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Current and future management of infections due to methicillin-resistant staphylococci infections: the role of quinupristin/dalfopristin

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The rise in the number of multidrug-resistant Gram-positive bacteria that has occurred in recent years has resulted in the development of infections that are difficult to treat, and also in severely restricted treatment options. In particular, the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased, with strains shown to cause up to 21% of skin infections and 59.6% of nosocomial pneumonia. Recently, strains of *S. aureus* with reduced susceptibility to vancomycin (glycopeptide-intermediate *S. aureus* or GISA) are causing great concern, particularly as vancomycin has been the agent of choice in the treatment of infection caused by MRSA. GISA has been identified in Japan, the USA and Europe. New agents that have anti-MRSA activity are now being investigated. These include the novel streptogramin, quinupristin/dalfopristin. This report examines the activity of quinupristin/dalfopristin against strains of *S. aureus* and coagulase-negative staphylococci, including multidrug-resistant MRSA and GISA.

Introduction

Despite advances in antibacterial therapy over the last 20 years, the incidence of infections caused by multidrug-resistant Gram-positive bacteria is increasing. Gram-positive bacteria are frequently resistant to most currently available antimicrobials, and the infections they cause are therefore extremely difficult to treat. In the two decades since the emergence of methicillin-resistant staphylococci (MRS), there has been a sharp increase in the incidence of MRS infections, particularly in association with foreign bodies and indwelling medical devices.[1] Increasing cross-resistance to β-lactams, macrolides, lincosamides and aminoglycosides has severely restricted treatment options. The prevalence of Gram-positive pathogens resistant to antibacterial agents in current use, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin- and erythromycin-resistant pneumococci, and vancomycin- and teicoplanin-resistant enterococci, is increasing. The recent identification of strains of *S. aureus* with reduced susceptibility to vancomycin (glycopeptide-intermediate *S. aureus* or GISA)[2–4] has caused great concern because vancomycin has been the antimicrobial agent of choice in the treatment of infections caused by MRSA. The likelihood that vancomycin resistance may also be transferred from enterococci to *S. aureus* and perhaps also to coagulase-negative staphylococci is of concern. Consequently, new antibacterial agents that are active against multidrug-resistant pathogens are urgently needed for the treatment of severe multiresistant hospital infections and community-acquired infections.[5,6]

Epidemiology of staphylococcal infections

The primary staphylococcal pathogens encountered in clinical practice are *S. aureus* and coagulase-negative staphylococci (CNS; *Staphylococcus epidermidis*, *Staphylo - coccus haemolyticus* and *Staphylococcus saprophyticus*). Gram-positive organisms were the causative agent in 59.6% of bloodstream infections reported in a study conducted at 43 medical centres throughout the USA. In this study, staphylococci were the most frequently isolated pathogens (38.6%).[7] In European Intensive Care Units (ICUs), 30% of all infections were attributable to *S. aureus*, with 60% being oxacillin-resistant or methicillin-resistant; 19% of infections were due to CNS.[8] Other recent studies have also documented high rates of coagulase-negative and -positive staphylococcal bacteraemia, especially in

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compromised patients (e.g. ICU or burn patients, those with malignant disease or agranulocytosis) resulting from use of colonized intravascular catheters.[9,10]

Skin and skin structure infections

Skin and skin structure infections are often caused by Gram-positive bacteria such as *S. aureus* and *Streptococcus pyogenes*. Infections caused by methicillin-resistant staphylococci (MRS) have been reported to account for up to 21% of skin infections.[11] These infections are often difficult to treat because of widespread cross-resistance to aminoglycosides, macrolides, lincosamides, tetracyclines, cephalosporins, carbapenems, β-lactamase inhibitor combinations, trimethoprim and the sulphonamides.[11]

Nosocomial pneumonia

Gram-positive bacteria are becoming an increasingly common cause of nosocomial pneumonia, with *S. aureus* accounting for the majority of such infections. *S. aureus* was the primary pathogen responsible for nosocomial pneumonia reported by the National Nosocomial Infection Surveillance (NNIS) study between 1985 and 1992, accounting for 20% of cases.[12] In the European Prevalence of Infection in Intensive Care (EPIC) study, *S. aureus* (31.7%) was the most frequently isolated pathogen in ICU patients with nosocomial pneumonia.[13] Of the ICU-acquired infections associated with *S. aureus*, 59.6% were reported to be MRSA strains.[13]

Bacteraemia

Gram-positive organisms are the predominant pathogens in catheter-related infections and there has been a particularly striking increase in the contribution of CNS between the 1980s and the 1990s. In the USA, CNS and *S. aureus* are implicated in 33% and 19% of nosocomial bacteraemia cases, respectively.[14] In Spain, CNS and *S. aureus* are implicated in 24% and 18% of all cases of nosocomial bacteraemia.[10] Intravascular catheters are the most frequent portal of entry for staphylococcal species and staphylococcal species are the most frequently implicated pathogen in catheter-related bacteraemia. Of 513 cases of bacteraemia at a Spanish hospital between 1981 and 1990, 50% and 25% were caused by *S. epidermidis* and *S. aureus*, respectively.[15] The prevalence of infection due to MRSA varies depending on the characteristics and size of the hospital. In the USA, approximately 25% of *S. aureus* bloodstream isolates are resistant to methicillin and higher rates of MRSA have been reported at institutions where MRSA strains are endemic. In addition, the incidence of methicillin-resistant CNS rose from 20% to 60% as reported by the recent SCOPE project.[16]

Therapeutic strategies

The glycopeptides (vancomycin and teicoplanin) have been one of the last therapeutic options for infections due to multidrug-resistant Gram-positive organisms, including MRSA.[17] Despite this, the glycopeptides are far from perfect antimicrobial agents.

Vancomycin, in particular is only slowly bactericidal against staphylococci. Also, glycopeptides do not penetrate well into cerebrospinal fluid, and high doses of vancomycin must be given if the drug is to be used for the treatment of meningitis. In addition, glycopeptides are potentially nephrotoxic, and rapid infusion of vancomycin often produces symptomatic histamine release ('red-man' syndrome).[18] Despite these drawbacks, glycopeptides have been useful in the management of multidrug-resistant infections, as there have been few, if any, alternative antimicrobial agents with activity against these bacteria.

Vancomycin resistance became a significant clinical problem in the 1980s with the development of vancomycin-resistant *Enterococcus faecium* (VREF).[19–21] During this decade there were sporadic reports of cases of vancomycin and/or teicoplanin resistance, or reduced susceptibility, among clinical strains of *S. epidermidis* and *S. haemolyticus*.[11,19,22] Fortunately, glycopeptide resistance did not spread to *S. aureus*. Because of these concerns, in the USA the Centers for Disease Control and Prevention have discouraged the widespread use of vancomycin.[23] Even so, in 1996 a strain of *S. aureus* with reduced susceptibility to vancomycin (glycopeptide-intermediate *S. aureus* or GISA) was identified in Japan.[2] Two cases involving GISA strains were later identified at different locations in the USA in 1997 and in 1995 a GISA strain was isolated from the bloodstream of a 2-year-old child in France.[3,4,24] Decreased teicoplanin susceptibility has also been reported in clinical MRSA isolates.[25] Furthermore, under laboratory conditions it has been possible to transfer high-level vancomycin resistance from *Enterococcus faecalis* to *S. aureus*.[26] Vancomycin has been the antimicrobial agent of choice of MRSA for more than 15 years,[1] and the impending emergence of *S. aureus* with complete resistance is causing great concern.[27]

Alternatives to vancomycin in the treatment of MRSA infections

Fusidic acid, rifampicin, chloramphenicol, imipenem and ciprofloxacin all have potential activity against MRSA.[28,29] Rahman[29] states that he had never found an isolate of MRSA that was not sensitive to at least five different classes of antibiotics available in the UK. However, because of the concern regarding increasing vancomycin resistance, there is now a clinical need for new types of compounds for the treatment of MRSA pathogens that are also effective against other Gram-positive and -negative

organisms. Several investigational compounds with anti-MRSA activity exist, including quinupristin/dalfopristin (a novel streptogramin), glycylcyclines, oxazolidinones and several new quinolones (Table I). Glycylcyclines are new tetracycline analogues, still in development, which exhibit activity in MRSA and vancomycin-resistant enteroccoci.[30] The new quinolones, such as clinafloxacin, have also shown activity against *S. aureus* and in particular, against MRSA.[31,32]

Quinupristin/dalfopristin: antimicrobial activity and pharmacology

There is a clear need for antimicrobial agents with activity against multidrug-resistant Gram-positive staphylococci regardless of resistance phenotype. Quinupristin/dalfopristin, the first injectable streptogramin antibiotic, is an innovative treatment for multidrug-resistant Gram-positive infections. It is composed of two semisynthetic streptogramin molecules derived from *Streptomyces pristinaespirali*, quinupristin (a group B or type I streptogramin) and dalfopristin (a group A or type II streptogramin). The combination of these two derivatives in a 30:70 (w/w) mixture has synergic antibacterial activity *in vitro* against a wide range of Gram-positive organisms. Quinupristin/dalfopristin is active against most strains of *S. aureus* and CNS (e.g. *S. epidermidis*, *S. haemolyticus*), including multidrug-resistant, MRSA and GISA strains.[5,6,33–46] Quinupristin/dalfopristin has proven effective in experimental animal models of infection (e.g. endocarditis, septicaemia, soft tissue) caused by *S. aureus* including erythromycin-susceptible or -resistant MRSA.[34,36,47–51]

Clinical efficacy of quinupristin/dalfopristin in staphylococcal infections

Skin and skin structure infections. Two randomized, open, multicentre trials have compared quinupristin/dalfopristin 7.5 mg/kg bd with standard therapy in patients with complicated Gram-positive skin and skin structure infections. Standard therapy was either oxacillin 2 g qds or vancomycin 1 g bd in the USA trial[52] and cefazolin 1 g tds or vancomycin 1 g bd in the global trial.[53] The USA trial and the global trial enrolled 450 and 443 patients, respectively, and the treatment duration was 4–14 days. The predominant pathogens isolated at baseline were staphylococci (mainly *S. aureus* and some CNS, which were generally *S. epidermidis*). The clinical success rate and bacteriological success rate for patients with staphylococci as a baseline pathogen were equivalent in those treated with quinupristin/dalfopristin or comparators.[54]

Nosocomial pneumonia. Fagon *et al.*[55] determined the efficacy and tolerability of quinupristin/dalfopristin 7.5 mg/kg tds plus aztreonam 2 g tds versus vancomycin 1 g bd plus aztreonam 2 g tds for 5–14 days in a randomized, non-blind, multicentre study. A total of 298 patients with acute Gram-positive nosocomial pneumonia were enrolled. The addition of tobramycin was permitted if *Pseudomonas aeruginosa* was isolated, and imipenem could be substituted for aztreonam if aztreonam-resistant organisms were isolated. The predominant baseline pathogen was *S. aureus*. The clinical success rate (Table II) and bacteriological success rate (Table III) for patients with *S. aureus* as a baseline pathogen were equivalent in those treated with quinupristin/dalfopristin or vancomycin in combination with aztreonam.

Bacteraemia. Talbot *et al.*[56] performed an efficacy analysis of quinupristin/dalfopristin for patients with positive blood cultures in global phase III studies. A total of seven studies were analysed, five of which were comparative and two were non-comparative. The indications in the comparative studies were nosocomial pneumonia, community-acquired pneumonia, and complicated skin and skin structure infection, while the non-comparative studies were part of the emergency-use programme. The dosage of quinupristin/dalfopristin was 7.5 mg/kg either twice or three times daily. Depending on the indication, comparator agents were vancomycin, ceftriaxone plus erythromycin, or oxacillin plus cefazolin at clinically appropriate dosages. The global

Table I. New compounds with anti-MRSA activity

Group	Compound	Manufacturer	Development phase
Streptogramin	quinupristin/dalfopristin	Rhône-Poulenc Rorer	available 1999
Glycylcyclines	DMG-DMDOT		
	DMG-MINO	Wyeth-Lederle	preclinical
Oxazolidinones	linezolid	Pharmacia & Upjohn	phase III
Quinolones	clinafloxacin	Parke Davis	phase III
Polypeptides	daptomycin	Cubist Pharmaceuticals	phase II
	LY 333328	Lilly	phase I

Table II. Clinical success rate[a] following treatment with quinupristin/dalfopristin or vancomycin in combination with aztreonam in bacteriologically evaluable patients with acute *S. aureus* nosocomial pneumonia[55]

	No. of patients (%) cured or improved	
Patients with *S. aureus* infection at baseline	quinupristin/dalfopristin + aztreonam	vancomycin + aztreonam
All patients[b]	27/51 (52.9)	27/54 (50.0)
Patients with monomicrobial infection	14/28 (50.0)	16/28 (57.1)
Patients with polymicrobial infection	13/23 (56.5)	11/26 (42.3)
Patients intubated at baseline[b]	22/43 (51.2)	19/43 (44.2)

[a]Clinical success rate was defined as: (cured + improved)/total.
[b]Primary efficacy criterion. The analysis of the difference in clinical success rates between quinupristin/dalfopristin and vancomycin treatment was (95% CI: –16.8, 12.8), indicating equivalence. Equivalence was also demonstrated between the treatment groups for the patients intubated at baseline (95% CI: –16.1, 17).

Table III. By-pathogen bacteriological success rate[a] following treatment with quinupristin/dalfopristin or vancomycin in combination with aztreonam in bacteriologically evaluable patients with acute *S. aureus* nosocomial pneumonia[55]

	No. of pathogens (%) eradicated, presumed eradicated or satisfactorily reduced	
Organism	quinupristin/dalfopristin + aztreonam	vancomycin + aztreonam
All *S. aureus* isolated	30/52 (57.7)	33/55 (60.0)
methicillin-resistant	8/21 (38.1)	13/20 (65.0)
methicillin-sensitive	21/30 (70.0)	16/30 (53.3)
methicillin test not done	2/2	4/5

[a]Bacteriological efficacy was analysed by number of patients (by-patient analysis) or pathogens (by-pathogen analysis) with success rate defined as (eradication + presumed eradication + satisfactory reduction)/total.

analysis involved only patients with bacteraemia with or without a primary site of infection. A total of 2672 patients were enrolled into the global phase III studies. Among the 1193 bacteriologically evaluable patients, 150 (12.6%) were bacteraemic at study entry. By indication, the percentage of bacteraemic patients among bacteriologically evaluable patients ranged from 8.0% for complicated skin and skin structure infections to 27.3% for nosocomial pneumonia. Clinical success rates ranged from 57.1 to 85.2% in the quinupristin/dalfopristin group and from 17.6 to 88.9% in the comparator groups (Table IV). In the Emergency-use programme, quinupristin/dalfopristin demonstrated success rates of approximately 80% in central catheter-related bacteraemia.[57] The bacteriological success rate in the evaluable population with *S. aureus* (including MRSA) was 8/14 (57.1%) for patients treated with quinupristin/dalfopristin and was slightly lower for those treated with comparators (10/22 patients, 45.4%). There were no cases of bacteraemia caused by CNS in this series of patients. In a multicentre open Phase II study, quinupristin/dalfopristin (5.0 mg/kg every 8 h (n = 11) or 7.5 mg/kg every 8 h (n = 14)) was shown to be at least as efficacious as vancomycin (1000 mg every 12 h, n = 13) in the treatment of catheter-related, Gram-positive bacteria (Table V).[57] Overall success rates were slightly higher for both quinupristin/dalfopristin groups than for vancomycin.[57]

Conclusions

Most ICU patients receive empirical therapy with antibiotics, which, if used appropriately, can dramatically improve prognosis. However, the use of broad-spectrum antibiotics also greatly increases the risk of development of resistant strains. Empirical therapy must therefore be chosen judiciously.

Gram-positive nosocomial pathogens such as *S. aureus* and CNS are becoming an increasingly frequent cause of severe infections in hospital patients. The steady worldwide increase in the prevalence of multidrug-resistant pathogens highlights the need for new therapeutic options. Increasing cross-resistance to β-lactams, macrolides, lincosamides, aminoglycosides and vancomycin has severely restricted treatment options.

Table IV. Bacteraemia analysis: clinical and bacteriological success rates[56]

Criteria	No. of patients or pathogens/total (%)	
	Q/D	comparator
Clinical success rate[a]		
complicated skin and skin structure infection	8/14 (57.1)	8/14 (57.1)
community-acquired pneumonia	23/27 (85.2)	24/27 (88.9)
nosocomial pneumonia	4/7 (57.1)	3/17 (17.6)
emergency-use programme	30/44 (68.2)	NA
Bacteriological success rate (by-pathogen)[a,b]		
complicated skin and skin structure infection		
S. aureus (including methicillin-resistant)	2/6	4/6
S. epidermidis	1/2	1/1
total	9/15 (60.0)	9/15 (60.0)
community-acquired pneumonia		
S. aureus	–	1/3
total	23/27 (85.2)	26/28 (92.9)
nosocomial pneumonia		
S. aureus	4/6	5/13 (38.5)
total	5/7	7/17 (41.2)
emergency-use programme		
S. aureus	2/2	NA
total	33/44 (75.0)	NA
all infections combined		
S. aureus (including methicillin-resistant)	8/14 (57.1)	10/22 (45.4)
S. epidermidis	2/3	1/1

[a]Clinical success rate (in the bacteriologically evaluable population) was defined as: (cured + improved)/total; bacteriological success rate (in the bacteriologically evaluable population) was defined as number of patients (by-patient analysis) or pathogens (by-pathogen analysis) with: (eradication + presumed eradication)/total.
[b]Only pathogens isolated from ⩾1 patient are listed separately; all pathogens are included in the totals.
NA, not applicable.
Q/D, quinupristin/dalfopristin.

Table V. Central catheter-related bacteraemia: clinical and bacteriological success rates (clinically and bacteriologically evaluable patients) from a phase II comparison with vancomycin[57]

Population	Number of patients or pathogens/total		
	Q/D 5.0 mg/kg 8-hourly	Q/D 7.5 mg/kg 8-hourly	vancomycin 1 g 12-hourly
Overall success rate[a]	5/7	5/6	2/4
Clinical success rate	5/6	5/7	2/4
S. aureus	1/2	3/5	1/2
CNS	4/4	2/2	1/2
Bacteriological success rate (by-pathogen)	6/7	7/8	2/4
S. aureus	1/2	5/6	1/2
methicillin-resistant	–	2/2	–
CNS	5/5	2/2	1/2
methicillin-resistant	1/1	1/1	–

[a]Primary efficacy criterion.
Q/D, quinupristin/dalfopristin.

Quinupristin/dalfopristin is active against a range of Gram-positive bacteria that are resistant to other available antimicrobials, and is effective in the management of multidrug-resistant Gram-positive infections, including those occurring in severely ill patients. For selected indications and patients, quinupristin/dalfopristin might reduce the principal disadvantages of other antimicrobial classes, such as allergic reactions, limited antibacterial spectrum of activity, toxicity or inconvenient administration. The focused spectrum of activity of quinupristin/dalfopristin suggests that it will be particularly effective as single agent therapy in the treatment of monomicrobial infections, or in combination with an antibiotic with activity against Gram-negative pathogens in the treatment of polymicrobial infections. When resistance of Gram-positive pathogens to all other antibacterial agents, including glycopeptides, is an issue, or in patients who are allergic to glycopeptides, or in patients receiving concomitant nephrotoxic medication, quinupristin/dalfopristin may be the only therapeutic option.

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