Reply to Chou et al

To the Editor—We thank Dr Chou and colleagues for their letter, which accurately discusses the difference between superiority studies and noninferiority studies [1]. The question raised is, when a superiority study has negative results, what is a clinician to conclude? A good starting point for that discussion might be consideration of the number needed to treat (NNT). For example, when treating uncomplicated cellulitis, how many patients would we want to treat with trimethoprim-sulfamethoxazole in addition to a β-lactam in order for 1 person to benefit? Every clinician has his or her own threshold.

Because uncomplicated cellulitis is generally indolent (and the rare severe cases seem to be streptococcal), we think the NNT should be small. Personally, if we were going to treat uncomplicated cellulitis patients with 2 antibiotics instead of 1 antibiotic, we would want at least 10% to benefit from the extra antibiotic (ie, our personal NNT would be 10). The number needed to treat in our trial was 37 (ie, 1 divided by the risk difference of 2.7%) [2]. This suggests that 37 patients would have to have trimethoprim-sulfamethoxazole added to their cephalexin prescription for 1 of them to benefit. And this simple calculation does not begin to factor in the added cost and risk of diarrhea, allergies, and other adverse effects.

Taking this a step further, the upper bound of the 95% confidence interval of the point estimate in our paper was 15%, whose inverse is 6.7. This suggests that the smallest NNT that we would expect to find in a much larger trial is around 6.7. The possibility of a larger trial revealing such a small NNT is what motivated us to cite 2 ongoing trials in the original manuscript (NCT00729937 and NCT00730028, accessible on clinicaltrials.gov). To our knowledge, those are the only trials that hold out any hope of confirmation or refutation of our findings. Given the preponderance of evidence, the value of antibiotic stewardship, and the maxim *primum non nocere*, we think the right thing to do in the meantime is to treat uncomplicated cellulitis with a β-lactam alone, just as the Infectious Diseases Society of America recommends.

Much as we agree with the thrust of the letter by Chou and colleagues, it does seem important to correct an error they make in referring to "microbiologically confirmed cellulitis." Our original article summarizes a wealth of evidence that the vast majority of cellulitis cases are not amenable to "microbiological confirmation." We also note that while Chou et al cite Szumowski et al's retrospective study, as did we, they do not cite several other observational studies that found the opposite results [3]. Interested readers can find the citations in our publication [2].

Although it is true that no human trial has yet demonstrated benefit from the targeting of community-associated methicillin-resistant *Staphylococcus aureus* in the acute phase treatment of skin infections, we agree that it remains possible that such evidence could emerge in the future. We eagerly await the results of the ongoing trials mentioned above.

Notes

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