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Antimicrobial susceptibility of blood culture isolates of viridans streptococci: relationship to a change in empirical antibiotic therapy in febrile neutropenia

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This study investigated the antibiotic susceptibilities of 67 isolates of viridans streptococci from 61 cases of bacteraemia in immunocompromised paediatric patients with malignancy. The majority of patients (87%) had received prior courses of empirical antibiotic therapy, which consisted of ceftazidime plus amikacin during period 1 and piperacillin/tazobactam plus amikacin during period 2. Susceptibility to vancomycin and quinupristin/dalfopristin was 100%. Susceptibility to β-lactam antibiotics varied. For period 1, the geometric mean MICs of all β-lactams tested against blood culture isolates (n = 31) exceeded those against isolates (n = 36) collected from blood after the change in empirical therapy (by 3.3-fold for ceftazidime, 2.8-fold for piperacillin/tazobactam and 1.6-fold for penicillin). The selection of a β-lactam antibiotic for empirical therapy must be made with care, as repeated courses of certain agents may be more likely to select for viridans streptococci with diminished susceptibility.

Introduction

Resistance to penicillin amongst viridans streptococci is common in many hospitalized patients, with rates exceeding 50% in some reports.[1] Prior administration of penicillin and cephalosporin antibiotics has been reported to reduce the susceptibility of these organisms to β-lactam agents.[2]

Over the last 15 years viridans streptococcal bacteraemia has become associated with significant morbidity and mortality in neutropenic patients with malignancy.[3] Viridans streptococci form a major part of the commensal flora of the oral cavity and may gain access to the bloodstream via chemotherapy-induced oral mucositis.[3]

In the early 1990s empirical antibiotic therapy for episodes of febrile neutropenia at The Royal Hospital for Sick Children, Glasgow, consisted of standard combination therapy of the third-generation cephalosporin, ceftazidime, plus the aminoglycoside, amikacin. Towards the middle of the decade, viridans streptococci emerged as important pathogens responsible for 17% of total cases of culture-positive bacteraemia in immunocompromised patients in this hospital. In July 1996, to provide better antibiotic cover for streptococci while retaining good activity against Gram-negative pathogens, empirical therapy was changed to the ureidopenicillin/β-lactamase inhibitor, piperacillin/tazobactam in combination with amikacin. Between July 1996 and December 1999 the incidence of viridans streptococcal bacteraemia decreased significantly ($P < 0.005$) to 8% of total cases.

Patients undergoing therapy for malignancy commonly become predisposed to infection and will require empirical antibiotics for each episode of febrile neutropenia. This in turn inevitably exposes endogenous bacterial flora, such as viridans streptococci, to antimicrobial agents. To investigate whether the replacement of ceftazidime with piperacillin/tazobactam influenced susceptibility of viridans streptococci to several antibiotics, we compared the *in vitro* activity of seven antimicrobial agents against strains isolated from blood cultures from December 1994 to July 1996 (period 1) with that against strains isolated after the change, until the end of December 1999 (period 2). It is important to note that the susceptibility patterns of viri-

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dans streptococci isolated during the early weeks of period 2 may have been influenced, to some extent, by prior empirical therapy with ceftazidime. However, the date of change of therapy was considered the most appropriate point of comparison of the two populations of viridans streptococci.

Materials and methods

Patients and test organisms

During period 1, 31 isolates of viridans streptococci were collected from blood culture in 28 cases of bacteraemia in paediatric patients with cancer (82% with haematological malignancy and 18% with solid tumours). During period 2, 36 isolates were collected from 33 cases (94% with haematological malignancy and 6% with solid tumours). In 95% of all cases, the patients were neutropenic. In both groups, 93% of cases received co-trimoxazole prophylaxis against infection by *Pneumocystis carinii*; therefore, any selective pressure exerted by this agent was a constant factor throughout. During period 1, previous courses of empirical antibiotic therapy had been administered in 26 cases, compared with 27 cases throughout period 2. The first two cases in period 2 had received recent prior empirical therapy with ceftazidime. The cytotoxic chemotherapy regimens used throughout the two time intervals did not differ significantly.

Isolates of viridans streptococci, identified to species level using the API Rapid ID32 STREP system (bioMérieux, Basingstoke, UK) consisted of *Streptococcus oralis* (23 isolates before change in empirical therapy and 25 post), *Streptococcus mitis* (four pre and six post), *Streptococcus sanguis* (two pre and three post), *Streptococcus parasanguis* (one pre and one post), one strain of *Streptococcus gordonii* (pre) and one strain of *Streptococcus salivarius* (post).

Antibiotic susceptibility tests

MICs were determined on Diagnostic Sensitivity Test agar with 5% lysed horse blood (E & O Laboratories, Bonnybridge, UK) using the Etest method (AB Biodisk, Solna, Sweden). Antimicrobial agents tested were ceftazidime, piperacillin/tazobactam, penicillin, cefpirome, meropenem, vancomycin and quinupristin/dalfopristin. Preparation of bacterial suspensions, inoculation of plates and application of Etest strips were performed according to the manufacturer's instructions. The plates were incubated for 24 h at 37°C in air. Control organisms used were *Streptococcus pneumoniae* ATCC 49619 and *Staphylococcus aureus* NCTC 6571. Species-related susceptibility patterns were not compared because the frequency of isolation of *S. oralis* (72%) far exceeded that of any other species of viridans streptococcus.

Results

The MIC distributions for the 67 isolates of viridans streptococci are shown in Tables I and II. During period 1, geometric mean MICs for all β-lactam antibiotics were greater than those for period 2. The geometric mean MICs of ceftazidime and piperacillin/tazobactam for organisms isolated before the change in empirical therapy were 3.3- and 2.8-fold greater, respectively, than those following the change. MICs of piperacillin/tazobactam were consistently lower than those of ceftazidime.

There were high rates of resistance to penicillin amongst viridans streptococci with 45% of isolates from period 1 and 36% from period 2 expressing high-level resistance (i.e. an MIC $\geqslant$ 2 mg/L). In contrast, cefpirome and meropenem demonstrated significant activity against viridans streptococcal strains isolated throughout both study periods. MIC results for both vancomycin and quinupristin/dalfopristin covered a narrow range, with all isolates inhibited at $\leqslant$2 mg/L, indicating 100% susceptibility.

Discussion

Antibiotics chosen for empirical therapy of episodes of febrile neutropenia must be active against the majority of Gram-negative pathogens, as these bacteria are associated with high mortality. However, with the emergence of viridans streptococci as significant pathogens in immunocompromised patients, the ideal empirical regimen should also have activity against these organisms.

During period 1 of this study, prior use of empirical ceftazidime, with variable activity against viridans streptococci, may have been more likely to result in selection of resistant strains of these organisms, producing a bacterial loading effect in the oral cavity and gastrointestinal tract of haematology/oncology patients. This in turn may have influenced the development of bacteraemia in patients with mucositis, and may, in part, be related to the higher incidence of viridans streptococcal infection while ceftazidime was used as empirical therapy. In the study of Bradley and colleagues,[4] which also compared ceftazidime with piperacillin/tazobactam as empirical therapy in febrile neutropenia, clinical cases of infection with glycopeptide-resistant enterococci were observed only when carriage rates were high and only during the ceftazidime phase of the study.

In the mouths and gastrointestinal tracts of patients receiving piperacillin/tazobactam for empirical therapy, bacterial loading effects may be less likely to occur. Piperacillin/tazobactam is more active than ceftazidime against viridans streptococci and would therefore not tend to select for overgrowth with these organisms. The *in vitro* results of the present study also suggest that empirical therapy with piperacillin/tazobactam is less likely to be associated with reduced susceptibility to other β-lactam agents.

The glycopeptide antibiotic, vancomycin, demonstrated

Table I. MIC distributions for viridans streptococci isolated during period 1 (ceftazidime + amikacin as empirical therapy)

	Number of isolates of viridans streptococci (n = 31) with stated MIC (mg/L)													
Antibiotic	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	GM[a] MIC
Ceftazidime	–	1	2	–	6	3	1	–	3	6	4	3	2	9.56
Pip/tazo	3	3	1	3	2	2	–	8	8	1	–	–	–	2.28
Penicillin	5	4	4	–	4	8	3	3	–	–	–	–	–	0.66
Meropenem	9	4	3	12	3	–	–	–	–	–	–	–	–	0.23
Cefpirome	4	6	3	1	10	6	1	–	–	–	–	–	–	0.48
Vancomycin	–	–	–	7	24	–	–	–	–	–	–	–	–	0.86
Quin/dalf	–	–	1	6	21	3	–	–	–	–	–	–	–	0.89

[a]Geometric mean.
Pip/tazo, piperacillin/tazobactam; Quin/dalf, quinupristin/dalfopristin.

Table II. MIC distributions for viridans streptococci isolated during period 2 (piperacillin/tazobactam + amikacin as empirical therapy)

	Number of isolates of viridans streptococci (n = 36) with stated MIC (mg/L)													
Antibiotic	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	GM[a] MIC
Ceftazidime	–	5	5	1	7	1	2	3	2	5	2	2	1	2.88
Pip/tazo	7	5	5	1	2	1	5	7	2	1	–	–	–	0.83
Penicillin	12	6	1	2	2	3	9	1	–	–	–	–	–	0.41
Meropenem	18	3	4	4	7	–	–	–	–	–	–	–	–	0.16
Cefpirome	12	8	1	2	5	8	–	–	–	–	–	–	–	0.27
Vancomycin	–	–	–	6	28	2	–	–	–	–	–	–	–	0.93
Quin/dalf	–	–	–	12	21	3	–	–	–	–	–	–	–	0.84

[a]Geometric mean.
Pip/tazo, piperacillin/tazobactam; Quin/dalf, quinupristin/dalfopristin.

high *in vitro* activity against viridans streptococci, unaffected by change in empirical therapy. Some authors have suggested that vancomycin may be a useful component of first-line empirical antibiotic therapy for episodes of febrile neutropenia in patients at high risk of developing viridans streptococcal bacteraemia.[5] However, with the widespread occurrence and spread of glycopeptide-resistant *Enterococcus* spp. in hospitalized patients and the emergence of strains of *S. aureus* with intermediate susceptibility to vancomycin,[6] it may be more prudent to reserve this antibiotic for therapy of proven infection by Gram-positive bacteria that are resistant to β-lactam antibiotics or as an adjunct to first-line therapy when clinical response is sub-optimal.

The streptogramin combination, quinupristin/dalfopristin, also demonstrated considerable *in vitro* activity against viridans streptococci with no cross-resistance with the other agents tested. Its clinical usefulness in the treatment of infection caused by these organisms remains to be determined. Continued monitoring of antibiotic susceptibility is necessary at both local and national levels to detect changing trends and to permit timely review of therapeutic options.

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