A Re-Emerging Class of Antimicrobial Agents: Streptogramins (Quinupristin/Dalfopristin) in the Management of Multiresistant Gram-Positive Nosocomial Cocci in Hospital Setting

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Abstract: Multiresistant gram-positive cocci, including *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus faecalis* and *Enterococcus faecium*, are emerging pathogens in the setting of immunocompromised, hospitalized patients, especially when surgery or invasive procedures are of concern, and patients are admitted in intensive care units. The spectrum of antimicrobial compounds available for an effective treatment of these infection is significantly threatened by the emerging and spread of glycopeptide-resistant strains. Quinupristin/dalfopristin is a novel streptogramine association, which represents an effective response to most of these problems, due to its innovative mechanim of action, its maintained activity against multiresistant pathogens, and its possibility of synergistic activity with other compounds. Problems related to the epidemiology of multiresistant gram-positive infection, potential clinical indications of quinupristin/dalfopristin, and updated data on efficacy and tolerability of this compound and its derivatives, are outlined on the ground of a review of available literature evidences.

Keywords*:* Streptogramins, quinupristin/dalfopristin, gram-positive cocci, multiple antimicrobial resistance, combination antimicrobial chemotherapy, immunocompromised patient, hospital-acquired infection.

GRAM-POSITIVE MULTIRESISTANT COCCI: AN EMERGIG BACTERIOLOGICAL AND CLINICAL PROBLEM

Among nosocomial pathogens, since early eighties a significant reversal of tendency was registered, characterized by a prevalence of gram-positive over gram-negative bacteria (which represented the most relevant issue in the two preceding decades [1]. The increased life expectancy, the extended survival of patients with various underlyng causes of immunodeficiency, the advances of surgical techniques and those of invasive diagnostic and therapeutic procedures, the diffusion of prosthetic materials and other biomaterials, and the increase resort to endovascular lines, prolonged hospital admission and the elevated tendency to develop massive colonization (especially in critical care settings), and (last but not least), the increased and prolonged administration of broad spectrum antimicrobial agents and their associations, extensively contributed to the re-emerging of gram-positive pathogens. Among these microorganisms, streptococci, and especially staphylococci and enterococci are of particular concern, because of their rising frequency, the severity of associated diseases, and the unpredictable spectrum of drug resistance [1-3].

Together with the modification of environmental conditions, characteristics of host and microbial flora, and the spectrum of currently available antiinfective compounds (Table **1**), other emerging features become prominent, related to the pathomorphism of clinical features of a number of these infections. While streptococcocal scarlet fever and rheumatic disease virtually disappeared, other streptococcal disorders gained frequency and importance, including the toxic shock syndrome (TSS), the necrotizing fasciitis. When considering staphylococci, non-negligible levels of morbidity and mortality are linked to coagulase-negative cocci (i.e. *Staphylococcus epidermidis* and related organisms, previously considered trivial contaminants or part of saprophytic flora), especially when vascular or bone-joint prosthetic devices and central vascular lines are of concern. In the mean time, also *Staphylococcus aureus* ranked first in the majority of nosocomial pathogens, and even in this case novel syndromes characterized by the predominant role of bacterial toxemia are emerging: the so-called staphylococcal scalded skin syndrome (or SSSS) is the paradigmatic clinical picture.

In developed countries of the world, the rate of methicillin (oxacillin) resistance of staphylococci among hospitalized patients overcomes 20-25% of cases, with an extremely elevated frequency registered in intensive care units and bone marrow and solid oran transplant centres [1, 4]. An important multicentre survey of nosocomial bacteremia carried out in 49 United States hospitals during a three-year period, allowed to recognize a prevalence of gran-positive pathogens of 64%, among over 10,000 identified microorganisms [4]. When analyzing these microorganisms, coagulase-negative staphylococci (32%) preceded *S. aureus* (16%), and enterococci (11%). The overall level of methicillin resistance was around 29% of isolated organisms, with peaks reaching 80%, when coagulase-negative staphylococci were specifically considered [4]. Among these microorganism with predominant hospital isolation, the appearance of methicillin resistance is generally associated to an almost complete lack of *in vitro* susceptibility to all beta-lactam derivatives, but also macrolides, lincosamides, and a large part of aminoglycosides and fluoroquinolones, therefore leading to a very limited therapeutic choice [1-3, 5]. Even

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Table 1. Evolution of Bacterial Infection: Supporting Factors Related to the Host, Environment, Microbial Agents, and Antimicrobial Compounds

• **Host features**
- increased mean age of patients
- underlying immunodeficiency status
- concurrent disorders, and end-organ failure
- hospitalization
- invasive diagnostic and therapeutic procedures
• **Environmental features**
- need of a permanent local microbiological monitoring, compared with national and international surveillance data
- study of colonization features, environmental reservoirs, spread into the community of nosocomial pathogens
• **Pathogenic microorganisms**
-emergering and re-emerging of different microbial organisms
-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
• **Antimicrobial agents**
- most prescribed drugs, on the whole
- progressive enlargement of the available pharmacological spectrum (over 100 molecules in the year 2004!)
- modest diffusion and awareness of pharmacokinetic and farmacodynamic basis
- exaggerated use of broad spectrum molecules (distorted perception of the underlying concept, increase of resistances, false feeling of confidence, increased costs)

though the spectrum of underlying conditions which can limit both microbiological and clinical efficacy of an antimicrobial treatment *in vivo* (Table **2**), however the selection and spread of drug-resistant bacterial strains represents the main feature responsible for their severely reduced activity in c current clinical practice.

Also guidelines for empiric antimicrobial chemotherapy of the immunocompromised and/or neutropenic patient took into careful account of the ethiological shift from gram-negative towards gram-positive organisms, which occurred during the last two decades. In fact, recommendations strongly pointed out the inclusion of drugs highly active against methicillin-resistant gram-positive cocci, but concomitanly contributed to the appearance and further spread of mutant strains, which test "intermediate" or "resistant" to glycopeptides (vancomycin and teicoplanin), i.e. the reference molecules for the management of multiresistant gram-positive cocci [1, 3]. An Italian survey referred to years 1997-1998 [6], 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 prevalence 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*, and 64% for coagulase-negative staphylococci [6]. When evaluating the episodes of nosocomial sepsis, a 1998 study [7] attributed the most elevated incidence to coagulase-negative staphylococci, followed by *S. aureus* and *Enterococcus* spp., whose mortality rate proved 21%, 25%, and 32% of reported cases, respectively. *Enterococcus* spp. organisms show an antibiotic susceptibility profile remarkably differentbetween *E. faecalis* and *E. faecium*: this last pathogen is increasingly isolated during recent years, in association with methicillin resistance levels often greater than 50% of tested strains. The incidence of methicillin resistance among coagulase-negative staphylococci (with *S. epidermidis* as the leading organism) is even higher (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), first identified in Japan in 1996 [8]. Its incidence is estimated to be still contained, although it is more commonly recognized in countries where the frequent resort to glycopeptide administration supported a specific selective pressure.

In our own clinical-microbiological experience, focused during the last decade on the treatment of patients with HIV infection and related disorders, since the years preceding the introduction of highly active antiretroviral therapy (HAART), we observed a more favorable *in vitro* antimicrobial susceptibility profile of both *S. aureus* and *E. faecalis*, compared with that of the same microoganisms identified from all the remaning Divisions of our tertiary care teaching Hospital; temporal varations were very limited, and a total sensitivity to glycopeptides was maintained. During the 6-year period from 1990 and 1995, methicillin resistance levels of *S. aureus* strains isolated from our HIV-infected subjects accounted for about 17% of cases, *versus* 39% of HIV-negative patients hospitalized in other Divisions [9].

Table 2. Factors Concurring to the Choice and Outcome of Antimicrobial Chemotherapy

EPIDEMIOLOGY	
	ETHIOLOGICAL DIAGNOSIS
PATIENT'S CONDITIONS	
	PREDISPOSING FACTORS
IMMUNE COMPETENCE	
	APPROPRIATE PRESCRIPTION
SPECTRUM OF ACTIVITY	
	DRUG DIFFUSION
BIOAVAILABILITY	
	RESISTANCE
METABOLISM	
	INTERFERENCES
PHARMACOKINETICS / PHARMACODYNAMICS (PK / PD)	
	DURATION OF THERAPY
MINIMAL BACTERICIDIAL CONCENTRATIONS (MBC)	
	PEAK LEVELS
MINIMAL INHIBITORY CONCENTRATIONS (MIC)	
	AREA UNDER THE CURVE (AUC)
SERUM AND TISSUE HALF-LIFE	
	PROTEIN LINK
TOLERABILITY	
	COMPLIANCE
COSTS	
	PHARMACO-ECONOMIC ISSUES

Also after the sharp drop of frequency of all the opportunistic infections which followed the large-scale introduction of HAART in mid-1996 (from 16.5 to 7.9 episodes of bacterial infection per 100 patients-year in our series, comparing years 1994-1995, with years 1997-1998) [10], bacterial complications maintained an appreciable frequency, as noticed with skin-soft tissue infections [11], because of multiple supporting factors also related to the "lifestyle" of patients (i.e. i.v. drug addiction). In this observational study, *S. aureus* proved the predominant pathogen (50% of documented episodes), but the methicillin-resistance rate was limited to 21.7%, as expected in the event of predominantly community-acquired infections, such as those of skin and soft tissues [11]. Still during HIV disease, the enterococcal origin of a number of bacterial complications (especially urinary tract infection and bacteremia), is frequently underestimated: the analysis of 148 consecutive episodes occurred in a decade allowed to demonstrated a neat prevalance of *E. faecalis*, and a potential mortality in the most immunocompromised patients and in those with other concurrent AIDS-related illnessess [12]. The *in vitro* sensitivity assays confirmed a complete efficacy of glycopeptides, and an activity over 90% or more strains was also demonstrated by penicillin G, ampicillin and piperacillin, while erithromycin, chloramphenicol and clindamycin were effective in nearly 70% of tested microbial strains [12].

Finally, when considering 1,249 consecutive *E. faecalis* strains isolated from urine of patients followed at whatsoever Division of our Hospital, a substantial steadiness or even a reduction of antibiotic resistance levels was seen in a three-year period (1999 to 2001), with confirmed efficacy of penicillin, ampicillin, piperacillin and nitrofurantoin (besided the expected, complete activity of both teicoplanin and vancomycin) [13]. Another two year surveillance study conducted at our Hospital in the years 2000 and 2001, including over 5,500 bacterial isolates, underlines a temporal increase of *E. faecium* isolation and a complete sensitivity to glycopeptides, also confirming the different resistance pattern of *E. faecalis* (highly susceptible to semisinthetic penicillins, nitrofurantoin, and levofloxacin, and quinupristin/dalfopristin), and *E. faecium* (clinically sensitive only to gentamicin, linezolid, and infrequently to streptogramins) [14].

Focusing again our attention on *S. aureus* strains isolated in critical care units, a prospective study of ours considered only bacteria cultured from blood or "protected" respiratory secretions, responsible for confirmed sepsis or lower respiratory tract infection, in a three-year period from 1998 to 2000 [15]. Of 535 examined strans (49 from blood cultures), the mean level of methicillin resistance was 62.2%, being more elevated in the respiratory intensive care unit, and significantly lower inferiore in the neonatal-pediatric critical care division, in absence of temporal

variations. When examining the sole methicillin-resistant strains (333 isolates on the whole), a complete *in vitro* efficacy of glycopeptides was confirmed, together with the maintanance of a significant activity also by netilmicin, rifampicin, chloramphenicol, and cotrimoxazole (which tested effective *in vitro* on 46 to 80% of tested strains). This last feature could be exploited when association chemotherapy is needed [15].

A NEW STREPTOGRAMIN ASSOCIATION: QUINUPRISTIN/DALFOPRISTIN

The parenteral streptogramin association quinupristin/dalfopristin is an innovative antibiotic, composed by two different molecules (combined in a 30:70 proportion), which express a highly synergistic activity against susceptible microbial pathogens, based on a double blockade of the polypeptide chain extension (Fig. **1**). This association proves effective against a broad spectrum of gram-positive organism, even when they become resistant to glycopeptides (i.e. streptococci, pneumococci, and especially coagulase-positive and coagulase-negative staphylococci, *Clostridium* and *Peptostreptococcus* spp., and enterococchi, with the partial exception of multiresistant *E. faecium* (whose susceptibility index is however around 20% of tested strains) [6, 16]. The *in vitro* spectrum of activity of quinupristin/dalfopristin is also extended towards multiple relevant gram-negative pathogens, including *Legionella pneumophila*, *Moraxella catarrhalis*, and *Mycoplasma pneumoniae* [3, 5]. The breakpoint values of quinupristin/dalfopristin recommended for *in vitro* dilution techniques for minimum inhibitory concentrations (MIC) determination are $\leq$1 μg/mL for sensitive microorganisms, 2 μg/mL for moderately susceptible (or "intermediate") organisms, and $\geq$4 μg/mL per isolates defined as resistant [5]. The development of induced (acquired) resistance against quinupristin/dalfopristin is expected to be a very rare event: the frequency of mutations occurring in staphylococcal and enterococcal strains ranges from 10^{-9} and 10^{-11} [5], while confirmed *in vivo* resistance is approximately 2% of treated episodes, and may be responsible for clinical failure [3].

Due to its prolonged post-antibiotic effects (ranging from 2-6 hours for methicillin-resistant *S. aureus*, to over 18 hours for *Streptococcoccus pyogenes*) [3, 5, 16], the quinupristin/dalfopristin association has a potent *in vitro* synergistic activity (often confirmed by *in vivo* experiences) with an elevated number of other antimicrobial drugs, including rifampicin, glycopeptides, ciprofloxacin, ampicillin, and some cephalosporins, against meticillin-resistant staphylococci, and again glycopeptides, tetracyclines, and penicillins protected by beta-lactamase inhibitors, against *E. faecalis* strains which test resistant to vancomycin [3, 5].

Given the *in vitro* spectrum of activity, the clinical indications for quinupristin/dalfopristin administration presently include lower airways infections, infection of skin and soft tissues, and vancomycin-resistant *E. faecium* disease (regardless of the interested body site), due to the diffuculty to have an effective treatment of these severe pathologies determined by multiresistant strains [3, 6, 16]. The initial, current dosage (7.5 mg per Kg of body weight, every 8 hours), needs i.v. administration through extensive dilution in glucosate solution, and preferabily by a central venous line 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.

On the ground of the available clinical and literature evidences, 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 conditions borne by a high risk of presence of multiresistant gram-positive agents, which failed to respond (clinically or microbiologically) to at least three days of a teicoplanin- or vancomycin-including antimicrobial administration. A combination chemotherapy (including glycopeptides themselves, or rifampicin, aminoglycosides, cotrimoxazole, etc.), may be attempted on empiric basis or after *in vitro* susceptibility assays, in order to exploit the above-mentioned synergistic effects [3, 5, 7]. 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 and kidney failure). While quinupristin/dalfopristin dosage does not need adjustment until renal insufficiency becomes severe, when liver failure is

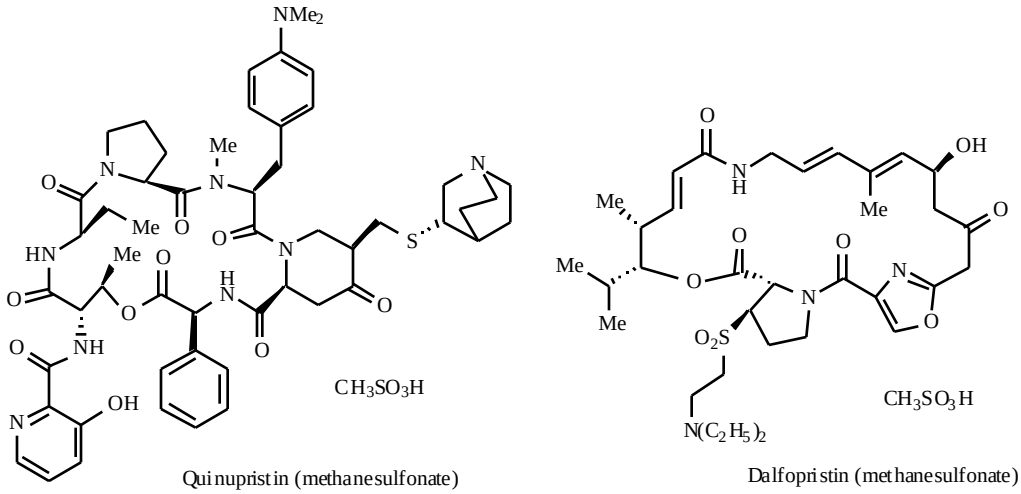

Fig. (1). Structure of Quinupristin and Dalfopristin (CAS Registry No. 126602-89-9).

of concern a reduced daily dosage and strict monitoring of hepatic function are recommended; should a end-organ liver disease is present, the administration of quinupristin/dalfopristin becomes contraindicated.

CLINICAL EXPERIENCES WITH QUINUPRISTIN/ DALFOPRISTIN

Relevant randomized multicentre clinical trials, and an extensive array of anecdotal case reports or small case series with quinupristin/dalfopristin administered on compassionate basis, confirmed the elevated efficacy of this novel streptogramine antibiotic in the treatment of pneumonia and severe skin-soft tissue infection, as well as surgical wound infection registered in nosocomial settings [3, 5, 17, 18, 19].

Among randomized clinical trials, a special interest is devoted the comparison of quinupristin/dalfopristin with vancomycin in the management of gram-positive nosocomial pneumonia in critical care units [17], the comparison with cefazolin, oxacillin, and vancomycin in the therapy of skin-soft tissue infection [18], and the study focused on *E. faecalis* disease [19]. The very favorable results obtained in these preliminary experiences hypothesized the use of quinupristin/dalfopristin in experimental protocols of eradication of methicillin-resistant staphylococcal colonization [20], and as an empiric choice for neoplastic patients with febrile neutropenia [21], as synthetized in the analysis published in the year 2003 by the reknown Cochrane Library.

As mentioned above, during the pre-registration period the drugs has been delivered on compassionate basis 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 first literature repors, we underline a wide spectrum ofdifficult-to-treat and life-threatening endocarditis,such as enterococcal endocarditis on a prosthetic valve [22], multiresistant *S. epidermidis* endocarditis [23], those due to multiresistant *S. aureus* occurring artificial valve and no chance of surgery [24], as well as *Enterococcus faecium* heart localization, where a combination with doxicyclin, rifampicin, and high-dose ampicillin was successfully experimented, and a demonstration of sinergystic activity given [25, 26].

Given the low cerebrospinal fluid concentrations obtained after parenteral administration of quinupristin/dalfopristin [27], 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. intratecal or intraventricular) [27-29], with a mean dosage of 2 mg, and in absence of significant untoward events; in one case of meningitis quinupristin/dalfopristin was concurrently administered at full dosage by i.v. route [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 [30].

Further clinical series confirmed the relevant role of quinupristin/dalfopristin in the treatment of *E. faecium* too, in the immunocompromised host [31].

Also in pediatric age, preliminary observations conducted on 11 overall children [32, 33], underlined the bacteriological and clinical efficacy and the safe tolerability profile of quinupristin/dalfopristin, in the management of vancomycin-resistant Enterococcal intrabdominal infection and septicemia, in patients who underwent bone marrow transplantation during treatment of hematological malignancies [32], and in other young patients with an underlying severe immunosuppression [33]; the association with teicoplanin showed a synergistic effect also in these last cases [32].

A concomitant kidney failure followed by organ transplantation did not impair the effectiveness of this streptogramin combination in multivisceral and disseminated infections caused by multiresistant *S. epidermidis* strains, sometimes in combination with chloramphenicol, and after failure of multiple therapeutic attempts carried out with glycopeptides [34]. A more recent experience of the same research group, enlarged to six patients undergoing hemodialysis (one submitted to renal transplantation, and four borne be a concomitant liver insufficiency), 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 [35]. However, especially when transplanted patients undergoing an immunosoppressive 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 [36].

Finally, the diffusion 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. *Streptococcus mitis* and *Streptococcus pneumoniae* in a broad surveillance study) [37], as well as some *E. faecium* isolates [38], which became intrinsecally resistant to streptogramins, regardless of the prior use of antibiotics belonging to the same of similar classes [37]. In these last reports, the concomitant resistance to all available glycopeptides indicated the novel oxazolidinone linezolid as the only potentially effective alternative therapeutic choice [38-41].

PRESENT AND FUTURE THERAPEUTIC INDICATIONS OF THE ASSOCIATION QUINUPRISTIN/-DALFOPRISTIN

As can be drawn from the results of the above-mentioned controlled studies, and the numerous, intriguing case reports and case series, quinupristin/dalfopristin appears 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 [40]. The same antimicrobial combination proved effective in five more cases of severe staphylococcal infection, recently reported by Sgarabotto and coworkers [42]. The spectrum of activity of this dual streptogramin combination, since it remains restricted to gram-positive cocci, recommends the association with other antinmicrobial agents with elarged spectrum of action, when a polymicrobial infection is suspected, or a mixed flora containing gram-positive and gram-negative organisms is of concern [3, 5, 26, 39, 42].

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 [5]. 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) / 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.

Both quinupristin and dalfopristin are modified by the liver activity into different main metabolites, which contribute to the antimicrobial action of quinupristin/dalfopristing, thanks to its intrinsic activity, and the maintained synergistic acivity between themselvels and the administered molecules [3, 5]. Since the metabolism is principally operated by the hepatic cytochrome system P450, pharmacological interactions with all drugs which interact with the same detoxification system are expected: in particular, terfenadine, astemizole, cisapride, disopiramide, quinidine, lidocaine, nifedipine and midazolam, as well as drugs borne by the possibility to give a prolongation of QT interval (antiarrhitmics, neuroleptics, antidepressive drugs, antimalaric compounds, fluoroquinolones, azole antifungal agents, and macrolides). A permanent monitoring of serum levels (when possible) or clinical effect of these last drugs, and extreme clinical attention to possible adverse events, and eventual need of dosage adjustment, are strongly warranted for patients who required a continued administration of the above-mentioned drugs, concurrently with that of quinupristin/dalfopristin [3, 5]. 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 dosage adjustment deserve careful attention [5, 35].

The adverse events registsred upon administartion of quinupristin/dalfopristin include predominantly gastrointestinal tract disturbancess (nausea, vomiting, and diarrhea), followed by hyperbilirubinemia, cutaneous rash, and diffuse arthromyalgia [3, 5, 41]. These last symptoms seem to be more frequent among hepatopathic and transplanted patients, and those treated with cyclosporin, although the mechanism of action of this untoward event still remains unknown [44]. The administration of quinupristin/dalfopristin in hospital setting, and through central venous lines and appropriate fluid dilution, significantly reduces the risk of local phlogosis (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 *E. faecium*, *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 lines, or tunnellized catheters: 16 subjects out of 37 (43.2%) showed mild-to-moderate local intolerance, during or after i.v. drug infusion [45].

CONCLUSIONS

The recent availability of quinupristin/dalfopristin and that 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.

During the next future, 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 now the two above-mentioned recent molecules [3]. Among the more promising agent under final development in the year 2004 we can quote novel cephalosporins (BAL-9141 e RWJ-54428), which are expected to overcome methicillin resistance, further glycopeptide derivatives such as oritavancin and dalvavancin, and especially the lipopeptide daptomycin. Among the topoisomerase inhibitors, several fluoroquinolones are awaited, including gemifloxacin, sitafloxacin, and garenoxacin. Finally, when considering inhibitors of bacterial protein synthesis, the ketolides telitromycin and cetromycin, the novel oxazolidinones (further to linezolid), and the glycylcyclines (with tigecyclin as the first compound of this class) [46-48], are very promising agents for the fight against severe and life-threatening resistant gram-positive infections.

REFERENCES

[1] Karchmer, A.W. *Clin. Infect. Dis.*, **2000**, *31* (Suppl. 4), S139.
[2] Wenzel, R.P.; Edmond, M.B. *Clin. Infect. Dis.*, **1998**, *27*, 245.
[3] Linden, P.K. *Drugs*, **2002**, *62*, 425.
[4] Edmond, M.B.; Wallace, S.E.; McClish, D.K.; Pfaller, M.A.; Jones, R.N.; Wenzel, R.P. *Clin. Infect. Dis.*, **1999**, *29*, 239.
[5] Lamb, H.M.; Figgitt, D.P.; Faulds, D. *Drugs*, **1999**, *58*, 1061.
[6] Nicoletti, G.; Bonfiglio, G.; Bartoloni, A.; Mattina, R.; Nicoletti, P.; Pecile, P.; Rescaldani, R.; Romeo, M.A.; Russo, G.; Savarino, O.; Stefani, S.; Paradisi, F. *Int. J. Antimicrob. Agents*, **2000**, *15*, 265.
[7] Marshall, S.A.; Wilke, W.W.; Pfaller, M.A.; Jones, E.N. *Diagn. Microbiol. Infect. Dis*.,**1998**, *30*, 205.
[8] Anonymous. *MMWR*, **1997**, *46*, 624.
[9] Manfredi, R.; Nanetti, A.; Ferri, M.; Coronado, O.V.; Mastroianni, A.; Chiodo, F. *J. Antimicrob. Chemother.*, **1996**, *38*, 910.
[10] Manfredi, R.; Nanetti, A.; Ferri, M.; Chiodo, F. *AIDS*, **1999**, *13*, 1274.
[11] Manfredi, R.; Calza, L.; Chiodo, F. *J. Cutan. Pathol.*, **2002**, *29*, 168.

[12] Manfredi, R.; Nanetti, A.; Valentini, R.; Calza, L.; Chiodo, F. *New Microbiol.*, **2002**, *25*, 179.
[13] Manfredi, R.; Nanetti, A.; Valentini, R.; Morelli, S.; Ferri, M.; Calza, L.; Chiodo, F. *Recenti Progr. Med.*, **2002**, *93*, 681.
[14] Manfredi, R.; Nanetti, A.; Valentini, R.; Morelli, S.; Calza, L. *Infect. Dis. Clin. Pract.*, **2004**, *12*, 163.
[15] Manfredi, R.; Nanetti, A.; Valentini, R.; Calza, L.; Chiodo, F. *Infect. Dis. Clin. Pract.*, **2002,** *11*, 427.
[16] Speciale, A.; La Ferla, K.; Caccamo, F.; Nicoletti, G. *Int. J. Antimicrob. Agents*, **1999**, *13*, 21.
[17] Fagon, J.; Patrick, H.; Haas, D.W.; Torres, A.; Gibert, C.; Cheadle, W.G.; Falcone, R.E.; Anholm, J.D.; Paganin, F.; Fabian, T.C.; Lilienthal, F. *Am. J. Respir. Crit. Care Med.*, **2000**, *16*, 753.
[18] Nichols, R.L.; Graham, D.R.; Barriere, S.L.; Rodgers, A.; Wilson, S.E.; Zervos, M.; Dunn, D.L.; Kreter, B. *J. Antimicrob. Chemother.*, **1999,** *44*, 263.
[19] Moellering, R.C.; Linden, P.K.; Reinhardt, J.; Blumberg, E.A.; Bompart, F.; Talbot, G.H. *J. Antimicrob. Chemother.*, **1999**, *44*,251.
[20] Loeb, M.; Main, C.; Walker, C.; Eady, A. *The Cochrane Library*, Issue 1, **2003**.
[21] Paul, M.; Vidal, L.; Cohen, M.; Clark, O.; Soares-Weiser, K.; Leibovici, L. *The Cochrane Library*, Issue 1, **2003**.
[22] Furlong, W.B.; Rakowski, T.A. *Clin. Infect. Dis.*, **1997**, *25*, 163.
[23] Larkin, J.; Busciglio, L.; Fontanet, H.; Gamouras, G. *Clin. Infect. Dis.*, **1998**, *26*, 1239.
[24] Viale, P.; Scolari, C.; Colombini, P.; Cristini, F.; Cadeo, B.; Pagani, L. *J. Chemother.*, **2002**, *14*, 526.
[25] Matsumura, S.; Simor, A.E. *Clin. Infect. Dis.*, **1998**, *27*, 1554.
[26] Thompson, R.L.; Lavin, B.; Talbot, G.H. *South Med. J.*, **2003**, *96*, 818.
[27] Garey, K.W.; Tesoro, E.; Muggia, V.; Pasquier, O.; Rodvold, KA. *Pharmacotherapy*, **2001**, *21*, 748.
[28] Tan, T.Y.; Pitman, I.; Penrose-Stevens, A.; Simpson, B.A.; Flanagan, P.G. *J. Infect.*, **2000**, *41*, 95.
[29] Williamson, J.C.; Glazier, S.S.; Peacock, J.E. Jr. *Clin. Neurol. Neurosurg.* **2002**, *104*, 54.
[30] Summers, M.; Misenhimer, G.R.; Antony, S.J. *South Med. J.*, **2001**, *94*, 353.
[31] 31.Cassell, J.; Balakrishnan, I.; Samarasinghe, D.; Mistry, P.; Prentice, H.G.; Gillespie, S.H. *J. Infect.*, **1998**, *36*, 324.
[32] Carretto, E.; Barbarini, D.; Locatelli, F.; Giraldi, E.; Pellegrini, N.; Perversi, L.; Grossi, P.; Marone, P.; Bonetti, F. *Haematologica*, **2000**, *85*, 1158.
[33] Gray, J.W.; Darbyshire, P.J.; Beath, S.V.; Kelly, D., Mann, J.R. *Pediatr. Infect. Dis. J.* **2000**, *19*, 234.
[34] Mundlein, E.; Von Baum, H.; Geiss, H.K.; Springsklee, M.; Zeier, M.; Andrassy, K. *Infection*, **1997**, *25*, 252.
[35] Schwenger, V.; Mundlein, E.; Dagrosa, E.E.; Fahr, A.M.; Zeier, M.; Mikus, G.; Andrassy, K. *Infection*, **2002**, *30*, 257.
[36] Stamatakis, M.K.; Richards, J.G. *Ann. Pharmacother.*, **1997**, *31*, 576.
[37] Kugler, K.C.; Denys, G.A.; Wilson, M.L.; Jones, R.N. *Diagn. Microbiol. Infect. Dis.*, **2000**, *36*, 269.
[38] McNeil, S.A.; Clark, N.M.; Chandrasekar, P.H.; Kauffman, C.A. *Clin. Infect. Dis.*, **2000**, *30*, 403.
[39] Eliopoulos, G.M. *Clin. Infect. Dis.*, **2003**, *36*, 473.
[40] Scotton, P.G.; Rigoli, R., Vaglia, A. *Infection*, **2002**, *30*, 161.
[41] Raad, I.; Hachem, R.; Hanna, H.; Afif, C.; Escalante, C.; Kantarjian, H.; Rolston, K. *J. Antimicrob. Chemother.*, **2004**, *53*, 646.
[42] Brown, J.; Freeman, B.B. *Ann. Pharmacother.*, **2004**, *38*,677.
[43] Sgarabotto, D.; Cusinato, R.; Narne, E.; Scano, F.; Zignol, M.; Gambino, A.; Cattelan, A.; Meneghetti, F.; Cadrobbi, P. *Scand. J. Infect. Dis.*, **2002**, *34*, 122.
[44] Carver, P.L.; Whang, E.; VandenBussche, H.L.; Kauffman, C.A.; Malani, P. *Pharmacotherapy*, **2003**, *23*,159.
[45] Rehm, S.J.; Graham, D.R.; Srinath, L.; Prokocimer, P.; Richard, M.P.; Talbot, G.H. *J. Antimicrob. Chemother.*, **2001**, *47*, 639.
[46] Abbanat, D.; Macielag, M.; Bush, K. *Expert Opin. Investig. Drugs*, **2003**, *12*, 379.
[47] Guay, D.R. *Pharmacotherapy*, **2004**, *24*, 58.
[48] Hershberger, E.; Donabedian, S.; Konstantinou, K.; Zervos, M.J. *Clin. Infect. Dis.*, **2004**, *38*, 92.