Letters to the Editor

Haque et al.7 described two of their seven cases of IE, due to USA300 MRSA, as healthcare-associated; however, they did not clarify how they defined community-associated. It may be presumed that, due to the fact that these two patients had a prior hospital admission, the authors deemed the MRSA to be hospital-acquired as per the CDC criteria (http://www.cdc.gov/ncidod/dhqp/ar_mrsa_ca_clinicians.html#4). This further highlights the inadequacies of the CDC criteria, which do not take into account the microbiological characteristics of the isolates but focus largely on the epidemiological characteristics of the patient.

Overall, the emergence of CA-MRSA over the last decade and its relative difference from HA-MRSA in terms of its epidemiology, microbiology and treatment now require proper categorization so that authors and readers are clear as to the nature of the MRSA isolate being described. Therefore, when MRSA isolates are being reported, further microbiological work should be undertaken to ensure that a correct classification of the isolate as CA-MRSA/HA-MRSA is given.

Transparency declarations
None to declare.

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Transparency declarations
None to declare.

References

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Comment on: Therapy for Whipple’s disease

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Sir,

We read with much interest the article by Knaapen and Barrera1 recently published in JAC on Whipple’s disease treatment. It is fascinating as it shows, in this intriguing and rare disease, how successive deductive opinions finally came to be considered as established facts. There are no comparative studies on therapy of Whipple’s disease and, until recently, treatment recommendation was empirical, based on anecdotal reports of failures or relapses.2 We believe that this is confusing.

Relapse rates depend on the length of treatment and follow-up. As tetracyclines have been used for many years before co-trimoxazole in the treatment of Whipple’s disease, there are more reports on failures with the tetracyclines than with co-trimoxazole.2 There is no published evidence of the superiority of any regimen in terms of relapse rate during 5 years post-treatment follow-up.

The situation is also confusing for primary treatment failure. Whipple’s disease can exacerbate when treated, as during leprosy with lepromatous reaction or as in immune reconstitution. These immediate ‘failures’ are not antibiotic failures and when they are excluded, the only difference in failure rates between treatment regimens in the single published comparative study (tetracycline versus co-trimoxazole)2 is observed in patients with initial neurological manifestations. In these patients, doxycycline is poorly effective. In addition, treatment with co-trimoxazole is associated with failures caused by acquired resistance3 and, in our clinical experience, has a frequency of ~3%.2

We should base our recommendations on objective information such as in vitro data, genome analysis and clinical trials. Antibiotic susceptibility testing in vitro demonstrated that doxycycline alone was bacteriostatic rather than bactericidal, against Tropheryma whippelii, although the addition of hydroxychloroquine makes doxycycline bactericidal. T. whippelii is intrinsically resistant to trimethoprim (the gene coding for the target enzyme of this compound is missing in the genome of T. whippelii),4,5 and it has been confirmed in vitro that trimethoprim is ineffective.5 Thus, only the sulphonamide component of co-trimoxazole is active against T. whippelii, and there is no objective reason to prescribe co-trimoxazole instead of a sulphonamide compound alone.

The antibiotic susceptibility of T. whippelii to sulfadiazine has never been evaluated in vitro. We therefore determined the MICs of sulfadiazine for T. whippelii Twist and Neuro 20 strains using quantitative real-time PCR with methods as previously described.5 Experiments were conducted in 24-well plates. Cultures were centrifuged at 7500 rpm for 10 min. Pellets were resuspended to 1/100 in axenic medium. Antibiotics were diluted in culture medium at the concentrations of 0.25, 0.5, 1 and 2 mg/L. Antibiotic-free wells served as growth controls and experiments were performed in triplicate. During the experiments, cultures were harvested at day 0, day 14 and day 21 and frozen at −20°C, until DNA extraction for quantitative PCR.
Fig. 1. Kinetic of growth of T. whipplei Twist strain cultured in axenic medium in the presence of sulfadiazine (0.5–2 mg/L) as determined by quantification of number of DNA copies (log) by real-time quantitative PCR. Control=kinetic of growth of T. whipplei Twist strain in the absence of sulfadiazine.

assays. The MICs were determined by the measurement of the number of DNA copies by real-time quantitative PCR assay, compared with the number of DNA copies at day 0 of the experiment. MICs were defined as the minimal antibiotic concentrations allowing complete inhibition of bacterial growth. This was determined by measuring DNA copies using quantitative PCR assay when compared with a growth control at the beginning of the experiment. The MICs for the two strains of T. whipplei ranged from 0.5 to 1 mg/L for sulfadiazine versus 0.5 mg/L for sulfamethoxazole (Figure 1 shows an example of MIC determination for sulfadiazine and the Twist strain). Therefore, sulfadiazine is as effective as sulfamethoxazole in vitro.

In view of these new in vitro data, we believe that it is time to change from co-trimoxazole to sulfadiazine. Currently, two clinical studies are in progress to evaluate treatment strategies using either a combination of doxycycline (2 × 100 mg/day) with hydroxychloroquine (600 mg/day) associated with a sulphonamide in the case of neurological involvement (i.e. a positive PCR in CSF and/or neurological symptoms), or induction therapy with parenteral ceftriaxone, or a carbapenem for 14 days followed by 1 year of treatment with oral co-trimoxazole. We suggest only using a sulphonamide if the patient has neurological symptoms or a positive T. whipplei PCR assay on CSF. In our experience, preliminary results with this regimen are encouraging. Because sulfadiazine has better penetration into CSF, a longer plasma and CSF half-life, and higher plasma concentrations compared with sulfamethoxazole, this compound may be valuable in the treatment of Whipple’s disease when a sulphonamide is required.

In conclusion, with advances in knowledge of T. whipplei, the diagnosis of Whipple’s disease will be easier and more accurate than previously found. The evidence used to form past recommendations has been impaired by the lack of information on, for example, inclusion criteria and follow-up methods.

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References


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Therapy for Whipple’s disease—authors’ response

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Keywords: antibacterial agents, antibiotics, doxycycline, hydroxychloroquine, drug combinations, Tropheryma whipplei

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Sir,

We agree with many of the points made by Bakkali et al. in their letter responding to our paper ‘Therapy for Whipple’s disease’ published in JAC last year.

In their comment, the group of Dr Raoult provides in vitro evidence for the susceptibility of Tropheryma whipplei to sulfadiazine, which is in line with the previously demonstrated susceptibility to sulfamethoxazole. These findings are not unexpected since both sulphonamides are competitors for the same target enzyme, dihydropteroate synthetase. In their previous review, the authors suggested using a high dose of sulfadiazine or sulfamethoxazole instead of co-trimoxazole in case of neurological involvement. They now choose the former drug in view of the experiment. The MICs for the two strains of