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Risk of the hemolytic-uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 infections

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### Authors

Aragon, Tomas J  
Fernyak, Susan E  
Reiter, Randy

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**Figure 1.** Lesions of the Skin (Panel A) and Mouth (Panel B) in a Patient with Post-Polycythemic Myeloid Metaplasia.

serious exacerbation of post-polycythemic myeloid metaplasia in a patient who was receiving epoetin may be uncommon, but it is striking and should be recognized as a potential sequela of such treatment.

ABDUL RAHMAN JAZIEH, M.D., M.P.H.  
University of Cincinnati  
Cincinnati, OH 45267

MOHAMMAD J. KYASA, M.D.  
University of Arkansas for Medical Sciences  
Little Rock, AR 72205

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### Risk of the Hemolytic–Uremic Syndrome after Antibiotic Treatment of *Escherichia coli* O157:H7 Infections

*To the Editor:* Wong et al. (June 29 issue)<sup>1</sup> report an association between antibiotic treatment in children with acute diarrhea caused by *Escherichia coli* O157:H7 and the development of the hemolytic–uremic syndrome. In Chile, shigella species cause 30 percent of cases of bloody diarrhea in children and enterohemorrhagic strains of *E. coli* cause 37 percent of such cases<sup>2</sup> — a situation that may also be common in developing countries. For children with acute bloody diarrhea in these countries, the most widely accepted recommendation is to obtain a stool culture and initiate empirical antibiotic treatment for shigella, because appropriate treatment shortens the duration of the diarrhea, decreases the incidence of complications, and reduces the risk of transmission by shortening the duration of bacterial shedding.<sup>3</sup>

Given these points, the results presented by Wong et al. raise several questions. Knowing that *E. coli* O157:H7 and shigella species cannot be differentiated early in the clinical course on the basis of clinical findings or simple laboratory tests, does the potentially increased risk of the hemolytic–uremic syndrome associated with empirical antibiotic treatment of *E. coli* O157:H7 infections outweigh the risk of not treating shigella infections during the 72 hours needed to obtain culture results? In Chile, 70 percent of cases of the hemolytic–uremic syndrome are associated with serotypes of *E. coli* other than O157:H7.<sup>4</sup> Can the increased risk of the hemolytic–uremic syndrome in children who receive antibiotics for *E. coli* O157:H7 infections be extrapolated to other strains of the organism?

We worry that the message of this study will be extended prematurely to the treatment of bloody diarrhea worldwide. In places where the prevalence of shigella and *E. coli* infections is similar and strains of *E. coli* other than O157:H7 are common, withholding antibiotic therapy until the cause of the diarrhea is known may have more risks than benefits.

MIGUEL O'RYAN, M.D.

VALERIA PRADO, M.D.

University of Chile  
Santiago, Chile

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*To the Editor:* We question some of the epidemiologic concepts and analyses used by Wong et al. They justified the

**TABLE 1.** NUMBER OF CHILDREN INFECTED WITH *ESCHERICHIA COLI* O157:H7 IN WHOM THE HEMOLYTIC-UREMIC SYNDROME DEVELOPED, ACCORDING TO WHETHER THEY WERE TREATED WITH ANTIBIOTICS.

CHARACTERISTIC	ANTIBIOTICS	NO ANTIBIOTICS
	no. of children	
Hemolytic-uremic syndrome	5	5
No hemolytic-uremic syndrome	4	57
Total	9	62

cohort study design because “the severity of illness might confound the association with antibiotic treatment.”

The severity of illness is not a potential confounder. To cause confounding bias, “a variable must be a risk factor for the disease among the nonexposed persons, must be associated with the exposure of interest in the population from which the cases derive, but must not be an intermediate in the causal pathway between the exposure and disease.”<sup>1</sup> The severity of illness is probably a marker for an intermediate factor in the causal pathway or an early symptom or sign of the hemolytic-uremic syndrome. Its association with antibiotic treatment could result in what has been called “susceptibility” bias<sup>2</sup> (thus requiring a stratified or multivariable analysis). However, antibiotic treatment was not associated with any indicator of severity, and therefore, this source of bias was unlikely. The results in Table 3 of the article confirmed this point: the univariate odds ratio of 14.3 does not meaningfully differ from the adjusted odds ratio of 17.3. The analysis can actually be reduced to a two-by-two table, which provides a more accurate and precise measure of risk (Table 1).

The risk of the hemolytic-uremic syndrome among the children who were given antibiotics was 56 percent (5 of 9 children), and the risk among the children who were not treated with antibiotics was 8 percent (5 of 62 children). The relative risk was 6.9 (95 percent confidence interval, 2.5 to 19.2). In cohort studies, one can directly calculate the relative risk.<sup>3,4</sup> Instead, Wong et al. used the odds ratio to approximate the relative risk. Direct estimation is preferable, and when the incidence is high, as it was in this study, the odds ratio overestimates the relative risk.

TOMÁS ARAGÓN, M.D., DR.P.H.  
SUSAN FERNYAK, M.D., M.P.H.  
RANDY REITER, PH.D., M.P.H.

San Francisco Department of Public Health  
San Francisco, CA 94102

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The authors reply:

*To the Editor:* O’Ryan and Prado are correct; we cannot directly extrapolate our findings to infections with Shiga-toxin-producing strains of *E. coli* other than O157:H7. However, the same cautious approach should apply, especially since antibiotics cause the release of Shiga toxin from non-O157:H7 strains of the organism.<sup>1,2</sup> We also realize that *E. coli* and shigella can infect the same people and can have similar clinical manifestations.<sup>3</sup> However, with the probable exception of infections with *Shigella dysenteriae* serotype 1 (which are rare in this country), we believe that the potential harm from antibiotic treatment of an infection with a Shiga-toxin-producing strain of *E. coli* exceeds the harm from delaying treatment of shigellosis until the culture results are available.

We agree with Aragón et al. that the relative risk can be directly calculated from our data. However, we were concerned that the simple comparison of the group of patients who received antibiotics with the group of patients who did not receive antibiotics might have been compromised by differences in the severity of illness between the two groups — an effect that is often termed “confounding by indication.”<sup>4</sup>

Because we considered a priori markers of the severity of illness as potential confounders, adjustments for these factors were important despite the lack of statistical significance.<sup>5</sup> Although the association between the initial white-cell count and the use of antibiotics was not significant, physicians often use leukocytosis to justify the use of antibiotic therapy. Furthermore, the initial white-cell counts in our study were usually obtained before antibiotic therapy was given, making it unlikely that this marker of the severity of illness was an intermediate factor in the causal pathway of the hemolytic-uremic syndrome. Therefore, to address the question of interest, we found it necessary to adjust for the severity of illness in a multivariate logistic-regression analysis; the adjusted odds ratio can readily be estimated on the basis of this analysis.

Our data further support the inference of a causal relation between antibiotic therapy and the subsequent development of the hemolytic-uremic syndrome. The temporal sequence of events was appropriate; antibiotic therapy preceded the development of the hemolytic-uremic syndrome. To emphasize the prospective cohort design of our study, we thought it was appropriate to report our findings as estimates of the relative risk using the odds ratios. We acknowledge the limitations of the odds ratio to estimate the magnitude of the relative risk. However, for the purposes of our study, the analytic paradigm was sufficiently justifiable to answer the question of whether or not antibiotic therapy was associated with the development of the hemolytic-uremic syndrome after adjustment for the severity of illness.

CRAIG S. WONG, M.D., M.P.H.  
SANDRA L. WATKINS, M.D.  
PHILLIP I. TARR, M.D.

Children’s Hospital and Regional Medical Center  
Seattle, WA 98105

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### Transfusion of Soluble Hemoglobin

*To the Editor:* In their encouraging report of the use of a bovine hemoglobin solution, HBOC-201, to sustain life when red-cell transfusion was impossible, Mullon et al. (June 1 issue)<sup>1</sup> discuss the possible role of HBOC-201 in promoting an episode of severe gram-negative sepsis. We wish to suggest a mechanism by which cell-free hemoglobin may increase the pathophysiologic effects of sepsis.

Gram-negative bacteria can shed outer-wall material containing lipopolysaccharide (bacterial endotoxin) into the bloodstream. Lipopolysaccharide causes much of the toxicity associated with gram-negative bacterial sepsis and produces a state of clinical sepsis indistinguishable from that produced by live bacteria. We<sup>2</sup> and Krishnamurti et al.<sup>3</sup> have demonstrated that infusion of cell-free hemoglobin can increase the rate of lipopolysaccharide-induced death in animals. (Current preparations of cell-free hemoglobin are, in themselves, extremely safe in the absence of lipopolysaccharide.) Furthermore, infusion of hemoglobin can augment the lipopolysaccharide-induced secretion of tumor necrosis factor,<sup>4</sup> a cytokine believed to have a central role in the sepsis syndrome.

In the patient described by Mullon et al., the presence of circulating HBOC-201 during the episode of sepsis may have exacerbated the clinical response to endotoxemia, independently of a possible stimulatory effect on bacterial proliferation. This is an important distinction because life-threatening endotoxemia can occur in the absence of bacteremia (i.e., clinical sepsis may be accompanied by sterile blood cultures). Furthermore, sepsis with endotoxemia is likely to be present in many patients who would be candidates for a hemoglobin-based oxygen carrier, such as patients who are in shock or who have had serious trauma. Therefore, it is important that future evaluations of hemoglobin-based oxygen carriers include recognition of the presence of sepsis and its correlation with outcome.

ROBERT I. ROTH, M.D., PH.D.

Weinberg Group  
San Francisco, CA 94105

JACK LEVIN, M.D.

University of California, San Francisco, School of Medicine  
San Francisco, CA 94143

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The authors reply:

*To the Editor:* Roth and Levin make excellent points regarding the possible role of free hemoglobin in augmenting the cytokine response to sepsis or endotoxin infusion. They postulate that the transfusion of hemoglobin may have worsened the clinical course of our patient in this way. Although this is certainly a possibility, there is no practical way to separate the effects of the transfused bovine hemoglobin from those of preexisting hemolysis in this patient, since hemolysis itself induces the release of cytokines such as tumor necrosis factor, interleukin-1, interleukin-6, and interleukin-8.<sup>1</sup>

We believe that acute hemolytic anemia and neutropenia caused by chemotherapy are sufficient to account for our patient's clinical course; the role of transfused hemoglobin in the immune response is purely speculative at this time. We agree that the effect, if any, of transfused hemoglobins on the clinical course of human sepsis is worthy of further investigation.

JOHN MULLON, M.D.

1st Special Forces Group  
Fort Lewis, WA 98431

GEORGE GIACOPPE, M.D.

Madigan Army Medical Center  
Fort Lewis, WA 98431

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### The Disappearing Arsenal of Antiparasitic Drugs

*To the Editor:* Parasitic infections remain scourges to people worldwide.<sup>1</sup> Increasing international travel and immigration from countries where parasitic infections are endemic ensure that clinicians in the United States will be required to treat patients with these infections. Although safe and inexpensive treatments are available for most of these infections,<sup>2</sup> there are few incentives for the pharmaceutical industry to make these drugs available in the United States.

In the past 10 years, several drugs — quinacrine, the most effective medication for giardia infection; niclosamide, the main treatment for tapeworm infection; and diethylcarbamazine, the best treatment for lymphatic filariasis — have been withdrawn from the U.S. market. Diloxanide, perhaps the best drug to eradicate gastrointestinal passage of amebic cysts, was formerly distributed by the Centers for Disease Control and Prevention (CDC), but it too is no longer commercially available. Intravenous quinine, the standard treatment for severe malaria in most of the world, was distributed by the CDC until 1991. At that time, quinidine was recommended for the intravenous treatment of severe malaria, because of its widespread availability as a treatment for arrhythmias.<sup>3</sup> However, safer and more effective antiarrhythmic drugs have since become available, and quinidine is now no longer routinely available. Furthermore, halofantrine, an important treatment for chloroquine-resistant malaria, was approved by the Food and Drug Administration but was never marketed in the United States. Most recently, in June 2000, praziquantel was withdrawn from the U.S. market.