Correspondence

Is Azithromycin the First-Choice Macrolide for Treatment of Community-Acquired Pneumonia?

SIR—The article by Sánchez et al. [1] in the 15 May 2003 issue of *Clinical Infectious Diseases* addressed an important issue: treatment choice for community-acquired pneumonia (CAP). The aim of this retrospective study was to compare outcomes, including mortality, for patients with CAP who were treated with either clarithromycin or azithromycin. However, there are a number of methodological problems with this study that may have biased the results, thus distorting the specified comparison.

The main methodological problem involves the route of administration for the 2 study medications, clarithromycin and azithromycin. As indicated by Sánchez et al. [1], clarithromycin was administered either as an intravenous infusion or as an oral tablet. In contrast, azithromycin was available for administration only as an oral tablet. Although the Pneumonia Patient Outcomes Research Team (PORT) severity scores do not show significant differences between the 2 treatment groups (table 1 in [1]), it is possible that patients thought to have more severe CAP were treated with clarithromycin, because this would permit continuation of intravenous therapy (after the initial treatment with ceftriaxone for all patients). If physicians believed that patients had mild or moderate CAP, they may have been more likely to select azithromycin and discontinue intravenous therapy.

Related to this, the duration of treatment for clarithromycin was specified as $\geqslant$10 days, whereas the duration of treatment for azithromycin was specified as 3 days. Among patients with equivalent CAP severity, the length of hospital stay reported for the azithromycin group may thus have been less than that for the clarithromycin group because of delays in switching from intravenous to oral therapy among patients who received clarithromycin, rather than because of more-rapid symptom improvement due to azithromycin therapy.

There are also a number of issues associated with the patient population included in this study. Patients with more severe CAP are likely to require intensive care unit (ICU) admission and may experience acute respiratory failure. Patients with acute respiratory failure requiring mechanical ventilation were excluded from this study; however, no information is provided on how many of these patients had been treated with azithromycin, compared with the number treated with clarithromycin. If the proportions of excluded patients in the 2 treatment arms were different, the patient populations included in the study would not represent equivalent groups; this could bias the overall mortality rate and length of stay. In addition, in the Results section, Sánchez et al. [1] indicate that, "[f]or hospitalized patients who no longer needed ICU admission, therapy with azithromycin plus a ceftriaxone remained a significant predictor of good outcome" (p. 1241). In the Discussion section, the authors also specify the "outcome of patients with CAP who do not require ICU admission" [1, p. 1243]. ICU admission is not listed as an exclusion criterion earlier in the article. Furthermore, no information is provided on the proportion of azithromycin versus clarithromycin patients requiring ICU admission, nor is there data on the outcomes for patients who did require ICU admission. Because the number of patients included in the multivariate analysis is not provided (table 3 in [1]), it is unclear how many patients were included in the study and whether the subgroups selected are representative of all patients with CAP treated with azithromycin or clarithromycin.

Finally, there are a number of issues with regard to the study's analysis that are problematic, particularly the selection of the reference group and the selection of variables in the multivariate analysis of mortality. Table 3 in their article [1] summarizes results of multivariate analysis of the impact of macrolide choice on the odds of having a length of stay >7 days. However, in controlling for CAP severity, the comparison group used in this analysis comprised patients with a PORT score $\leqslant$3. Because all patients with a PORT score of 1 or 2 were not hospitalized [2], including their length of stay (i.e., 0 days) in the analysis would bias the results if more of these patients with mild CAP were treated with azithromycin than with clarithromycin. The appropriate comparison group would be patients with a PORT score of 3, rather than those with a score of $\leqslant$3.

In addition to controlling for CAP severity using PORT score, the multivariate analysis of mortality controlled for age (table 3 in [1]). Age, however, is a component of the PORT score. Because the azithromycin patient population was older than the clarithromycin population, including age twice in these regressions (as both an independent predictor variable and a component of the PORT score) may have biased the results. Furthermore, although age was included as an independent variable in the multivariate analysis of mortality, sex was not included in this analysis. In the multivariate analysis of length of stay, sex was included, whereas age is not. No explanation of the rationale

for including different predictor variables in the 2 analyses was provided.

Mortality and length of stay associated with CAP are vital issues, and Sánchez et al. [1] are to be congratulated for undertaking this study. However, it is important to recognize that this is a retrospective, nonrandomized study. Although such retrospective studies are valuable and provide critical information on "real-world" treatment patterns and outcomes, they must involve appropriate methodologies to control for potential selection bias in the nonrandomized choice of treatments. Without further information with regard to the treatment patterns, study populations, and analysis methodologies, it is difficult to assess the results presented in this study.

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Reply

Sir—My colleagues and I [1] appreciate very much the critical comments of Halpern and Cifaldi [2]. Our work was just an attempt to offer another therapeutic, but modest, point view for one of the most debated issues in modern medical practice: whether a macrolide is needed in combination with a β-lactam to improve the outcome of patients with community-acquired pneumonia (CAP). We did not have any a priori preference or expectation of superiority for either of the 2 macrolides studied (clarithromycin and azithromycin).

As noted in our article [1], since 1999, the severity of CAP in patients who have received a diagnosis of CAP in our hospital has been scored using the Pneumonia Patient Outcomes Research Team (PORT) classification, PORT data have been entered in a database, and such patients have been prospectively followed [1]. Although the study protocol was prospective, the analyses were, obviously, retrospective. We were surprised to observe that those patients for whom azithromycin was the second antibiotic prescribed had better outcomes. This result was the reason for attempting to evaluate whether severity factors described by Fine et al. [3] (i.e., PORT scores), rather than the prescribed macrolide, were the actual cause of such outcomes.

The route of administration for the antibiotics did not affect length of hospital stay because, according to our protocol, all patients who achieved stable apyrexia within 3 days after the initial dose of antimicrobials were switched to oral therapy, either a β-lactam or a macrolide. Oral administration of antibiotics such as amoxicillin-clavulanate, alone or combined with clarithromycin, did not delay the time to hospital discharge. Patients discharged from the emergency department (all patients with PORT scores of 1 or 2 and some patients with a score of 3) were not included in the length of stay analysis, as my colleagues and I [1] indicated in table 2 of our article. In our study, patients who required treatment in the intensive care unit (i.e., those who were receiving mechanical ventilation, either invasive or noninvasive) were not considered for analysis. Patients undergoing ventilation do not receive oral antimicrobial therapy in our hospital, and parenteral azithromycin therapy was not available when the study was done. Those patients who died within the first hours after admission to the hospital were not included in the analysis involving the assessment of the effect of antimicrobial drugs.

The higher mean age among those patients in the azithromycin group was another surprising finding, as well. Because of this unexpected result, age and sex (female sex subtracts 10 points off the score) were removed from inclusion in the recorded PORT score, and scores were recalculated for each patient. All severity factors, including sex, were incorporated separately in the univariate analysis. Stepwise multivariate analysis included age, PORT score, and type of macrolide administered as independent factors associated with mortality, and the factors included in the length of stay analysis were the same, except for the replacement of age with male sex. Although the ORs were 2.74 and 2.61 for mortality and length of stay, respectively, the 95% CIs were not statistically significant.

In short, we agree with Halpern and Cifaldi [2] that the main weakness of our study was that choice of treatment was not randomized and that the results may not be applicable to severely ill patients with CAP. However, this is the main reason why, at the end of our article, we suggested that additional prospective and randomized studies should be performed to set up authoritative conclusions.

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Malaria in Pregnancy: The "Cortisol" and "Prolactin" Hypotheses

Bouyou-Akotet et al. [1] have recently resurrected the "cortisol hypothesis" of McGregor [2] and Vluegels et al. [3] to account for plasma high levels of cortisol, measured at the time of delivery, in the plasma of primi- and multiparous Gabonese women with *Plasmodium falciparum* infection. Citing a letter of mine [4], in which I posit a possible role for prolactin in cases of anemia associated with the pathology of maternal malaria, Bouyou-Akotet et al. [1] seem to imply that their findings of high prolactin concentrations in multiparous women (who, among pregnant women, do happen to be least susceptible to malaria) contradict my "prolactin hypothesis." The authors do not cite, however, another missive of mine [5] in which I do discuss the relationship between prolactin and natural killer cells in maternal malaria. Like [1], I cite the work of Montero et al. [6], but my interpretation of the work of the latter investigators is slightly different from that of Bouyou-Akotet et al.

Even though I did state, as paraphrased by Bouyou-Akotet et al. [1], that, "starting at the second trimester and continuing through to the postpartum period (lactation), increased pulsatile levels of prolactin are witnessed" [4], I avoided discussing, for good reason, the complex cascade of endocrine-associated events at parturition or delivery. I merely wished to show that the increase in prolactin levels fit the new findings, reported by Diagne et al. [7], of malaria susceptibility among pregnant women.

The 24-h period preceding and following delivery is a well-studied endocrinological series of events that includes a complex, amphoteric synergism between cortisol and prolactin; space allows for only a brief synopsis. During normal labor, primiparous women have been observed to have higher antepartem and early postpartum cortisol levels [8], whereas prolactin levels decrease during labor [9, 10]. There is no reason to believe that mothers and infants who survive until term do not have a normal physiological parturition. I know of no studies that have looked at prolactin, specifically in light of parity issues among multiparous women during or after labor. However, Grajeb and Perez-Escamilla [8] note that multiparous women have earlier onset of lactation—which might mean that prolactin levels in multiparous women return to normal earlier after delivery (possibly because of less stress during labor) than do such levels in primiparous women. Thus, I would argue that parturition is not the time to assay for hormonal involvement in maternal malaria and that the findings reported by Bouyou-Akotet et al. [1] might only reflect the normal course of events at delivery.

The interest in adrenal corticoids in malaria-like infections predates the work of McGregor [2]. In the early 1950s, cortisone had been employed in mice [11] and primates [12] in an attempt to induce malaria relapse. Also, Applegate and Beaudoin [13], attempting to elucidate the mechanism of "spring relapse" in birds that were infected with "*Plasmodium relictum,*" treated house sparrows with corticosterone (the avian corticoid) and gonadotropin and concluded, finally, that some other factor must be involved in malaria relapse and migration. At nearly the same time, Meier et al. [14] were working out the complex synergy between corticosterone and prolactin in avian migration, prompting some to call prolactin the "migration hormone." In a recent paper [15], I hypothesized that prolactin is the "relapse hormone" in the hemosporidian infections that relapse. Recently, I have also theorized that prolactin might explain the unique pathologic conditions in pregnant women with HIV and malaria coinfection [16].

Both Duffy [17, p. 91] and Desowitz [18, p. 140] have recently elucidated some of the shortcomings of the "cortisol hypothesis." I only desire that the "prolactin hypothesis" receive similar scrutiny. In the end, we may find that the 2 hypotheses are not mutually exclusive but, rather, are contravening expressions of a terribly complex pathology.

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Reply

Our study [1] compared the ex vivo natural killer (NK) cell cytotoxicity against *Plasmodium falciparum*–infected erythrocytes in association with cortisol and prolactin concentrations in plasma samples obtained from primiparous and multiparous women at the time of delivery. The highest cortisol concentrations were found in the plasma of *P. falciparum*–infected primiparous women. A positive correlation was found between cortisol concentration and parasite load, and a negative correlation was found between the magnitude of the NK cell cytotoxicity effect and cortisol production. Thus, we suggested that depressed NK cell cytotoxicity against *P. falciparum*–infected erythrocytes may contribute to increased susceptibility to malaria during pregnancy, particularly among primiparous women.

Pearson [2] supports the "prolactin hypothesis" of malaria susceptibility among pregnant women. Citing various studies [3–5], Pearson [2] points out that higher cortisol levels and lower prolactin levels are found during normal labor in primiparous women, and he argues that our findings only reflect the normal course of events during delivery.

We would like to summarize the various arguments discussed by Pearson [2]. We are aware that the main weakness of our work [1] is that the samples were obtained at delivery. As stated in our article [1], it would be more accurate to monitor women throughout pregnancy until the postpartum period, and we are currently investigating this aspect. Indeed, pregnant women living in areas where malaria is endemic are more susceptible to malaria from the second trimester through the early postpartum period [6], and the corticosteroid concentration is increased during the second trimester of pregnancy, with the highest levels in primigravidae and malaria-infected women [7]. Our study [1] is the first to assess concentrations of pregnancy hormones in association with *P. falciparum* infection, parity, and NK cell cytotoxicity. We clearly showed that NK cell activity was significantly decreased in women with higher cortisol production, whereas it was increased in those with higher prolactin levels. Of interest, cortisol directly inhibits NK cell activity [8–10]. In contrast, prolactin is an immunostimulatory "cytokine" [11, 12] that induces membrane-receptor expression of IL-2, IFN-γ release [13], and NK cell proliferation [14]. It has also been reported that induction of IFN-γ by the prolactin/receptor complex upregulates the release of endogenous TNF-α, IL-6, and IL-1β, which could trigger antiparasitic activity [15]. To date, besides its association with anemia, as reported by Pearson [16], there are no data associating prolactin concentrations with the presence of *P. falciparum* malaria. We think that increased susceptibility to maternal malaria in primigravidae can be explained, at least partly, by their high cortisol levels, which inhibit NK cell activity.

We wonder if the missing factor in the "mechanism of spring relapse" described by Applegate and Beaudoin [17] is NK cell cytotoxicity. Indeed, we and others have shown that an increased susceptibility to infections is associated with a significant decrease in NK cell activity [18–20]. The functional defects of NK cells in HIV-infection [21, 22] might be crucial in the increased susceptibility of HIV-infected women to maternal malaria. We appreciate the concerns of Dr. Pearson [2] about the time at which pregnancy hormones were assessed, but we believe that our findings adequately address the involvement of cortisol levels and NK cell cytotoxicity in increased susceptibility to maternal malaria.

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Outbreak of Shiga Toxin–Producing *Escherichia coli* O111:H8 Infection

Sir—We were very pleased to read the report on the outbreak of Shiga toxin–producing *Escherichia coli* (STEC) O111:H8 infection by Brooks et al. [1]. We have been alerting the scientific community for more than 10 years that STEC belonging to serogroup O111 are important pathogens [2]. An outbreak in Australia, in which strains belonging to this serogroup played a dominant but not exclusive role [3], came after our warning. This outbreak, in which the main source of infection was contaminated mettwurst (a type of salami), involved, in addition to STEC O111:H− and O111:H8, STEC belonging to O serogroups O26, O113, and O157. This led us to conduct an extensive serological investigation [4, 5]. These studies revealed that the severity of disease manifested in the individual affected patients depended on the number of STEC serogroups to which they were exposed, as evidenced by development of antibodies. We would urge Brooks and colleagues to perform such an investigation, because there is a strong likelihood that the type of outbreak they describe may well have involved additional serogroups of STEC. Having only isolated STEC O111:H8 from 2 of their patients and having found antibodies to both O111 and O157 in some of their patients may well suggest that other serogroups of STEC played a role in the outbreak described by Brooks et al. [1].

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Reply

Sir—We appreciate the letter from Bettelheim and Goldwater [1] regarding our investigation [2]. We considered the possibility of infection with *E scherichia coli* O157 or a Shiga toxin–producing *E. coli* (STEC) of a serotype other than O111. Stool specimens had been refrigerated for >10 days when they were first evaluated for STEC. Despite this compromise to bacterial recovery, none of 21 stool specimens yielded *E. coli* O157 on selective media, but 2 of the 11 specimens yielded *E. coli* O111. In convalescent-phase serum samples obtained from a convenience sample of campers 38 days after the first illness, levels of both IgM and IgG to O111 lipopolysaccharide (LPS) differed significantly in the campers with clinically-defined cases, compared with control campers. However, no case patient had a positive IgM response to O157 LPS, and the very low titers of IgG to O157 LPS were similar in case and control campers. We interpreted these data as being consistent with recent exposure to STEC O111 without recent exposure to STEC O157,

and we attributed the minimally positive anti-O157 LPS IgG responses to nonspecific reactions or historical exposures in both case patients and control subjects. With no data to indicate that the campers were exposed to multiple STEC serotypes, we did not believe it fruitful to examine serum samples for IgM and IgG antibodies to other STEC serotypes. Although none of these data can prove absolutely that STEC O111 was the only pathogen present, we believe the evidence justified applying the principle of Ockham's razor ("Plurality is not to be assumed without necessity").

Our investigation underscores the importance of recognizing outbreaks of STEC infection rapidly and obtaining early stool specimens (and possibly serum samples) from all patients, particularly those with hemolytic uremic syndrome, to facilitate identification of the etiology. Further work is needed to more fully understand the meaning of titers positive for antibody to multiple STEC serotypes in patients with acute infection and the likelihood of multiple serotypes causing an outbreak.

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