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Co-trimoxazole versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia: a retrospective cohort study

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Objectives: To evaluate the efficacy and safety of co-trimoxazole versus that of vancomycin in adults with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia.

Patients and methods: Retrospective matched cohort study. Thirty-eight patients with MRSA bacteraemia, treated with co-trimoxazole as the main therapeutic agent, were matched with 76 patients treated with vancomycin as the main agent. The groups were matched for age, sex, functional status, endovascular source of infection, appropriateness of empirical antibiotic therapy, presence of a foreign body, sepsis severity and Charlson score. The outcomes collected were 30 day mortality, persistent bacteraemia [defined as positive blood culture (BC) >14 days after the first positive BC, but within 30 days], relapse (defined as recurrence of the same phenotype >30 days after the first positive BC within 12 months) and adverse events.

Results: The groups were well matched. Thirty day mortality was not significantly different between the groups [co-trimoxazole 13/38 (34.2%); vancomycin 31/76 (40.8%); odds ratio 0.76, 95% confidence interval 0.34–1.7]. There was only one case of relapse in the co-trimoxazole group (2.6%) compared with nine cases in the vancomycin group (11.8%). Incidence of relapse or persistent bacteraemia was lower in the co-trimoxazole group (3/38, 7.9%) than in the vancomycin group (13/76, 17.1%), although the difference was not statistically significant ($P=0.182$). Development of renal failure was similar [co-trimoxazole 11/38 (28.9%); vancomycin 21/76 (27.6%)].

Conclusions: Within the limitations of a small retrospective study, co-trimoxazole had a safety and efficacy profile similar to that of vancomycin and may offer an attractive additional therapeutic option for MRSA bacteraemia. A prospective, randomized controlled trial is warranted.

Keywords: trimethoprim/sulfamethoxazole, glycopeptides, staphylococci, outcomes, MRSA

Introduction

Staphylococcus aureus remains one of the most significant pathogens in terms of morbidity and mortality in both the community and hospital settings. Mortality of inpatients with *S. aureus* infection is five times higher than in other patients.[1] One of the factors contributing to the high mortality rate is scarcity of effective and safe treatments, especially in the case of methicillin-resistant *S. aureus* (MRSA), which is a common pathogen.[2] Vancomycin is currently the 'therapy of choice' for treating MRSA. However, the emergence of vancomycin-resistant *Enterococcus* (VRE), vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) in several countries,[3,4] further reduces treatment options and indicates that therapy with vancomycin could become obsolete sooner or later.

Co-trimoxazole (trimethoprim/sulfamethoxazole), an antibiotic in use for several decades, has been shown to be active against *S. aureus* (including MRSA) *in vitro*.[5] Its components have synergistic bactericidal activity against *S. aureus*.[6] In our

centre, susceptibility of nosocomial bloodstream MRSA isolates to co-trimoxazole increased from 73% in 1994–98 to 95% in 2001–04.[7] The same trends in susceptibility to co-trimoxazole were observed in the USA.[8,9]

Evidence for clinical efficacy of co-trimoxazole in *S. aureus* infections is limited. Only one randomized controlled trial has assessed co-trimoxazole for treatment of *S. aureus* infections, and was limited to an intravenous drug user population.[10] In this study, inferiority of co-trimoxazole to vancomycin was seen only for methicillin-susceptible *S. aureus* (MSSA), while cure rate and other clinical and microbiological outcomes were similar for both drugs against the MRSA group.

Other evidence for the efficacy of co-trimoxazole in *S. aureus* infections is limited to small non-randomized studies, animal studies and case reports. Successful treatment of *S. aureus* endocarditis, meningitis and osteomyelitis with co-trimoxazole has been reported[11–16] and a few cases of right-sided MRSA endocarditis were included in the randomized trial.[10] However, co-trimoxazole was inferior to cloxacillin, teicoplanin and vancomycin in an animal model of *S. aureus* aortic endocarditis.[17] Two reviews attempting to summarize the data concerning co-trimoxazole treatment for *S. aureus* infections emphasize the need for further clinical studies comparing this drug with other available options, specifically vancomycin.[18,19]

We retrospectively collected data from patients treated with co-trimoxazole for MRSA bacteraemia in our institution and compared them with patients from the same cohort who were treated with vancomycin.

Patients and methods

This was a parallel-group retrospective cohort study. All consecutive patients ≥18 years old who had MRSA bacteraemia were included in the study. Data were retrieved from medical records of patients with clinically significant MRSA bacteraemia between the years 1998 and 2007. We identified patients with co-trimoxazole-susceptible MRSA bacteraemia treated with co-trimoxazole as the main therapeutic agent, defined as at least one continuous week of treatment with intravenous or oral co-trimoxazole alone or with another drug other than vancomycin, daptomycin, linezolid or quinupristin/dalfopristin, administered within 2 weeks of growth in the culture. We matched them in a 1:2 ratio with patients treated with intravenous vancomycin as the main agent, as defined for co-trimoxazole. The groups were matched for age, sex, functional status, endovascular source of infection and, whenever possible, appropriateness of empirical antibiotic therapy, presence of a foreign body, presence of septic shock, Charlson score and type of other antibiotics administered with vancomycin/co-trimoxazole. When more than two vancomycin-treated patients could be matched, we selected two patients randomly. Functional status was stratified as follows: class 1, patient is independent; class 2, patient requires assistance in daily activities; and class 3, patient is bedridden.

Demographic, bacteriological and clinical data, including the presumptive focus of infection and outcomes, were retrieved retrospectively. The outcomes collected were 30 day all-cause mortality, persistent bacteraemia, relapse and adverse events. Persistent bacteraemia was defined as positive blood culture for the same phenotype >14 days after the first positive blood culture, but within 30 days. Relapse was defined as recurrence of the same phenotype >30 days after the first positive blood culture within 12 months. The study was approved by the institutional review board. Informed consent was waived due to the retrospective study design.

For statistical analysis, dichotomous variables were compared using the χ^2 test [Mantel–Haenszel common odds ratio (OR) and 95% confidence interval (CI) shown] and continuous variables were compared using the *t*-test or Mann–Whitney test, as appropriate. Statistical analysis was performed using SPSS software.

Results

During the study period, there were 1005 clinically significant consecutive episodes of *S. aureus* bacteraemia in 954 patients. MRSA bloodstream infection was documented in 451 (47.2%) of the patients. We identified 38 patients with MRSA bacteraemia who received treatment with co-trimoxazole as the main therapeutic agent. We matched these patients with 76 patients who were treated with vancomycin as the main therapeutic agent. The demographic and clinical characteristics of patients in both groups are specified in Table 1. Overall, the groups were well matched with no significant differences in the baseline characteristics, including functional capacity, underlying conditions and baseline laboratory and clinical variables upon infection onset. Data collection from vancomycin-treated patients began earlier, and therefore continued over a longer period of time (see Table 1). Two patients in the co-trimoxazole group received additional antibiotics with possible activity against MRSA (both received fusidic acid) as opposed to six patients in the vancomycin group (fusidic acid, two patients; rifampicin, two patients; and aminoglycosides, two patients). Infection was hospital acquired or healthcare associated[20] for all patients (excluding undocumented cases).

Thirty day mortality did not differ significantly between the groups [co-trimoxazole 13/38 (34.2%); vancomycin 31/76 (40.8%); OR 0.76, 95% CI 0.34–1.7] (Table 2). There was only one case of relapse in the co-trimoxazole group (2.6%) compared with nine cases in the vancomycin group (11.8%). Two (5.3%) patients in the co-trimoxazole group suffered from persistent bacteraemia, compared with five (6.6%) in the vancomycin group (OR 0.79, 95% CI 0.15–4.27). Incidence of relapse or persistent bacteraemia was lower in the co-trimoxazole group (3/38, 7.9%) than in the vancomycin group (13/76, 17.1%), although the difference was not statistically significant (OR 0.42, 95% CI 0.11–1.56). Duration of fever was similar in both groups, while the average length of hospital stay was shorter in the co-trimoxazole group, but this did not reach statistical significance. There was no significant difference between the groups in renal failure as a complication [co-trimoxazole 11/38 (28.9%); vancomycin 21/76 (27.6%); OR 1.07, 95% CI 0.45–2.53] (Table 2).

Discussion

The overall results from this study suggest that the efficacy and safety of co-trimoxazole are similar to those of vancomycin. Co-trimoxazole is comparable to vancomycin with respect to 30 day mortality rate and renal failure. Although with wide confidence intervals, there was more relapse of MRSA bacteraemia in the vancomycin group.

There is a pressing need for compounds active against *S. aureus* in general and MRSA in particular. In the era of stagnation of novel antimicrobial production, rational use of new antistaphylococcal agents has become more crucial than ever. We should ‘squeeze’ every older option existing in our

Table 1. Characteristics of patients with MRSA bacteraemia treated with co-trimoxazole versus vancomycin[a]

Variable	Co-trimoxazole group ($N=38$), n (%)	Vancomycin group ($N=76$), n (%)
Time period, month year, median (range)	May 2006 (Mar 2002–Dec 2007)	Oct 2004 (Oct 1998–Dec 2007)
Age, years, mean ± SD	74.7 ± 15.9	75.8 ± 13.7
Female gender	26 (68.4)	51 (67.1)
Bedridden patients	17 (44.7)	34 (44.7)
Hospital-acquired infection	20 (52.6)	43 (56.6)
Hospital- or healthcare-associated infection	37 (97.4)[b]	73 (96.1)[b]
Diabetes mellitus	15 (39.5)	34 (44.7)
Congestive heart failure	9 (23.7)	20 (26.3)
Ischaemic heart disease	15 (39.5)	28 (36.8)
Cerebrovascular disease	11 (28.9)	20 (26.3)
Decubitus ulcers	6 (15.8)	12 (15.8)
McCabe score on admission		
none	11 (28.9)	18 (23.7)
ultimately fatal disease	20 (52.6)	40 (52.6)
rapidly fatal disease	5 (13.2)	12 (15.8)
Charlson score on admission, mean ± SD	3.53 ± 2.46	3.21 ± 2.29
Endovascular source of infection	9 (23.7)	18 (23.7)
Skin and soft tissue source of infection	7 (18.4)	19 (25)
Presence of any vascular catheter	25 (65.8)	46 (60.5)
Appropriate empirical antibiotic treatment	12 (31.6)	26 (34.2)
Septic shock at onset	10 (26.3)	27 (35.5)
White blood cells at onset, cells/mm^3, mean ± SEM	14.8 ± 1.1	17.0 ± 2.5
Albumin at onset, mg/dL, mean ± SEM	2.76 ± 0.14	3.16 ± 0.3

[a]Differences between the groups were not statistically significant for any of the variables.
[b]Place of acquisition was undetermined for one patient in the co-trimoxazole group and for three patients in the vancomycin group.

Table 2. Outcomes of patients with MRSA bacteraemia treated with co-trimoxazole versus vancomycin[a]

Outcomes	Co-trimoxazole group ($N=38$), n (%)	Vancomycin group ($N=76$), n (%)
Duration of fever, days, median (range)	3 (0–23)	4 (0–20)
Length of hospital stay, days, median (range)	21.5 (3–158)	25 (2–244)
Relapse of MRSA bacteraemia	1 (2.6)	9 (11.8)
Persistent MRSA bacteraemia	2 (5.3)	5 (6.6)
Relapse of bacteraemia or persistent bacteraemia	3 (7.9)	13 (17.1)
30 day mortality	13 (34.2)	31 (40.8)
Acute renal failure	11 (28.9)	21 (27.6)

[a]Differences between the groups were not statistically significant for any of the outcomes.

arsenal against this specific pathogen. Among the antibacterial agents currently on the market are linezolid, daptomycin and tigecycline. Although these agents are also active against Gram-positive bacteria, including MRSA, there are increasing reports of resistance and patient tolerance issues with these agents.[21–23]

The efficacy of daptomycin in treating MRSA pneumonia is compromised by interaction with pulmonary surfactant, making this new agent, along with vancomycin, inferior (at least theoretically) to co-trimoxazole for treating MRSA pneumonia.[24] Linezolid and quinupristin/dalfopristin are both bacteriostatic and results concerning their efficacy in MRSA infections are not very different from those for vancomycin while their safety profiles are unfavourable.[25–27]

Co-trimoxazole is an old compound, extensively used for various indications in countries with limited resources. It might offer an additional option in the battle against MRSA owing to its low cost, acceptable toxicity profile, availability in both oral and intravenous routes and bactericidal activity. Its superiority to vancomycin has been shown against intracellular phagocytized MRSA, achieving higher clearance rates than vancomycin.[28] Previous time–kill studies showed the rapid bactericidal activity of co-trimoxazole.[18,29] Data from previous clinical studies are inconclusive, but promising, requiring further comparisons in better-designed studies.

As previously mentioned, more than a decade ago, Markowitz *et al.*[10] performed the only randomized blinded trial comparing co-trimoxazole and vancomycin. Cure rates were lower in the co-trimoxazole arm, but cure was not clearly defined. Moreover, when MSSA and MRSA were analysed separately, co-trimoxazole was non-inferior to vancomycin in the small group of patients ($n=45$) with MRSA infection.

The retrospective design is the main limitation of our study. Selection bias is a major consideration. We attempted to compensate for this by matching our cases with similar controls. Our treatment groups were well matched and had similar demographic and clinical characteristics. Since we had a limited number of controls to match according to the pre-planned criteria, we were unable to match for time period, and therefore patients receiving vancomycin came from earlier dates when compared with the co-trimoxazole group. The outcome of the co-trimoxazole-treated cases may have been favoured, since other treatments for these patients have improved over the years. Another limitation is the small sample size precluding statistical significance in the various comparisons. However, differences in the main outcomes were small and at least regarding relapse and persistent bacteraemia, tended to favour co-trimoxazole rather than vancomycin.

We conclude that within the limitations of a small retrospective study, co-trimoxazole had a safety and efficacy profile similar to that of vancomycin in the treatment of MRSA bacteraemia. Co-trimoxazole may offer an attractive additional therapeutic option for MRSA bacteraemia. However, a well-designed prospective, randomized controlled trial should be performed in order to strengthen the evidence and enable its use in clinical practice.

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None to declare.

Author contributions

E. G., M. P., L. L. and J. B.: conception and design; analysis and interpretation of data; drafting the article; and final approval. O. T., Z. S., M. R. and R. H.: acquisition of data; revising the article; and final approval.

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