococci and streptococci), this novel compound adds significantly to the still reduced spectrum of antimicrobial weapons for the treatment of serious Gram-positive infections, and it is also effective against several anaerobes (Clostridium and Propionibacterium spp.), while no activity is expressed against Gram-negative pathogens. The in vitro potency against multiresistant Gram-positive cocci is comparable to that of linezolid and daptomisinquinupristin, at the proposed breakpoint of 0.2 mg/L, but with a more rapid bactericidal activity. Some synergistic activity has been shown against vancomycin-resistant Enterococci with the use of rifampin, and at a lesser extent with ampicillin and tobramycin. Although the possibility to generate in vitro resistant bacterial strains is apparently negligible, also due to the lack of transferable elements, however anecdotal reports emerged since early experiences, after prolonged exposure of Staphylococci to the relevant drug.

At the dosage of 4 mg/Kg i.v. once daily, daptomycin has been shown to be efficacious in two blinded trials of complicated skin and soft tissue infections conducted on even 1,092 patients, which led to a clinical success rate similar for daptomycin and comparators (either vancomycin or penicilinase-resistant penicillins), but with a rapid bactericidal activity. Among patients successfully treated with i.v. daptomycin, 63% required only 4-7 days of therapy, as opposed to 33% of comparator-treated patients (p<.0001).

Until now, daptomycin is therefore approved for the management of complicated skin-skin structure infections, including infected surgical wounds, and complications of burns and diabetic foot. The potential for shorter course regimens should demonstrate faster resolution rates, and may decrease the risk of resistance development, toxicity, and treatment-related direct and indirect costs. Unfortunately the modest daptomycin penetration into the lung tissue and the local drug competition with surfactant (which is implicated in sequestering this particular lipopeptide drug), poses this novel compound at an elevated risk of clinical failure in the treatment of respiratory infections, so that no indication is expected to date in this last setting.

On the other hand, a daptomycin dose of 6 mg/Kg is under investigation for the management of endocarditis and bacteremia. In a recently published case series of 31 patients with bacteremia and endocarditis, i.v. daptomycin at 4-6 mg/day tested safe and effective, even when considering the elevated prevalence of vancomycin-resistant enterococci
Telavancin is another semisynthetic glycopeptide with a long half-life and extensive tissue penetration. In association with a very long terminal half-life (around 40 hours), these features allow twice-daily administration. The efficacy of tigecyclin seems to be best predicted by the ratio of the area under the concentration-time curve to the MIC, due to its linear pharmacokinetic profile.

Tigecyclin may be administered by i.v. route (at 50 mg, twice daily, preceded by a loading dose of 100 mg, the first day), and until now it has been studied in the management of serious polymicrobial infections, i.e. complicated skin and skin structure infections, surgical wounds, and intraabdominal infections, where it resulted effective and well tolerated in phase III clinical studies, carried out in adults, and non-pregnant women. Equivalence to imipenem in intraabdominal infections, and to vancomycin plus aztreonam in skin and soft tissue infections have been preliminarily achieved.

The drug disposition is not affected by age, renal disease, or food, and the limited metabolic encompasses a reduced kidney and liver engagement. Besides a low rate of gastrointestinal complaints (nausea, vomiting, and diarrhea), only mild and self-limiting adverse effects on blood chemistry or haematology have been observed.

In conclusion, this novel drug is likely to find a key role also as a monotherapy in the treatment of mixed infections due to multiresistant pathogens, including beta-lactamase producers and methicillin- and vancomycin-Gram-positive organisms.

Novel glycopeptide antibiotics

This drug class still contains the reference standard antimicrobial choices for methicillin-resistant Gram-positive cocci, i.e. vancomycin and teicoplanin. Among the novel compounds representing the evolution of this class, the new glycopeptides dalbavancin, ortavancin, telavancin, and ramoplanin appear very promising for an upcoming commercial release in the next few months or years, although there are remaining concerns about the possible microbial resistance spread, based on existing antimicrobial compounds which belong to the same drug class. In particular, ortavancin is a semi-synthetic glycopeptide with a long half-life (around 150-200 hours), and elevated intracellular penetration, as well as an effective diffusion into the brain. Its bacteriological activity includes vancomycin-resistant Enterococci, methicillin-resistant Staphylococci, vancomycin-intermediate and vancomycin-resistant S. aureus. Telavancin is another glycopeptide compound with an half-life which allows once-daily administration. Its dual mechanisms of action (impairment of synthesis of peptidoglycan, and cell wall lipid structures) is a distinguishing property. Finally, ramoplanin is a glycolipiodepsipeptide, with an excellent activity against Gram-positive cocci and bacilli, including those which became resistant to currently glycopeptides. Its endothelial toxicity is a present limitation for i.v. delivery, so that ramoplanin is presently studies for the management of difficult-to-treat intestinal Clostridium difficile.

The first agent in the pipeline appears to be the semisynthet-
ic lipoglycopeptide dalbavancin, developed for once-weekly i.v. treatment of serious Gram-positive infections, including a wide range of glycopeptide-resistant organisms. The mechanism of action replicates that of other glycopeptides, but dalbavancin resulted more potent in vitro. It has a very elevated in vitro activity against a variety of Gram-positive organisms, save vancomycin-resistant Enterococci possessing the VanA gene.

During Phase II-III clinical trials, dalbavancin proved effective and safe in the management of skin and skin-structure infections, and catheter-related bloodstream infections. The only available double-blind randomized clinical trial compared i.v. dalbavancin (1 g at day 1, 500 mg at day 8), with linezolid (600 mg i.v. or orally twice daily for 14 days), in the treatment of complicated skin-structure infections caused by suspected methicillin-resistant S. aureus strains. Dalbavancin and linezolid proved comparable from a clinical point of view (leading to a 88.9% and 91.2% success rate, respectively), and microbiological success was attained in both arms in over 85% of cases, although the rate of methicillin resistance was retrospectively recognized around 51% of isolated strains.

Thanks to its prolonged half-life (6-10 days) a once-weekly i.v. administration becomes possible. Pharmacokinetic analyses conducted on 532 patients, the majority of them treated with 1000 mg-dose on day 1 and 500 mg-dose on day 8, showed a dual-compartment model, with a clearance influenced by body surface area and creatinine clearance. No evidence of metabolic substrates, inhibitors, or inducers of the liver cytochrome P450 was found, thus eliminating the risk of competing drugs at the same hepatic site. At a preliminary assessment, adverse events were very mild and limited in frequency: pyrexia, headache, nausea, diarrhea and other gastrointestinal disturbances were the most commonly described adverse events.

Among adverse events, gastrointestinal complaints seem to represent the most frequent occurrence. In the quoted randomized trial, linezolid showed a slightly more elevated rate of overall adverse events compared with dalbavancin (32.2% versus 25.4% of enrolled subjects).

**Novel cephalosporins, fluoroquinolones, and other agents under advanced development**

Among the more promising agents under advanced development against multiresistant Gram-positive cocci, we can quote novel cephalosporins (i.e. BAL-9141 and RWJ-54428), which are expected to overcome methicillin resistance.

Furthermore, among the topoisomerase inhibitors, several fluoroquinolones are awaited, including gemifloxacin (which recently entered commercialization), sitafloxacin, and especially garenoxacin.

Finally, when considering the class of inhibitors of bacterial protein synthesis, the ketolides telitromycin and cetromycin, and the novel oxazolidinones (further to linezolid), are very promising agents for the fight against severe and life-threatening resistant Gram-positive infections.

**Conclusions and Outlook**

The proportionally recent availability of quinupristin/dalfopristin and of linezolid determined significant changes in the scenario of the management of severe infections due to multiresistant Gram-positive pathogens, usually acquired at the hospital and by a somewhat immunocompromised host.

A recent, extensive survey conducted on 258 Gram-positive bacterial organisms isolated from blood cultures at a United States cancer reference centre allowed to compare the in vitro activity of daptomycin, linezolid, and quinupristin/dalfopristin. Vancomycin-resistant Enterococci represented the largest proportion of tested organisms (32%), followed by methicillin-resistant coagulase-negative Staphylococci (23%), and vancomycin-sensitive Enterococci (14%). Through a detailed analysis of both MIC and MBC values, daptomycin showed a bactericidal activity against the majority of tested organisms, by killing almost 100% of bacteria within six hours. Quinupristin/dalfopristin was bacteriostatic against Staphylococci and bacteriostatic against the majority of Enterococci. Linezolid was bacteriostatic against all evaluated organisms, but a correlation between the in vitro features and the clinical outcome demonstrated an elevated potential of all these novel compounds, which now deserve controlled studies in the setting of the management and prevention of serious infection in the immunocompromised host, including HIV/AIDS patients, subjects with hematologic malignancies or solid tumors, and those undergoing bone marrow or organ transplantation, or major surgery and hospitalization in intensive care units.

**Highlights**

- In the meantime, the overall understanding of the epidemiology and virulence of community-acquired multiresistant Gram-positive pathogens continued to grow, leading to major attention devoted to developing compounds, but also a re-examination of many older, but still active agents (including long-acting tetracyclines, fluoroquinolones, rifampicin, cotrimoxazole, and clindamycin), which certainly retain some non-negligible therapeutic role, especially when a synergistic activity can be demonstrated.

- Through novel laboratory assays like the so-called E-test synergy and time-kill methods will perhaps become possible to measure to extent of synergistic activity between differently combined molecules against glycopeptide-resistant gram-positive cocci (i.e. daptomycin and rifampicin against multiresistant Enterococci).

- As summarized above, during the next future the therapeutic research promises the development of novel compounds aimed at intervening favorably against the unavoidable increase of drug resistance frequency and levels against the present reference compounds (i.e. the glycopeptides vancomycin and teicoplanin), and later the two above-mentioned recent molecules, i.e. quinupristin/dalfopristin and linezolid. On the other hand, the clinical use of the streptogramin combination quinupristin/dalfopristin, which retains optimal activity against methicillin-resistant S. aureus and vancomycin-resistant E. faecium, is limited because its need to be administered in large volume of fluids, while its activity in severe pneumonia is somewhat lower.

The oxazolidinone linezolid is active against methicillin-resistant Staphylococci and glycopeptide-resistant Enterococci, but resistant organisms and sparse treatment failures have been reported, while unexpected tolerability issues are becoming of concern.
- Furthermore, we have to remind that in many cases the most relevant therapeutic intervention for complicated Gram-positive abscesses, cellulitis, complicated skin and soft tissue diseases, but also osteomyelitis, infected bone and joint prosthesis, and brain abscesses, remains an adequate surgical drainage and curettage of purulent fluid collections, and the elimination of affected, necrotic tissue.  
  Subsequently, the antimicrobial selection should be driven by disease severity, susceptibility patterns, clinical response to therapy, and also related costs (seen from a comprehensive point of view) (Table 3). Also special population such as the pediatric and neonatal ones, are going to benefit from specifically-designed trials, which could address in the next future the major issues in the setting of epidemiology, mechanisms of virulence, continued changes in pathogenicity and antimicrobial susceptibility of involved organisms, and potential use of novel antimicrobial compounds, like daptomycin, glicyclines, newer glycopeptides, beta-lactamase-stable cephalosporins, and ketolides  
  - Finally, only randomized, comparative assessments of the novel molecules on the market will assist us to plan well-founded recommendations for the treatment of serious Gram-positive infections, and parallel comprehensive pharmacoeconomic issues should be carefully deserved.

| Table 3. Pharmacoeconomic variables of antimicrobial agents to be evaluated (modified from Nathwani D, personal communication, 2006) |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| **COSTS**                                      | **TIME HORIZON**                                 | **PERSPECTIVE**                                  |
| Direct                                         | Short-term                                       | Society                                          |
| Indirect                                       | Medium-term                                      | Patient                                          |
| Intangible                                     | Long-term                                        | Payer                                            |
|                                                 |                                                 | Provider                                         |

| Table 4. Some key mode and resource use with antimicrobials specific for resistant Gram-positive infections |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Vancomycin                                      | Teicoplanin                                      | Quinupristin/Dalfopristin                        |
| Linezolid                                       | Daptomycin                                       | Tigecycline                                      |
| Dalfavancin                                     |                                                  |                                                  |
| I.v. and oral route                             | No*                                              | Yes                                              |
|                                                  | No*                                              | No                                               |
| Ambulatory administration                       | Yes                                              | ?                                                |
| Need of drug level monitoring                   | Yes                                              | Yes?                                             |
| Frequency of administration                     | Yes                                              | No                                               |
| Frequency of administration                     | At least twice daily, to 24-hour continue infusion | Twice daily                                      |
|                                                  | Once daily                                       | Once daily                                       |
|                                                  |                                                  | Twice daily                                      |
|                                                  |                                                  | Once weekly                                      |

| *oral therapy limited to the treatment of Clostridium difficile-associated diarrhea |

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