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Equivalence Between Oral and Intravenous Antibiotics When Treating Serious Staphylococcal Infections?

SIR—I read with interest the article by Schrenzel et al. [1], which compared intravenous and oral antibiotic regimens for the treatment of severe staphylococcal infection. The aim of the study was to show "the equivalence of the treatments" [1, p. 1287]. Equivalence studies have been plagued by methodological deficiencies [2, 3], and this study is no exception.

First, such studies require that a predefined range of equivalence be established [4]. The range has to be wide enough to ensure a reasonable sample size but narrow enough to ensure practical significance. If the authors allow the outcomes in the oral and intravenous antibiotic treatment groups to differ by 30%, is it still meaningful to call the 2 treatment arms equivalent? The fact that, midway through the study, the differences between the 2 groups were noted to be much smaller does not mean that the original sample size could be decreased. On the contrary, the smaller the range, the larger the sample size needed to establish equivalence.

This leads us to the major deficiency of this study: it was underpowered to detect equivalence at clinically relevant ranges (i.e., 5%–20%), and because the investigators were unable to recruit 260 participants, the study was even underpowered to detect equivalence at clinically dubious ranges (i.e., 30%–40%). A P value >.05 (i.e., not significant) for the 3 outcomes measured does not imply equivalence. This highlights 2 important points: first, the shortcomings of P values, and second, the importance of 95% CIs to demonstrate uncertainty. For example, the relative risk for the intention-to-treat population was 1.1, with a 95% CI of 0.7–1.6 (i.e., the range of effectiveness of the oral regimen varied from being 30% less effective to being 60% more effective than the intravenous regimen in treating staphylococcal infections) and a P value of .66. If we are to believe the P value, then we cannot reject the null hypothesis that a significant difference exists between the 2 treatment groups. Thus, we must deduce that there is a difference between intravenous and oral therapy. The 95% CIs, however, tell the real story. For all 3 outcomes (intention-to-treat, clinically evaluable, and microbiologically evaluable), the range of the 95% CIs far exceeds even the excessive pre-hoc range of equivalence of 30%. This article [1] shows how easily an underpowered study can be misinterpreted as showing equivalence. The results of this important study are, unfortunately, inconclusive. A reasonable clinician should not make a decision to use an oral regimen to treat a serious staphylococcal infection in one of his patients on the basis of this study. Although the authors should be commended for undertaking a most difficult trial, the conclusions presented in their article are misleading. The major benefit of this study is that it provides estimates that can be used to power a more definitive trial.

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References

1. Schrenzel J, Harbarth S, Schockmel G, et al. A randomized clinical trial to compare fleroxacin-rifampicin with flucloxacillin or vancomycin for the treatment of staphylococcal infection. Clin Infect Dis **2004**; 39:1285–92.
2. Greene WL, Concato J, Feinstein AR. Claims of equivalence in medical research: are they supported by the evidence? Ann Intern Med **2000**; 132:715–22.
3. Krysan DJ, Kemper AR. Claims of equivalence in randomized controlled trials of the treatment of bacterial meningitis in children. Pediatr Infect Dis J **2002**; 21:753–8.
4. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. BMJ **1996**; 313:36–9.

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Reply to Richards et al. and Ghanem

SIR—We thank Richards et al. [1] and Ghanem [2] for their stimulating criticisms of our study [3]. We agree that this clinical trial has a number of methodological limitations, including its small sample size (making it statistically impossible to prove the equivalence of both treatment regimens) and the pooled analysis of 2 different study arms. However, we disagree with several comments by Richards et al. [1]. First, as suggested in the CONSORT statement [4], the measure of effect of a study medication can be expressed as a risk ratio (or relative risk), with confidence intervals to indicate the precision of the treatment effect. Second, the 95% CIs of the effect estimates in our study cannot rule out some difference between the 2 treatment regimens that we compared. Considering the small differences in outcome for both treatment regimens, it remains unlikely, however, that a large, clinically important difference in failure rates has been missed. Third, we were surprised that Richards et al. [1] did not carefully evaluate tables 2 and 3 of our article [3]. These tables and the related Results section summarized the per-protocol analysis, which compared patients according to the treatment that they actually received and included only those clinically and microbiologically evaluable patients who satisfied the entry criteria and properly followed the protocol [5]. This per-protocol analysis did not show results that were different from those of the intention-to-treat analysis. Finally, we believe that our study results may still be

of valuable help for those clinicians who have used fluoroquinolone-rifampicin combinations for outpatient treatment of staphylococcal infections for >10 years [6]. Nonetheless, the evidence provided by this study will need further confirmation in a large randomized trial.

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References

1. Richards J, Black J, Marshall C. Methodological errors in staphylococcal equivalence study. Clin Infect Dis **2005**; 40:771–2 (in this issue).
2. Ghanem KG. Equivalence between oral and intravenous antibiotics when treating serious staphylococcal infections? Clin Infect Dis **2005**; 40:772 (in this issue).
3. Schrenzel J, Harbarth S, Schockmel G, et al. A randomized clinical trial to compare fleroxacin-rifampicin with flucloxacillin or vancomycin for the treatment of staphylococcal infection. Clin Infect Dis **2004**; 39:1285–92.
4. Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med **2001**; 134:663–94.
5. Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. BMJ **1996**; 313:36–9.
6. Stengel D, Bauwens K, Sehouli J, Ekkernkamp A, Porzsolt F. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis **2001**; 1:175–88.

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Glutamine Supplementation for Patients with Severe Cryptosporidiosis

Sir—We read with interest the article by Bushen and colleagues [1] on the effect of glutamine supplementation in patients with AIDS and chronic diarrhea. The authors observed not only a significant improvement in symptoms but also an improvement in antiretroviral drug absorption after oral glutamine supplementation. We describe a patient with a severe case of *Cryptosporidium* diarrhea. A dramatic improvement in the patient's clinical condition was associated with parenteral administration of glutamine.

A 30-year-old man with fever, dry cough, diarrhea, and weight loss of 12 kg received a diagnosis of HIV infection. His CD4 cell count was 40 cells/mm^3, and his HIV RNA load was 641,000 copies/mL. Because of the worsening of diarrhea and the onset of vomiting, he was admitted to our hospital (Ospedale Generale; Bolzano, Italy) on 25 August 2004. Examination of stool samples revealed infection with *Cryptosporidium parvum* but no other pathogenic microorganisms. Cryptococci were isolated by culture from CSF, blood, urine, and sputum samples. Induction antifungal treatment consisted of 3 weeks of treatment with liposomal amphotericin B at a dosage of 3 mg/kg/day, which was combined, for 2 weeks, with treatment with flucytosine at a dosage of 100 mg/kg/day and was followed by treatment with difluconazole at a dosage of 200 mg b.i.d.

On 1 September, total parenteral nutrition was begun because, despite the administration of methoclopramide and omeprazole, the patient's vomiting was persistent. Administration of flucytosine was interrupted for 1 week to see whether vomiting would lessen, but it did not. Neither treatment with the antiemetic ondansetron, given first at a dosage of 8 mg/day and then at a dosage of 24 mg/day, nor sedation with chlordemethyldiazepam or chlorpromazine reduced the vomiting. The intake of liquids, food, and pills all prompted vomiting. During week 4 of hospitalization, gastroscopy was performed. Histologic examination of gastric biopsy specimens revealed multiple cryptosporidia on the surface of and within the gastric pits. From 15 September through 19 September, azithromycin, 500 mg/day, was given endovenously to combat *Cryptosporidium* infection, but there was no evident reduction in diarrhea. Beginning on 18 September, 14 g of glutamine was added to the parenteral nutrition on a daily basis because of the persistent diarrhea.

After 5 days of glutamine supplementation, the frequency of the patient's bowel movements decreased from 10 movements/day to 5 movements/day, and fluids could be taken without vomiting. Therefore, azithromycin at a dosage of 500 mg/day po and paromomycin at a dosage of 500 mg t.i.d. were given to treat *Cryptosporidium* infection. Two days later, antiretroviral therapy with stavudine, lamivudine, and indinavir was commenced. Indinavir was chosen because it had been shown to be less toxic for enterocytes and to directly inhibit the development of *Cryptosporidium* species in in vitro experiments [2]. Unfortunately, on the same day that antiretroviral therapy commenced, a central venous catheter had to be removed because of an entry-side infection with thrombosis of the right jugular vein and part of the subclavian vein.

During the next week, total parenteral nutrition was stopped. Despite treatment with azithromycin, paromomycin, and antiretroviral drugs, the patient's diarrhea worsened, and his clinical condition became life-threatening. It was impossible, via the oral route and via the peripheral vein, to sufficiently replace potassium and protein that had been lost. Serum potassium levels decreased to 1.9 mEq/L, and serum albumin levels decreased to 1.8 g/dL. On 4 October, a Groshong central venous catheter was placed in the left subclavian vein to provide long-term total parenteral nutrition. Parenteral nutrition again included 14 g of glutamine. From the third to the fourth day of administration of parenteral nutrition, the loss of fluids through watery diarrhea was reduced from 3.7 L to 1.7 L, and, 2 days later, diarrhea and vomiting had resolved. Within 11 days after the start of antiret-