In vitro activity of vancomycin combined with rifampin, amikacin, ciprofloxacin or imipenem against methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*

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In spite of great advances in the antimicrobial chemotherapy era, staphylococci are still the most important nosocomial pathogens in many countries. The methicillin-resistant strains are often resistant not only to β-lactam agents but also to chloramphenicol, clindamycin, tetracyclines and aminoglycosides. Vancomycin and teicoplanin are the drugs of choice for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Since the relationship between plasma levels of teicoplanin and clinical outcome is not well established, vancomycin remains the preferred agent.

Various in vitro antibiotic combinations have been tested in attempts to find a better treatment regimen for staphylococcal infections [1–4]. Because vancomycin is the drug generally available for multiresistant staphylococcal species, the synergistic activities of vancomycin with rifampin, amikacin, ciprofloxacin or imipenem were tested.

Five MRSA and five methicillin-sensitive *Staphylococcus aureus* (MSSA) strains isolated from blood, pus and catheters of patients hospitalized in different intensive care units of the same hospital were used in the study, and *S. aureus* ATCC 29213 was used as the control strain. The antibiotics were kindly provided by the manufacturers: vancomycin (Lilly, USA), amikacin (Eczacıbaşı, Turkey), rifampin (Sifar, Turkey), ciprofloxacin (Bayer, Turkey) and imipenem (MSD, USA). Methicillin-resistant strains were identified by the disk diffusion method with a 1-μg oxacillin disk. The minimum inhibitory concentrations (MICs) were determined by the broth microdilution method as described by the NCCLS [5]. According to MIC values of the antibiotics, checkerboard microdilution panels were prepared and fractional inhibitory concentrations (FICs) of vancomycin–rifampin, vancomycin–amikacin, vancomycin–ciprofloxacin and vancomycin–imipenem were determined as described elsewhere [6]. Fractional inhibitory concentration indices (FICIs) were determined for each combination. FICI≤0.5 was defined as synergy, 0.5<FICI≤4 as indifference and FICI>4 as antagonism [6].

The MIC ranges of the antibiotics tested are given in Table 1. The mean FICIs of the antibiotic combinations are given in Table 2. Vancomycin–amikacin was synergistic for all MSSA strains and one MRSA strain. Vancomycin–rifampin was indifferent against the *S. aureus* strains tested, either methicillin sensitive or

Table 1 MIC ranges of antibiotics tested against 10 *S. aureus* isolates

Antibiotics	MSSA (n=5) MIC range (mg/L)	MRSA (n=5) MIC range (mg/L)
Vancomycin	0.5–1	0.5–1
Amikacin	1–2	0.25 to >64
Rifampin	0.002–0.009	0.009 to >0.6
Ciprofloxacin	0.03–0.25	0.12 to >2
Imipenem	0.12	0.12–8

MIC, minimum inhibitory concentration; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

Table 2 Mean FIC indices of antibiotic combinations against 10 *S. aureus* isolates determined by checkerboard microtitration

	V+A	V+R	V+C	V+I
MSSA (strain no.)				
1	0.456	1.140	0.374	1.037
2	0.398	0.861	0.437	1.127
3	0.496	1.228	0.500	1.087
4	0.435	1.250	0.863	1.108
5	0.382	0.603	0.745	1.116
MRSA (strain no.)				
1	0.661	0.980	1.920	0.480
2	0.499	1.045	1.851	0.482
3	0.819	1.017	1.150	0.434
4	1.108	1.233	1.124	0.498
5	0.983	1.191	1.150	0.472

V, vancomycin; A, amikacin; R, rifampin; C, ciprofloxacin; I, imipenem.

methicillin resistant. All MRSA strains except one were resistant to ciprofloxacin and the final effect with the vancomycin combination was indifferent, whereas the same combination showed synergistic activity against most MSSA strains. Vancomycin–imipenem had in vitro synergistic activity against all MRSA strains. This combination was indifferent for MSSA strains. No antagonism was detected among the antibiotics tested.

MRSA strains have become a major problem in hospitalized patients. Most of the MRSA strains are also resistant to many other antibiotics, including fluoroquinolones and imipenem. Various combinations of antibiotics have been tested for the treatment of staphylococcal infections; imipenem and other β-lactam antibiotics, glycopeptides and imipenem or meropenem, vancomycin and rifampin, rifampin and β-lactams, and vancomycin and ciprofloxacin, are some of the combinations tested [1,7–11].

In our study, vancomycin showed synergistic activity with amikacin against the MSSA strains, and vancomycin–ciprofloxacin was synergistic against most of the MSSA strains. In the case of MRSA, the only combination having synergistic activity was vancomycin–imipenem. The MIC of vancomycin–imipenem was 16–32-fold lower than the MIC of imipenem alone. This synergistic activity could not be detected in MSSA strains with the same combination. However, since a small number of strains was used in the study, additional in vitro and in vivo tests are needed to evaluate how representative our findings are. Moreover, our MRSA strains may be heterogeneously resistant to imipenem and the results might be somewhat different with homogeneously resistant strains. Vancomycin is usually combined with rifampin in the treatment of staphylococcal endocarditis or osteomyelitis. Our in vitro test results did not show any synergistic activity with these antibiotics. The in vitro and in vivo data concerning the efficacy of vancomycin–rifampin against *S. aureus* strains have been conflicting. Indifferent or even antagonistic interactions were reported with the checkerboard technique, whereas synergistic activity has been shown by time kill curve or in vivo models [12–14]. In combination studies, imipenem and meropenem were reported to have synergistic activity with glycopeptide antibiotics against staphylococcal isolates [9,10,15]. We have also detected synergy with vancomycin–imipenem against some staphylococcal isolates. However, in vitro synergism of vancomycin–imipenem warrants further evaluation to determine whether this combination could be a possible treatment modality. In vitro methods do not always take account of the antibiotic concentration changes over time during combination therapy [16].

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References

1. Brandt CM, Rouse MS, Tallan BM, Laue NW, Willson WR, Steckelberg JM. Effective treatment of cephalosporin–rifampin combinations against cryptic methicillin-resistant beta-lactamase producing coagulase-negative staphylococcal experimental endocarditis. Antimicrob Agents Chemother 1995; 39(8): 1815–19.
2. Mülazımoğlu L, Drenning SD, Yu VL. In vitro activities of two novel oxazolidinones (U 100592 and U 100766), a new fluoroquinolone (trovafloxacin) and dalfopristin–quinupristin against *Staphylococcus aureus* and *Staphylococcus epidermidis*. Antimicrob Agents Chemother 1996; 40(10): 2428–30.
3. Zinner SH, Lagast H, Klastersky J. Antistaphylococcal activity of rifampin with other antibiotics. J Infect Dis 1981; 144(4): 365–71.
4. Proctor RA, Wick P, Hamill J, et al. In vitro studies of antibiotic combinations for multiply-resistant coagulase-negative staphylococci. J Antimicrob Chemother 1987; 20(2): 223–31.
5. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved Standard NCCLS document M7–A3. Villanova, PA: NCCLS, 1993.
6. Moody JA. Synergism testing: broth microdilution checkerboard and broth macrodilution methods. In Isenberg HD, ed. Clinical microbiology procedures handbook, Vol. 1. Washington DC: American Society for Microbiology, 1992: 5.18.1–28.
7. Matsuda K, Asahi Y, Sanada M, Nakagawa S, Tanaka N, Inoue M. In vitro activity of imipenem combined with beta-lactam antibiotics for methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 1991; 27: 809–15.
8. Oka S, Goto M, Koji Y, et al. Synergic activity of imipenem/cilastatin combined with cefotixam against methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 1993; 31: 533–41.

9. Barr JG, Smyth ET, Hogg GM. In vitro antimicrobial activity of imipenem in combination with vancomycin or teicoplanin against *Staphylococcus aureus* and *Staphylococcus epidermidis*. Eur J Clin Microbiol Infect Dis 1990; 9(11): 804–9.
10. Edwards JR. Meropenem: a microbiologic overview. J Antimicrob Chemother 1995; 36(suppl A): 1–17.
11. Van der Auwera P, Klastersky J. Bactericidal activity and killing rate of serum in volunteers receiving ciprofloxacin alone or in combination with vancomycin. Antimicrob Agents Chemother 1986; 30(6): 892–5.
12. Bayer AS, Morrison JO. Disparity between timed-kill and checkerboard methods for determination of in vitro bactericidal interactions of vancomycin plus rifampin versus methicillin-susceptible and resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 1984; 26(2): 220–3.
13. Watanakunakorn C, Guerriero JC. Interaction between vancomycin and rifampin against *Staphylococcus aureus*. Antimicrob Agents Chemother 1981; 19: 1089–91.
14. Bayer AS, Lam K. Efficacy of vancomycin plus rifampin in experimental aortic-valve endocarditis due to methicillin-resistant *Staphylococcus aureus*: in vitro–in vivo correlations. J Infect Dis 1985; 151: 157–65.
15. Debbia E, Varaldo PE, Schito GC. In vitro activity of imipenem against enterococci and staphylococci and evidence for high rates of synergism with teicoplanin, fosfomycin and rifampin. Antimicrob Agents Chemother 1986; 30(5): 813–15.
16. Blaser J. Interactions of antimicrobial combinations in vitro: the relativity of synergism. Scand J Infect Dis Suppl 1990; 74: 71–9.

Group A streptococcal contact within schools over a 1-year period

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We have previously established that there is a high streptococcal carriage rate among schoolchildren in Al Ain, United Arab Emirates (UAE) [1], with the mean carriage rate among children examined being 35.4%. Further work has demonstrated that the M and T types identified from these children were similar to those found in the USA and Europe and that the serotype M type 1 was prevalent, indicating the potential for serious disease in the community [2]. Indeed, post-streptococcal acute nephritis and acute rheumatic fever are well recognized as important local diseases. We were interested to learn what the natural history was of those in whom we detected streptococci and in those in whom we did not. No prophylaxis had occurred following our initial studies, and nor was there active treatment of those in whom group A streptococci were detected.

This paper reports the findings in the cohort of children examined previously for streptococcal carriage and compares the findings at a 1-year follow-up examination.

We proposed to re-examine the same cohort of schoolchildren that was studied exactly 1 year previously. Four schools were revisited and the children identified and retested in an identical manner to that described previously [1]. Two swabs were obtained from the pharynx of each child, one swab being used for culture and the other for antigen detection. Direct inoculation on sheep blood agar occurred as described previously and the Test Pack Strep A immunoassay was carried out (Abbott). The children were now aged between 6 and 8 years, and the examinations were performed in the 'winter' period of 1995–96, corresponding to the seasonal and calendar months of the prior study. As in the previous study, informed consent and ethical committee permission was obtained for the follow-up aspects.

From the original study of the 254 children, 146 children were antigen positive (57%) and 62 culture positive (24.4%) for group A β-hemolytic streptococci (GAS). At the 1-year follow-up, 110 children were antigen positive (43%) and 34 were culture positive (13%). However, of the 62 who were originally culture positive, only 16 were still culture positive (26%), and of the 143 who were originally antigen positive, 88 (61.5%) were still positive. Table 1 outlines the distribu-