Severe infections caused by meticillin-resistant Staphylococcus aureus (MRSA): co-trimoxazole compared with vancomycin

An open-label, non-inferiority study conducted in hospitals in Israel has compared co-trimoxazole with vancomycin for the treatment of severe infections caused by meticillin-resistant *Staphylococcus aureus* (MRSA). Non-inferiority of co-trimoxazole to vancomycin was not demonstrated for the primary end point of treatment failure at day 7. Co-trimoxazole is not a recommended option in UK guidelines for severe MRSA infection, and the new data reinforce that co-trimoxazole should not be used in such patients.

Overview and current advice

Meticillin-resistant *Staphylococcus aureus* is a bacterium that is resistant to a number of widely used antibiotics. MRSA can cause a range of infections including skin and soft tissue infections, pneumonia, bone and joint infections and bacteraemia. Between April 2014 and March 2015 there were 801 reported cases of MRSA bacteraemia in NHS acute trusts in England.

A guideline has been produced by the MRSA Working Party of the British Society for Antimicrobial Chemotherapy on the prophylaxis and treatment of MRSA infections in the UK. The guidance includes advice on the appropriate use of vancomycin. Co-trimoxazole is not a recommended treatment for severe MRSA infections. Although not recommended in current guidelines, co-trimoxazole may appear to be an attractive alternative to antibiotics with a higher risk of association with *Clostridium difficile* infection.

Public Health England produces information on *Staphylococcus aureus*: guidance, data and analysis, which includes advice on screening and suppression of MRSA in primary care and surveillance reports on MRSA bacteraemia infections.

The NICE guidance on Antimicrobial stewardship provides good practice recommendations on systems and processes for the effective use of antimicrobials. NICE has also produced a Prevention and control of healthcare-associated infections: Quality improvement guide, which discusses MRSA. The NICE Evidence summary: Medicines prescribing briefing discusses *Clostridium difficile* infection: risk with broad-spectrum antibiotics.
Vancomycin infusion is licensed for potentially life-threatening infections due to susceptible gram-positive organisms which cannot be treated by other effective, less toxic antimicrobial medicines, such as the penicillins and cephalosporins. Vancomycin is one of the agents of choice in treating severe MRSA infection. Co-trimoxazole is not licensed for the treatment of severe MRSA infections.

**New evidence**

An open-label study assessed whether co-trimoxazole is non-inferior to vancomycin for the treatment of severe infections caused by MRSA. This parallel-group, open-label, randomised controlled trial (RCT) was conducted across 4 hospitals in Israel, and enrolled adult inpatients (n=252, mean age 65.8 years) with severe infections caused by MRSA. Approximately half of the participants had undergone surgery in the last 30 days, over 40% were classified as being dependent or bedridden on admission and half the study population had at least one chronic condition (including diabetes mellitus, chronic obstructive pulmonary disease and chronic heart failure). The investigators excluded people who had received more than 48 hours’ treatment with co-trimoxazole or vancomycin prior to enrolment and people with suspected or confirmed left sided endocarditis, meningitis and chronic renal failure. People with MRSA-resistant to co-trimoxazole or vancomycin were also excluded.

Participants were randomised to intravenous co-trimoxazole 1920 mg (trimethoprim 320 mg and sulfamethoxazole 1600 mg) twice daily (which could be switched to oral therapy at the same dose if appropriate) [n=135] or intravenous vancomycin, starting dose 1 gram twice daily (n=117). In both groups, treatment was adjusted to renal function; in the vancomycin group, it was directed by serum concentrations. The minimum duration of treatment was 7 days, with a median duration of treatment in the per protocol population of 17 days in the co-trimoxazole group and 14 days for vancomycin. Potentially effective antibiotics against MRSA (mainly rifampin) were permitted, and received by 10% of people on co-trimoxazole and 7% of people on vancomycin (p=0.32). Across the study, 91 out of 252 people (36%) had bacteraemia, and most common sources of MRSA infection were complicated skin and soft tissue infections (88 out of 252, 35%) and bone or joint infections (71 out of 252, 28%). Baseline characteristics were similar for both groups, except there were more people with bacteraemia in the vancomycin group compared with the co-trimoxazole group (43% compared with 30%, statistically significantly difference, p=0.042).

The primary efficacy end point was treatment failure at 7 days, defined as a composite of death, persistence of fever, persistence of hypotension, no improvement in Sequential Organ Failure Assessment (SOFA) score or persistent bacteraemia. The predefined non-inferiority margin was 15%. The primary safety end point was all-cause mortality at 30 days.

There was no statistically significant difference in treatment failure at day 7 for co-trimoxazole compared with vancomycin (risk ratio 1.38, 95% confidence interval [CI] 0.96 to 1.99). The failure rate at day 7 in the co-trimoxazole group was 38% (51 out of 135) and in the vancomycin group was 27% (32 out of 117), with an absolute difference between groups of 10.4% (95% CI −1.2% to 21.5%). The upper limit of the 95% CI was above the non-inferiority boundary of 15%, meaning non-inferiority of co-trimoxazole to vancomycin was not demonstrated. After adjustment for differences between groups, treatment with co-trimoxazole was significantly associated with treatment failure (odds ratio 2.00, 95% CI 1.09 to 3.65). There was no statistically significant difference in all-cause 30 day mortality for co-trimoxazole (14%) compared with vancomycin (11%, risk ratio 1.27, 95% CI 0.65 to 2.45).
Commentary

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In a well-designed, real world reflective study of microbiologically confirmed severe MRSA infection, Paul et al. failed to demonstrate that co-trimoxazole is not inferior to vancomycin. The study non-inferiority margin (−15%) would likely be rejected as too large by regulatory authorities if this was a trial of an investigational antibiotic, in which a non-inferiority limit of −10% would usually be used. Co-trimoxazole clearly failed this conservative measure of non-inferiority. We can conclude that there is insufficient evidence for the efficacy of co-trimoxazole to justify its use in the treatment of severe MRSA infection, in preference to the most often used antibiotic, vancomycin. After adjustment for differences between groups, the risk of treatment failure was twice as high with co-trimoxazole versus vancomycin.

Notably, the latest study results need to be considered alongside human and animal model data that suggest co-trimoxazole is probably suboptimal for the treatment of staphylococcal left-sided endocarditis and meningitis. Thus, in more difficult to treat MRSA infections there are several sources of data to warn against reliance on co-trimoxazole. MRSA infections are often associated with worse outcomes than meticillin-susceptible S. aureus (MSSA) infections. Clearly, however, both MRSA and MSSA strains vary in their virulence, and host factors are likely to be key determinants of outcome. It is plausible that poorer patient outcomes are due to the higher co-morbidity rates in MRSA infected patients or use of antibiotics that are inferior to anti-staphylococcal penicillins, which remain the antibiotics of choice for treating MSSA infections.

Co-trimoxazole is not a recommended option in UK guidelines for severe MRSA infection, and the new data reinforce that it should be avoided in such patients. It has been suggested that intravenous co-trimoxazole could be used as an alternative to antibiotics with a higher association with Clostridium difficile infection; the latest data caution against such use in MRSA infection. In addition to the glycopeptides vancomycin and teicoplanin, there are several alternative antimicrobials available in the UK with dependable activity against MRSA (e.g. linezolid, daptomycin, ceftaroline, cefitibiprole, oritavancin); these have been demonstrated to be non-inferior to vancomycin, at least in regulatory clinical trials, albeit with their limited applicability to serious infections.

Study sponsorship

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