The antibiotics were subsequently given by the oral route (co-trimoxazole at the same dosage and ciprofloxacin at 250 mg tds) and, after 2 weeks, the dosages were reduced (co-trimoxazole 480 mg bd and ciprofloxacin 250 mg bd). The patient completed a 4 week course of this regimen, during which time she remained afebrile. She was discharged and, at a 6 month follow-up assessment, was well and exhibited no signs of relapse.

This case demonstrates that co-trimoxazole in combination with ciprofloxacin may be effective therapy in patients with IE caused by high-level gentamicin-resistant enterococci.

References

Teicoplanin-resistant coagulase-negative staphylococcal bacteraemia in patients with haematological malignancies: a problem of increasing importance


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Sir,

Coagulase-negative staphylococci have been increasingly recognized as important causes of nosocomial bacteraemia, especially in immunocompromised patients. Various factors have contributed to this increase, including the use of central venous catheters, the administration of more aggressive anti-neoplastic chemotherapy, greater awareness of the clinical significance of coagulase-negative staphylococci and improvements in microbiological techniques that have facilitated the identification of these pathogens. In recent years, there have been reports of higher incidences of resistance amongst coagulase-negative staphylococci strains, >50% of isolates having been shown to be resistant to methicillin. A consequence of the rising incidence of methicillin resistance has been the more widespread use of glycopeptides (vancomycin and teicoplanin) as empirical therapy of patients with haematological malignancies who present with fevers of unknown origin. This practice has, in turn, almost certainly contributed to the increase in teicoplanin resistance that has been observed amongst coagulase-negative staphylococci and, much less commonly, to the isolation of vancomycin-resistant strains. To the best of our knowledge, there have been no previous studies that have used a statistical approach to identify the clinical parameters that influence the development of drug resistance. We have therefore investigated the impact of bacteraemias caused by glycopeptide-resistant strains of coagulase-negative staphylococci on patients with haematological malignancies admitted under our care between January 1990 and December 1996 and have used univariate and multivariate statistical analyses to identify the risk factors associated with the development of resistance to teicoplanin amongst coagulase-negative staphylococci.

The diagnosis of coagulase-negative staphylococcal bacteraemia was based on the isolation of a strain of coagulase-negative staphylococci from at least two sets of blood cultures obtained from a patient with signs and symptoms consistent with septicemia. Cases were defined as those from whom coagulase-negative staphylococci strains resistant to teicoplanin were isolated, while controls were defined as those from whom strains susceptible to teicoplanin were isolated. The following data were recorded in respect of all patients included in the study: age; sex; type and stage of haematological malignancy; whether or not the patient was experiencing relapse of the underlying disease; duration of hospital stay; hospitalization within the previous month; and the pattern of in-vitro susceptibility of the pathogen to anti-staphylococcal antibiotics. The significance of each of the following additional factors which might be associated with the development of resistance to teicoplanin amongst coagulase-negative staphylococci strains causing bacteraemias was also assessed: number of circulating polymorphonuclear leucocytes (PMNL); use of steroids; administration of anti-neoplastic chemotherapy; recent administration of broad-spectrum antibiotics (in particular glycopeptides); prophylaxis with fluoroquinolones in the previous 30 days; presence of a central venous catheter; and presence of mucositis or decubitus ulcers. Neutropenia was defined as <0.5 × 10⁹ PMNL/L and nosocomial bacteraemia as an episode of bacteraemia presenting at least 48 h after hospital admission.

Antimicrobial susceptibility was determined by a microbroth dilution method, as recommended by the National Committee for Clinical Laboratory Standards. (1993). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically—Third Edition; Approved Standard M7–A3. NCCLS, Villanova, PA.
Committee for Clinical Laboratory Standards, and resistance to teicoplanin was confirmed by repeating the test. The chi-squared test and Student’s t-test were used for the statistical analyses of the characteristics of the two groups (cases and controls) and 95% test-based confidence intervals (CI) were used to determine the statistical significance of the odds ratio (OR). Multivariate analysis was used to adjust for possible confounding variables. The statistical analyses were performed with the software program, Egret (Statistics and Epidemiology Research Corporation, Seattle, WA).

Sixty-three bacteraemic episodes caused by coagulase-negative staphylococci, representing 37% of all episodes of bacteraemia occurring in haematological patients during the study period, were recorded. The aetiological agents were Staphylococcus epidermidis (56 cases), Staphylococcus hominis (two), Staphylococcus xylosus (two), Staphylococcus haemolyticus (two) and Staphylococcus cohnii (one). Seventy-one per cent of the episodes were nosocomial and 29% were community-acquired. The presumed foci of the bacteraemias included central venous catheters (61%), skin and soft tissues (11%), intravenous drug abuse (2%) and unknown (26%). Eighteen of the 56 (32%) isolates tested were resistant to teicoplanin (MICs ≥ 32 mg/L). During the study period, there was an increase in the incidence of isolation of teicoplanin-resistant strains, from 3% in 1990 to 7% in 1994 and 18% in 1996 (P = 0.03; χ² for trend). Of the other antibiotics to which susceptibilities were determined, 46 of 63 (73%) strains tested were resistant to methicillin, 41 of 53 (77%) were resistant to ciprofloxacin and 34 of 44 (77%) were resistant to gentamicin. None of the isolates was resistant to vancomycin, but many (51%) were resistant to multiple (i.e. three or more) agents.

Univariate analysis revealed that previous antibiotic therapy (P = 0.02; OR = 3.86; 95% CI = 1.07–14.35), neutropenia (P = 0.03; OR = 3.5; 95% CI = 1.32–9.08), central venous catheter usage (P = 0.02; OR = 4; 95% CI = 1.09–15.1) and prolonged duration of hospitalization (P = 0.03; χ² for trend) were significantly associated with resistance to teicoplanin amongst CoNS isolates. However, multivariate analysis showed only previous antibiotic therapy (P = 0.01; OR = 6.32; 95% CI = 2.31–17.51) and prolonged duration of hospitalization (P = 0.03; χ² for trend) to be independent risk factors for the development of resistance to this agent. Surprisingly, the previous administration of teicoplanin was not significantly linked to teicoplanin resistance, although the P value (0.06) approached statistical significance. No statistically significant association with resistance to teicoplanin was demonstrated for the following parameters: age; sex; type and stage of underlying malignancy; use of steroids; use of chemotherapy; use of antibiotic prophylaxis; or the presence of mucositis or decubitus ulcers.

All patients with bacteraemias caused by coagulase-negative staphylococci were initially treated with antibiotic regimens that included an agent with reliable activity against coagulase-negative staphylococci, although the regimen was subsequently modified, if necessary, when the results of susceptibility testing became available. The response to therapy was favourable in 56 (89%) episodes, while death was the outcome in seven (11%); relapses were observed on six (10%) occasions. With regard to the 18 episodes of bacteraemia caused by teicoplanin-resistant strains, four (22%) of the patients died. However, in all of these cases, the bacteraemic episodes could have been the terminal events in a setting of multiple opportunistic infections occurring in patients in the advanced stages of haematological malignancy. The outcome of bacteraemia was significantly affected by the stage of haematological disease (P = 0.01; OR = 3.21; 95% CI = 1.21–7.51) and causation by multidrug-resistant pathogens (P = 0.03; OR = 2.01; 95% CI = 1.11–7.65), but not by the administration of prophylactic antibiotics, the use of central venous catheters or profound neutropenia.

The results of this study confirm that the incidence of infections caused by coagulase-negative staphylococci in patients with haematological malignancies is rising, with high percentages (>50%) of isolates being resistant to both methicillin and ciprofloxacin, and emphasize the potential for teicoplanin resistance to develop in these pathogens. The progressive increase in the annual incidence of bacteraemic episodes caused by teicoplanin-resistant coagulase-negative staphylococci which was observed during the study period (from 3% to 18%) is probably related to a number of factors, including characteristics of both the host and the pathogen and increasing antibiotic pressures. As expected, multivariate analysis demonstrated that teicoplanin resistance is related to prolonged hospitalization and the previous administration of broad-spectrum antibiotics. Our findings also confirm that the excellent in-vitro activity of vancomycin against coagulase-negative staphylococci isolates has been preserved and that cross-resistance between glycopeptides is not inevitable. On the other hand, we believe that the inappropriate empirical use of vancomycin, e.g. in patients with fevers of unknown origin, could lead to the development of resistance to this agent amongst coagulase-negative staphylococci, a situation that has already been observed amongst Enterococcus spp.

In conclusion, we urge caution, especially in the use of teicoplanin as empirical therapy of neutropenic patients with fevers of unknown origin, and we stress the importance of monitoring glycopeptide resistance amongst coagulase-negative staphylococci isolated from patients with nosocomial infections.

References
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Extended high-level cross-resistance to antipseudomonal antibiotics amongst Pseudomonas aeruginosa isolates in a university hospital


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Sir,

Pseudomonas aeruginosa remains an important cause of hospital-acquired infections, particularly among immunocompromised patients, in whom such infections progress rapidly and are associated with high rates of mortality. The administration of appropriate antimicrobial therapy to these patients is therefore essential. However, because an innate characteristic of P. aeruginosa is the high frequency with which antibiotic-resistant variants emerge, knowledge of resistance rates among clinical isolates of this bacterium is necessary in order to ensure that effective antipseudomonal drugs are prescribed in different clinical settings throughout the hospital. In our region, high levels of antibiotic resistance among most bacterial species, especially Pseudomonas spp., have been reported. Furthermore, preliminary observations of the susceptibility patterns of P. aeruginosa strains isolated in our hospital confirm that a high percentage are resistant to commonly used antipseudomonal agents. The purpose of this study was to determine the in-vitro activities of and extent of cross-resistance among ten antimicrobials currently used as therapy for patients with infections caused by P. aeruginosa.

Two hundred and forty-seven non-replicate strains of P. aeruginosa were recovered from consecutive hospitalized patients with active infections during 1996/7 in AHEPA University Hospital, Thessaloniki, Greece, a 700-bed general hospital with medical, paediatric, and surgical services, specialist intensive care units, and a dialysis ward. Identification of the isolates to species level was performed with the PASCO system (Difco Laboratories, Detroit, MI, USA) according to the manufacturer’s instructions. MICs were determined by a microbroth dilution method as recommended by the National Committee for Clinical Laboratory Standards (NCCLS). The medium used was cation-supplemented Mueller–Hinton broth (Difco Laboratories) and the antimicrobial agents tested were amikacin, aztreonam, cefepime, ceftazidime, ciprofloxacin, imipenem, meropenem, piperacillin, piperacillin/tazobactam, and tobramycin. Stock solutions of each drug were prepared in concentrations of 2 g/L and stored at −20°C for a maximum of 1 month; imipenem solutions were prepared freshly on the day of testing. Fresh broth cultures of each bacterium were diluted to provide suspensions containing 5 × 10^8 cfu/L in microtitre plates containing the antibiotics in appropriate ranges of dilution. P. aeruginosa ATCC 27853 was used as a control. The MIC was defined as the lowest concentration of each antibiotic that allowed no visible growth, and susceptibility categories were assigned according to NCCLS interpretative criteria.

The MIC_{90}, MIC_{98}, ranges of MICs, and percentages of resistant strains are shown in the Table. On a weight-for-weight basis, meropenem was the most active agent, inhibiting 90% of strains at concentrations ≤ 16 mg/L, followed by imipenem and aztreonam, the MIC_{90} of which were 32 mg/L; the two aminoglycosides, tobramycin and amikacin, and ceftazidime and piperacillin were the least active agents (MIC_{98} > 128 mg/L). However, when the results were compared according to the percentages of resistant isolates, the activities of all the antimicrobials tested were broadly similar (range 15.8–27.5%). Meropenem was still the most active agent, even when compared with imipenem (to which 22.3% of strains were resistant). It has been proposed that meropenem deactivates the class C β-lactamases of P. aeruginosa more effectively than does imipenem and is therefore less affected by the mutational loss of the D2 outer membrane protein. This could explain the observation that a considerable number (19 of 55) of imipenem-resistant strains remained either susceptible or intermediately susceptible to meropenem. On the other hand, there were no strains...