

Correspondence

Paromomycin in Cryptosporidiosis

SIR—Hewitt and colleagues should be commended for publishing the findings of their placebo-controlled trial of paromomycin for the treatment of cryptosporidiosis [1]. Their results are similar to those noted in a previous placebo-controlled trial and in other open-label treatment studies [2, 3]. However, several weaknesses in the trial design and analysis may have led the authors to incorrect conclusions.

The planned analysis was intent-to-treat, but the data that were presented excluded information on individuals who dropped out during the study. Importantly, patients who dropped out were all in the placebo arm of the study, and all dropped out because of poor clinical response. Therefore, these patients who dropped out should have been included in the analysis as having failed treatment.

Including patients who dropped out or died as having failed treatment, and defining “response to treatment” as either partial or complete response, we recalculated the results of the study as follows: at week 3, 8 (84%) of 17 patients in the paromomycin arm had responded to treatment, and 5 (28%) of 18 patients in the placebo arm had responded ($P = .23$; χ^2 test); at week 6, 10 (59%) of 17 patients in the paromomycin arm had responded to treatment, and 8 (44%) of 18 patients in the placebo arm (who received placebo during the first 3-week period and paromomycin during the second 3-week period) had responded ($P = .40$; χ^2 test).

Thus, in this modified analysis, the difference in the response rates between the arms of the study approaches the difference anticipated in the trial design, with

a trend favoring paromomycin treatment over administration of placebo. However, the power of this study to achieve statistical significance was limited by the small sample size. On the basis of this difference between groups, a sample size of 108 subjects per study arm would be needed to have an 80% power of achieving significance with this level of difference (in contrast to the 17 and 18 subjects per study arm in this trial).

Although stool frequency is an important clinical end point, important confounding factors need to be considered. The poor correlation of parasitologic and clinical responses suggests that cryptosporidiosis was not always the cause of treatment failure. In previous short-term studies of patients with AIDS and cryptosporidiosis, we found high rates of coinfection with other opportunistic infections. Infections with mycobacteria, cytomegalovirus (CMV), or microsporidia were frequent causes of relapse, failure to respond to treatment, and/or death [2–4]. *Clostridium difficile* superinfection is also a concern. The high frequency of an elevated alkaline phosphatase level that was noted by Hewitt and colleagues [1] likely reflects either biliary tract involvement with *Cryptosporidium* species or coinfection with mycobacteria or CMV (in the biliary tract). Since paromomycin does not enter the biliary tract, patients with biliary disease may not be ideal candidates for assessing the drug’s efficacy.

These issues raise several questions. Were those patients who had either treatment failure or relapse or those who died examined for concomitant infection using biliary tract imaging, blood culture to detect mycobacteria, endoscopy for CMV infection, and stool studies? Did resolution in the patients in the placebo

arm of the study correlate with a higher CD4 cell count or with a short duration of illness? The drugs used for prophylaxis and treatment of mycobacteria have some activity against *Cryptosporidium* species [4, 5]. Were patients in the placebo arm treated with macrolides or rifabutin? We have noted significant changes in oocyst excretion (≤ 1 log reduction in the number of oocysts excreted) after changing a single nucleoside in a patient’s antiviral regimen. Was antiviral therapy modified for any of the patients? If so, did changes correlate with the response rate?

Given these concerns, we feel that the title of the article by Hewitt and colleagues [1] may be somewhat misleading. However, important conclusions can be drawn. First, the antiparasitic drugs that are currently available are, at best, modestly effective. Therefore, their efficacy will not likely be established by small placebo-controlled trials. As an alternative approach, treatment with combinations of drugs should be examined [4, 6]. A factorial design might allow for the evaluation of the efficacy of individual agents. Second, the disease and response rates are variable, and carefully controlled trials are needed to establish what regimens are effective. It is essential that these trials account for confounding variables, such as antiretroviral therapies and concomitant infections, by incorporating quantitative parasitologic end points into the trial design [4, 6].

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Clinical Infectious Diseases 2001;32:1516–7

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Reply

SIR—We thank Dr. White and colleagues for their interest in our article about paromomycin and the treatment of AIDS-related cryptosporidiosis [1]. We decided to present the as-treated analysis because, according to our interpretation of the data, there was no trend favoring treatment with paromomycin over administration of placebo. A *P* value of 0.23 from an intent-to-treat analysis represents an approximately 1 in 4 chance that a difference in efficacy does not actually exist. We did not consider this *P* value to be low enough to call it a trend.

The comments made by Dr. White and colleagues clearly point out the difficulty of conducting clinical research with enteric pathogens in immunocompromised hosts. Because coinfection with other

pathogens is likely when AIDS-related cryptosporidiosis is present, our exclusion criteria included *known* coinfection at the time of enrollment with any of the following organisms: active cytomegalovirus (CMV colitis), *Mycobacterium avium* complex, *Clostridium difficile*, and *Microsporidium*, *Giardia*, *Entamoeba*, *Isospora*, *Shigella*, *Salmonella*, *Yersina*, or *Campylobacter* species. Subsequent to enrollment, there were 3 patients in each arm of the study who had *Microsporidium* species detected in their stool. Evaluation of treatment failure encouraged investigation for coinfection but did not require it.

Biliary tract involvement is common in cases of cryptosporidiosis. Therefore, it would be quite difficult to exclude patients with biliary tract involvement in clinical trials of possible treatments. In addition, because biliary tract involvement is common, an agent deemed effective for AIDS-related cryptosporidiosis should be effective against all of the manifestations of the disease in the gastrointestinal tract.

Concurrent treatment with rifabutin, which might possibly prevent AIDS-related cryptosporidiosis, as has been recently shown [2], was allowed during the study, but treatment with macrolides was not allowed within 14 days of study entry or during the period when paromomycin was being administered. Changes to antiretroviral therapy were allowed but seldom occurred. In addition, CD4 cell count showed no discernible effect on the outcome of treatment, because entry criteria required a CD4 cell count of <150 cells/mm³. In fact, the median CD4 count was <30 cells/mm³ for both the paromomycin and the placebo groups.

In reviewing our experience with AIDS-related cryptosporidiosis, what we found most interesting is the wide clinical variability of the disease in HIV-infected persons. The ability of the disease to resolve or improve without intervention in patients who were given placebo was remarkable and, in a study with no placebo

control, could easily lead to the conclusion that a particular intervention did appear to be effective. We agree that there is still need for well-designed, placebo-controlled studies of any potential antimicrobial agent(s).

As Dr. White and colleagues imply, the best treatment for cryptosporidiosis in HIV-infected persons is highly active antiretroviral therapy [3]. Restoration of lost immune response has improved outcomes for a number of opportunistic infections, including cryptosporidiosis.

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Clinical Infectious Diseases 2001;32:1517

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Testing of Urinary *Escherichia coli* Isolates for Shiga Toxin Production

SIR—We read with interest the recent letter by Wilson et al. [1] on the prevalence of Shiga toxin-producing *Escherichia coli* (STEC) among isolates from urine samples. Wilson et al. concluded that routine screening of *E. coli* isolates from urine

samples for the production of Shiga toxins is not warranted. However, we believe that there are several reasons why this conclusion cannot be drawn from their study.

First, *E. coli* isolates that were present in urine samples were screened by Wilson et al. [1] for Shiga toxin production only if the isolates were sorbitol nonfermenting. The sorbitol-nonfermenting phenotype is specifically associated with the O157:H7 serotype of STEC; >50 other serotypes of STEC have been associated with disease in humans [2]. Therefore, use of this method as an initial screening tool will bias against isolation of non-O157:H7 STEC strains. The authors indicated that they used this method because most strains of STEC in the United States are of the O157:H7 serotype and thus are sorbitol nonfermenting. We disagree. Recent studies have revealed that a variety of STEC serotypes are associated with diarrheal disease in individuals in the United States [3, 4]. Estimates reported by the Centers for Disease Control and Prevention (Atlanta) in 1999 suggest that >100,000 cases of diarrhea caused by STEC occur in the United States each year; of these cases, one-third are of the non-O157:H7 serotype [5].

Furthermore, there is no reason to assume that hemolytic uremic syndrome (HUS) secondary to urinary tract infection (UTI) occurs exclusively after infection with STEC of the O157:H7 serotype. Although HUS appears to be a rare complication of UTI, there are published reports that link non-O157:H7 STEC with this phenomenon. Two recent case reports have described HUS in adults with UTI [6, 7]; both of the cases reported were due to non-O157:H7 STEC. In a recent literature review, 14 cases of HUS were reported to occur after STEC-associated UTI [8]. Only 6 of the 14 STEC isolates were serotyped; 5 of these 6 STEC isolates were of the non-O157:H7 serotype.

Although Wilson et al. [1] may be correct that routine screening of *E. coli* iso-

lates from urine samples for the production of Shiga toxins is unwarranted, this conclusion cannot be drawn from the results of their study. We do agree that HUS rarely occurs after UTI. It is possible that STEC-associated UTI is rare, or it may be that HUS rarely occurs after STEC-associated UTI. Unfortunately, the authors' study design did not permit evaluation of either of these possibilities. Until the true incidence of STEC-associated UTIs is known, it will be difficult to conclude how often HUS occurs after STEC-associated UTI and whether screening is warranted.

Recently, significant concerns have been raised that antibiotic treatment can increase expression of Shiga toxin by STEC [9] and that it can precipitate HUS in children with STEC-associated diarrhea [10]. One of the aforementioned case reports suggested that the use of a fluoroquinolone for the treatment of an elderly woman who had HUS and a case of UTI caused by nontypeable, Shiga toxin 2-producing *E. coli* may have worsened the patient's clinical status [6]. These data indicate that knowing whether an *E. coli* isolate from a urine sample is an STEC may be advantageous in certain situations.

Until we know the answers to some of the fundamental questions about the overall prevalence of STEC in *E. coli* isolates from urinary samples and about the links between HUS and STEC-associated UTI, it would be premature to conclude that it is unnecessary to screen *E. coli* isolates from urine sample for the production of Shiga toxins.

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Clinical Infectious Diseases 2001; 32:1517-8

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Treatment of Foodborne Listeriosis

SIR—In the third paragraph of the Treatment of Listeriosis section of Dr. Walter F. Schlech's recent article, "Foodborne Listeriosis," the author states, "Another regimen with precedence in the literature is the combination of trimethoprim-sulfamethoxazole (TMP-SMZ) and rifampin. A French study [36] has suggested that this regimen is superior to ampicillin and aminoglycoside therapy..." [1]. This

study by Merle-Melet et al. [2] does not mention the superiority of TMP-SMZ and rifampin for treatment of foodborne disease. Instead, it compares ampicillin-aminoglycoside with ampicillin-cotrimoxazole for the treatment of meningococcal meningitis and concludes that the latter regimen is superior. This combination is not even mentioned in Dr. Schlech's article.

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Clinical Infectious Diseases 2001;32:1518–9
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Reply

SIR—I thank Dr. Lapin for pointing out the error regarding the reference by Merle-Melet et al. [1] in my recent article “Foodborne Listeriosis” [2]. Indeed, the study by Merle-Melet et al. suggests that a combination of amoxicillin and trimethoprim-sulfamethoxazole (TMP-SMZ), *not* rifampin, may be preferable to ampicillin and aminoglycoside for the treatment of listeriosis.

The intracellular location of *Listeria monocytogenes* suggests that an antibiotic that has good intracellular activity, such as TMP-SMZ or rifampin, might eradicate this population of sequestered organisms. When used as a single agent, trimethoprim appears to have more activity than does sulfamethoxazole, but the combination of the 2 agents is highly active in vivo. Rifampin is also highly active in vitro and, although not synergistic, may be additive in its effect; therefore, a combination of rifampin and TMP-SMZ

would be worth consideration for the treatment of a patient who is allergic to penicillin. Although in vitro antagonism between ampicillin and rifampin has been demonstrated [3, 4], the combination is active in in vitro models of infection. An excellent review of antibiotic treatment of listeriosis recently has been published by Hof et al. [5].

A colleague has also pointed out an error in the title of table 1 in the same article. The title describes major “folklore” outbreaks of *L. monocytogenes* infections. Although these *foodborne* outbreaks have been the “stuff of legends” with regard to their elucidation, they are not mythical and have led to important observations about the epidemiology, clinical spectrum, and treatment of infection caused by this fascinating microorganism!

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Clinical Infectious Diseases 2001;32:1519
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Sir Thomas Sydenham Revisited

SIR—The thoughtful and carefully annotated essay “Skepticism: A Lost Clinical Art,” written by Dr. Mark J. DiNubile [1], provided a lucid perspective on the importance of prudent skepticism in clinical practice. The essay called to mind advice given by Thomas Sydenham (1624–1689) in his monograph “Medical Observations Concerning the History and Cure of Acute Diseases,” which was published in 1666 (translated by R. G. Latham [2]). Sydenham, a diligent and insightful observer of clinical issues, was the first true epidemiologist, although he realized only limited success in categorizing many diseases on the basis of the nature and the patterns of the fevers with which they were associated. Despite the frustrations that he experienced in his attempts to understand infectious diseases prior to the advent of the germ theory, his skepticism regarding the use of unproven treatment modalities are as applicable today as they were more than 330 years ago: “It is difficult to lay down any general rules for treating these fevers. Hence, in darkness so dense, I prefer nothing, upon the breaking out of a new fever, to a little delay; and I proceed especially towards greater remedies, with a slow foot and with circumspection.”

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Clinical Infectious Diseases 2001;32:1519
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Elimination of Efficacy by Additives in Zinc Acetate Lozenges for Common Colds

SIR—Upon reviewing the recently published report by Turner et al. [1] about the effects of zinc gluconate or zinc acetate lozenges on experimental and natural rhinovirus colds, I realized that I have some information that was inadvertently omitted and that is necessary to accurately discern the meaning of the report.

As a zinc ion availability (ZIA) consultant for Warner Lambert, I found that the 5 and 11.5 mg zinc lozenges whose formula was reported by Turner et al. [1] had theoretical ZIA values of 12 and 36, respectively. On the basis of ZIA analytical methods reported elsewhere [2], zinc acetate lozenges having these ZIA values (strengths) should have reduced the duration of colds by ~1 and ~2.7 days, respectively. However, hydrogenated palm kernel and cotton seed oils were also constituents of the lozenges, according to the list of ingredients provided with the commercial product (Halls Zinc Defense) marketed by Warner Lambert, which is also the supplier of the zinc acetate lozenge clinical prototypes studied by Turner et al. [1]. At the high temperatures (157°C) used in the manufacture of hard candy, these ingredients react with positively charged zinc ions (Zn^{2+} ions) derived from zinc acetate to yield zinc oleate, stearate, and palmitate waxes, which are incapable of releasing Zn^{2+} ions. Consequently, the ZIA value of the zinc acetate lozenges was 0, and no effect on colds could have been expected or resulted.

ZIA calculations involve, as variables, both the concentration of Zn^{2+} ions in saliva (calculated from the amount of zinc, the fraction of zinc ionizable at physiologic pH, and the total amount of saliva generated per lozenge dissolved) and duration of contact with oral mucosa (calculated from the dissolution time of lozenges and number of lozenges per

day), and they must take into account Fick's law of membrane permeability. Therefore, efficacy is not determined by the theoretical ZIA value but by the actual value, which takes into account the effect of additives. [2].

Attention to these omissions is critical if we wish to learn the effects of treating common colds with zinc lozenges, and if we wish to reconcile the negative report of Turner et al. [1] with the very positive reports of Petrus et al. [3] and Prasad et al. [4]. For example, Prasad et al. [4] showed that 50% of zinc acetate recipients were well in 3.8 days, compared with 7.7 days for 50% of placebo recipients. This duration data corresponds well with other generally accepted data [5].

In the report by Turner et al [1], the actual zinc compound exposed to the oral mucosa was not zinc acetate, but nonmiscible fat complexes of zinc. The zinc acetate lozenges were not described as producing a dry or astringent feeling in the mouth; in all cases where the ZIA value is sufficiently high to allow Zn^{2+} ions to shorten the duration and severity of common colds, there has been and there will be a dry or astringent feeling in the mouth. This dry feeling is identical to the "clean" mouth feeling produced by swishing water in the mouth for 30–60 s.

The cumulative effect of the above omissions teaches readers that zinc acetate lozenges in general do not have efficacy against common cold; however, properly made zinc acetate lozenges work very well in reducing the duration of common colds.

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Clinical Infectious Diseases 2001;32:1520–000

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