Correspondence

**Trimethoprim-Sulfamethoxazole as Toxoplasmosis Prophylaxis for Heart Transplant Recipients**

Sir—Toxoplasmosis is a disease that is highly transmissible to D+/R- patients (i.e., patients who are seronegative for *Toxoplasma gondii* IgG antibodies and who receive a heart transplant from donors who are seropositive for *T. gondii* IgG antibodies). This disease, along with disseminated aspergillosis, is associated with the highest mortality rate attributable to an infectious complication in heart transplant recipients. For these high-risk patients, 25 mg of pyrimethamine is given as toxoplasmosis prophylaxis for 6 weeks after surgery [1–3].

We read with interest the article on heart transplantation by Montoya et al. [1]. In their extensive review of the experience with heart transplantation patients at Stanford Medical Center (Stanford, CA), there was not enough data to experience with heart transplantation patients at Stanford Medical Center (Stanford, CA), there was not enough data to assess whether administration of trimethoprim-sulfamethoxazole (TMP-SMZ) for prophylaxis against *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) is sufficient to prevent toxoplasmosis in D+/R- patients. The authors concluded that, until more data are available, it seems prudent to recommend a 6-week course of pyrimethamine for these patients [1]. The problem is that pyrimethamine does not provide effective prophylaxis against *P. jiroveci*, so both drugs should be used simultaneously [4].

In 1994, reported experience with HIV-infected patients showed that TMP-SMZ might be useful as toxoplasmosis prophylaxis for heart transplant recipients [5]. On the basis of this experience, we decided to begin a trial of TMP-SMZ (a single double-strength tablet given 3 times each week) as prophylaxis against toxoplasmosis and *P. jiroveci*. Before the start date of the trial, we had followed standard recommendations and had used pyrimethamine for toxoplasmosis prophylaxis and TMP-SMZ for *Pneumocystis pneumonia* prophylaxis.

Since 1988, a total of 315 patients have undergone heart transplantation at Hospital General Universitario Gregorio Marañón (Madrid, Spain); of these patients, 32 (10.2%) were considered to be D+/R- patients with regard to *Toxoplasma* IgG antibody serostatus. Twelve of the patients received pyrimethamine, 17 received TMP-SMZ, and 3 did not receive any prophylaxis.

Two cases of toxoplasmosis occurred among all our heart transplant recipients; one case occurred in 1990 and was associated with pulmonary involvement, and the other case occurred in 1991 and was associated with meningitis, chorioretinitis, and myocardial involvement (the latter of which was proven by biopsy). None of the patients had been receiving any kind of prophylaxis. The first case of toxoplasmosis developed only 5 days after transplantation and before prophylaxis was started. Prophylaxis was not administered for the second case because the patient had severely impaired liver function. The 2 affected patients were treated with pyrimethamine and sulfadiazine with satisfactory outcome. The third D+/R- patient, who did not receive prophylaxis, died of non-infectious causes soon after surgery.

Seroconversion occurred in only 1 patient who received pyrimethamine but was not associated with clinically evident disease. Neither seroconversion nor toxoplasmosis occurred in any patient who was receiving TMP-SMZ.

Very little data are available on the use of TMP-SMZ as toxoplasmosis prophylaxis for solid-organ transplant recipients. Nevertheless, in one trial [6], 126 consecutively seen cardiac transplant recipients were given this drug for either 6 months ($n = 48$) or 12 months ($n = 78$); no patient who received TMP-SMZ for either 6 months or 12 months developed either toxoplasmosis or *Pneumocystis pneumonia* while receiving this prophylaxis. In 1 patient, toxoplasmosis occurred 77 days after cessation of a 6-month course of prophylaxis. The 126 patients receiving TMP-SMZ were compared with a group of 143 patients who were not receiving prophylaxis, 6 of whom developed clinically evident toxoplasmosis ($P = .05$). It is unfortunate that no serological analyses were performed.

There also are some observational data for liver transplant recipients that allow us to infer the effectiveness of TMP-SMZ in the prevention of toxoplasmosis as well as *P. jiroveci* infection, which was the initial indication for its use [7]. Our data support the safety and effectiveness of the use of a single tablet of TMP-SMZ (double-strength) given 3 times each week for the prevention of toxoplasmosis in D+/R- heart transplant recipients.

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**References**

Reply

Sir—We thank Muñoz et al. [1] for their correspondence regarding our article on infectious complications among heart transplant patients at Stanford University Medical Center (Stanford, CA) [2]. Dr. Muñoz and colleagues acknowledge that there are few published data to support the use of trimethoprim-sulfamethoxazole (TMP-SMZ) alone for the prevention of toxoplasmosis in heart transplant recipients. However, their data, along with findings on the use of TMP-SMZ for prophylaxis and treatment of toxoplasmosis in HIV-positive patients, are compelling.

We agree that the use of TMP-SMZ alone may be sufficient to prevent toxoplasmosis in patients who are seronegative for Toxoplasma gondii IgG antibodies and who receive a heart transplant from donors seropositive for T. gondii IgG antibodies (i.e., D+/R− patients). The optimal schedule of administration of TMP-SMZ to this group of patients is less clear and requires further study. Until these studies are performed, physicians must decide whether a schedule of daily administration or administration 3 times a week is to be used. For HIV-infected patients, we routinely recommend daily use of TMP-SMZ whenever feasible [3].

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References


Putting Salmonella Contamination in Perspective

Sir—The complexity of the food chain and the emergence of the “farm-to-fork” model of the animal feed/food-animal production cycle (and the model’s implied concomitant preventive controls) will remain formidable challenges for all who are objectively committed to minimizing and preventing hazards that cause foodborne illnesses. In support of their own study, Crump et al. [1] reintroduced a hypothesis that first surfaced ~30 years ago [2]. Clark et al. [2] described an outbreak of 17 cases of Salmonella enterica serotype Agona infection among persons in Paragould, Arkansas. This outbreak was traced to the consumption of poultry that had been reared on a Mississippi poultry farm. Epidemiological analysis indicated that the farm used fish meal imported from Peru as a protein supplement in the feed ration and that the fish meal had been contaminated with S. enterica serotype Agona. The convoluted farm-to-fork model has since been used as a basis for the early determination that bacterial contamination of animal feed could have an important causal relationship to foodborne illness in humans.

The study of Clark et al. [2] was amplified during Crump et al.’s [1] examination of the potential for feed and, especially, the animal protein component of feed to contribute to the bacterial colonization and infection of food-producing animals. Crump and colleagues suggested that such colonization and contamination could subsequently “contaminate animal carcasses at slaughter or cross-contaminate other food items, leading to human illness” [1, p. 859]. However, the study of Clark et al. [1] lacked many of the elements pointing to a finite causal association. Therefore, the concepts of “sufficient cause” and “component cause” require elucidation.

A cause of a disease event is an occurrence, condition, or characteristic that preceded the disease event, and that, without which, the disease outbreak would not have occurred. Component causes can be based on either strong or weak evidence. However, the causal inference proposed by Clark et al. [2], in which animal feed was linked to foodborne illness in humans, was based on little more than the mere co-occurrence of events and was an example of the logical fallacy of post hoc ergo propter hoc (i.e., “after this, therefore, on account of this”). Unfortunately, the report by Clark et al. [2] has been used to exacerbate the concerns of regulatory authorities regarding the implication of rendered animal protein feed as a possible source of foodborne disease in humans. However, the evidence was never more than anecdotal, because, in the “stellar” case reported by Clark et al. [2],