after admission, and a second episode occurred after 5 days of treatment that included erythromycin, 1000 mg iv (3 doses), and azithromycin, 500 mg iv (1 dose), 500 mg po (1 dose), and 250 mg po (3 doses). In our analysis, we classified only the second episode of bacteremia as breakthrough bacteremia.

Bishai [1] suggests that macrolides may have some anti-inflammatory effect that accounts for the lower mortality that we observed among case patients who received a macrolide. However, we pointed out that the case patients who received macrolides were younger than those who did not receive macrolides (mean age, 40 vs. 55 years). Age, independent of antibiotic treatment received, is a very important predictor of mortality [6] and is the single largest contributor to the Pneumonia Outcomes Research Team risk score [7]. When we used published age-specific mortality data to calculate the predicted mortality rate in the group of case patients who were taking a macrolide and who had bacteremia due to a macrolide-resistant isolate, the expected number of deaths in this group of 19 patients was 1.9. Hence, the finding of no deaths in this group was not unexpected.

Bishai [1] argues that the famous study of Austrian and Gold [6] is evidence that treatment failure occurs even when patients with bacteremia due to a susceptible strain of pneumococcus received penicillin (a highly active antibiotic). However, the key finding of Austrian and Gold [6] was that the patients who were expected to die during the first 5 days of illness received no benefit from antibiotic treatment, as Bishai himself emphasized in a recent editorial [8]. Moreover, Austrian and Gold [6] did not report any cases of breakthrough bacteremia that occurred during penicillin therapy, nor are we aware of any published reports of breakthrough bacteremia occurring in patients without meningitis receiving concurrent parenteral penicillin, although penicillin has a nearly 60-year history of clinical use.

The effort to maintain that macrolide therapy is effective regardless of resistance relies on fuzzy theoretical constructs, such as the role of anti-inflammatory effects and the relevance of the macrolide concentration in the so-called ELF (epithelial lining fluid). Such a claim flies in the face of extensive testing in animal models that has consistently shown that infections with macrolide-resistant pneumococci fail to respond to macrolides [9], an increasing number of publications describing macrolide treatment failure [10–12], a recent report of development of resistance during macrolide monotherapy, which resulted in the death of the patient [13], and the data presented in our article [2].

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P. carinii Pneumonia in African Children and the Ineffectiveness of TMP-SMX Prophylaxis

Sir—we appreciate the article by Madhi et al. [1] on Pneumocystis carinii (now Pneumocystis jiroveci [2]) pneumonia (PCP) in HIV–1–infected African children. The study provides us with important information on the high burden of PCP and on bacterial and viral coinfections in children with PCP. Furthermore, starting with the title of the article, the authors state that prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) was ineffective in this cohort of patients. On the basis of the study design, however, we believe that the conclusion should have been more prudent.

As Madhi et al. [1] state, their study was designed primarily to assess the burden of PCP among HIV–1–infected African children with severe pneumonia and to examine how PCP and HIV–1 infection interact with bacterial and viral pneumonia. Determination of the effectiveness of TMP-SMX prophylaxis, however, was not a prospective and well-defined objec-
tive of the study, thus casting doubt on the adequacy of its evaluation as one of the primary outcome measures. Rather, included patients were part of a larger cohort within which an antipneumococcal vaccine was evaluated.

Two points that we believe merit comment regard the procedures used for the diagnosis of PCP and for the evaluation of compliance with TMP-SMX prophylaxis. Madhi et al. [1] evaluated induced sputum samples and nasopharyngeal aspirates for diagnosis. Actually, owing to its high sensitivity and specificity, fiberoptic bronchoscopy with bronchoalveolar lavage is the recognized “gold standard” for diagnosis of PCP in HIV–infected patients. Although examination of induced sputum samples (and, to a lesser extent, nasopharyngeal aspirates) has emerged as a useful and cost-effective procedure for diagnosis of PCP, its diagnostic accuracy may be inappropriate for meaningful assessment of the effectiveness of a prophylactic regimen in clinical research [3, 4]. Whether examination of induced sputum samples is appropriate for a particular task depends ultimately on the predictive values in a specific setting; these, in turn, critically depend on the prevalence of the condition to be detected. We have recently evaluated, by meta-analysis, the diagnostic yield of procedures for examining induced sputum samples for the diagnosis of PCP in HIV–infected patients [5]. For immunofluorescence staining, the pooled sensitivity and specificity estimates of the meta-analysis were 67.1% and 96.5%, respectively, which are very similar to the rates provided by Ruffini and Madhi [3] for HIV–infected African children. However, although sensitivity and specificity remains constant when the technique is used for populations with different prevalences of disease, the related predictive values are subject to wide variation. On the basis of the sensitivity and specificity obtained from the meta-analysis, and using a Bayesian approach, we have calculated the predictive values for examination of induced sputum samples according to different prevalences of PCP. For instance, if the prevalence of PCP is 35%, then immunofluorescence staining of induced sputum samples has a positive predictive value (PPV) of 91.3% and a negative predictive value (NPV) of 84.5%; if the prevalence is 50%, then the PPV is 95.1% and the NPV is 74.6%.

Madhi et al. [1] used immunofluorescence staining of induced sputum samples and reported a prevalence of PCP of 36.2% among children who were receiving TMP-SMX prophylaxis, compared with a prevalence of 48.5% among children who were not receiving prophylaxis. When our estimate of NPV is applied to these figures, it becomes apparent that a negative result yields an ~10% greater possibility of false-negative results in the higher-prevalence group, compared with the lower-prevalence group (25.4% for children who were not receiving prophylaxis vs. 15.5% for children who were receiving prophylaxis). With regard to PPV, conversely, a positive result yields an ~4% additional chance of false-positive results among children who were receiving PCP prophylaxis, compared with those who were not (8.7% vs 4.9%, respectively). Thus, the overall accuracy of examination of induced sputum samples may have varied significantly among patient groups, leading to an imbalance in the rate of PCP diagnosis among children who were or were not receiving prophylaxis and to underestimations of the effectiveness of TMP-SMX prophylaxis.

Unquestionably, the widespread use of PCP prophylaxis before the introduction of HAART has had a major impact on the care of HIV–infected patients. Episodes of PCP are uncommon among patients who adhere to regimens of TMP-SMX prophylaxis. Breakthrough cases of PCP usually occur in patients who are not compliant with therapy or who have very low CD4 cell counts [6]. As Madhi et al. [1] note, in their study, compliance with prophylaxis was assessed only on the basis of record review and parental reports. Moreover, Madhi et al. [1] do not provide data on CD4 cell counts, although it is reasonable to assume progressive damage to the immune system occurred in this cohort of children, who did not have the opportunity to take advantage of antiretroviral therapy.

In the Discussion section of their article, Madhi et al. [1] correctly drew attention to several limitations of the study, including the accuracy of the diagnostic test used, the low proportion of patients receiving TMP-SMX, and the possibility of poor compliance with therapy. Certainly, the poor sensitivity in the assessment of compliance could have contributed to the finding of more episodes of PCP in this group of patients who were reported to have been compliant with prophylaxis. In conclusion, the contribution of this study is important in several ways, but the absence of prospective identification of the effectiveness of TMP-SMX prophylaxis as a primary outcome measure carries the risk of undue inference.

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Diagnosis based on examination of respiratory secretions obtained from immunocompromised individuals is associated with underlying PCP, the same may not hold true for individuals who are receiving TMP-SMX prophylaxis. This may explain the relatively low mortality rate among children who were purported to be receiving TMP-SMX prophylaxis and from whom P. jiroveci was isolated, compared with the rate among children who were not receiving prophylaxis at the time of documentation of P. jiroveci infection [2]. Further support for this hypothesis is found in a report of the continued isolation of P. jiroveci from respiratory secretions obtained up to 3 months after clinically successful treatment of PCP [6] and in a report of detection of P. jiroveci in otherwise healthy children with minimal respiratory symptoms [7].

References


CORRESPONDENCE • CID 2003:36 (1 April) • 939

Reply

Str—We thank Cruciani et al. [1] for their insightful comments on our article [2]. Cruciani et al. [1] raise the important issue of the need for a highly sensitive and specific method to measure the efficacy of an intervention. Nevertheless, we consider the positive and negative predictive values for the techniques used for diagnosis of PCP among HIV-1–infected children receiving trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis (91.3% and 84.5%, respectively, as estimated by Cruciani et al. [1]) to be adequate, if not optimal, for the diagnosis of Pneumocystis jiroveci infection in the context of our study. Diagnosis based on examination of bronchoalveolar lavage specimens may have documented a greater difference in the prevalence of infection among children receiving versus children not receiving TMP-SMX; unfortunately, this approach is completely impractical in our developing country. The 36.2% prevalence of P. jiroveci infection among children with pneumonia receiving prophylaxis remains a high figure, and, on the basis of the analyses of Cruciani et al. [1], it may have been an underestimate of the true burden of prophylaxis failure in these children.

Although it is important to confirm that the evaluation of TMP-SMX prophylaxis was not a primary objective of the study, we nevertheless thought that the high number of children who had apparent breakthrough episodes of P. jiroveci infection—despite purported receipt of TMP-SMX prophylaxis—deserved reporting. We concur that TMP-SMX prophylaxis has been effective in reducing the incidence of P. jiroveci infection, delaying progression to severe AIDS, and possibly prolonging life among HIV-1–infected children in developed and some developing countries [3,4]. Nevertheless, little is known about the effectiveness of the strategy in sub-Saharan African countries, where the burden of pediatric HIV-1 infection is high. The effectiveness of TMP-SMX prophylaxis in such countries undoubtedly depends on compliance with therapy. We do not suggest that TMP-SMX prophylaxis per se may not be useful for prevention of P. jiroveci infection among HIV-1–infected children. Rather, we argue strongly in favor of greater vigilance in the implementation of TMP-SMX prophylaxis for HIV-1–exposed infants in sub-Saharan Africa than is currently the case.

In conclusion, despite the limitations of our study, we believe that the findings raise a number of issues. Foremost, the results may be an important signal that we are being less than effective in implementing what is widely acknowledged as being an effective strategy for prevention of P. jiroveci infection among HIV-1–infected children. We would like to reiterate that it is imperative that a structural reappraisal of the manner in which TMP-SMX prophylaxis is administered to children, particularly with regard to issues of adherence, be evaluated in sub-Saharan Africa. Furthermore, we maintain that, given the widespread use of TMP-SMX in sub-Saharan Africa, the study also serves as a call for the need to evaluate whether there is emergence of P. jiroveci strains with reduced susceptibility to sulfa drugs [5]. Finally, although it is generally accepted that isolation of P. jiroveci from respiratory secretions obtained from immunocompromised individuals is associated with underlying PCP, the same may not hold true for individuals who are receiving TMP-SMX prophylaxis. This may explain the relatively low mortality rate among children who were purported to be receiving TMP-SMX prophylaxis and from whom P. jiroveci was isolated, compared with the rate among children who were not receiving prophylaxis at the time of documentation of P. jiroveci infection [2]. Further support for this hypothesis is found in a report of the continued isolation of P. jiroveci from respiratory secretions obtained up to 3 months after clinically successful treatment of PCP [6] and in a report of detection of P. jiroveci in otherwise healthy children with minimal respiratory symptoms [7].