Mosquito bites were observed on 18 patients (14.8%), 7 of whom had ≥5 bite marks. Using a multivariate logistic regression model adjusted for age, sex, CD4 count, HIV load, and HIV-transmission group, we identified an independent association between lipoatrophy and (1) a history of having been bitten by mosquitoes in the 3 months before the study (OR, 2.44; 95% CI, 1.06–5.59) and (2) the presence of mosquito bites at the time of physical examination (OR, 10.13; 95% CI, 2.65–38.73). No specific type of ART was found to be associated with mosquito bites.

Lipoatrophy has been increasingly described among individuals who receive nucleoside reverse-transcriptase inhibitors [1]. Lipoatrophic subcutaneous tissue may present a more accessible capillary network and an increased release of volatile substances from the skin surface. A similar mechanism, triggered by increased blood flow, has been suggested as an explanation for the attraction of mosquitoes to the skin of pregnant women [2, 3]. Whether the observed increase in mosquito bites may result in greater risk for insectborne infections, such as those caused by Leishmania and Plasmodium species, can only be speculated. The association of lipoatrophy with an increase in mosquito bites has no bearing on HIV transmission, because insect vectors play no role in the spread of HIV [4].

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Recurrent Nonmenstrual Toxic Shock

Str.—Andrews et al. [1] recently published a review entitled “Recurrent Nonmenstrual Toxic Shock Syndrome: Clinical Manifestations, Diagnosis and Treatment.” As their title suggests, although recurrent menstrual toxic shock is not uncommon, few reports of this syndrome have been published. The authors review 9 previous cases and report 3 of their own, including 1 in a patient with AIDS.

In 1992 we described 5 patients with a recalcitrant, erythematous desquamative disorder associated with toxin shock toxin-1 (3 patients), staphylococcal enterotoxin A (1 patient) and staphylococcal enterotoxin B (1 patient) [2]. Three of the 5 patients died; autopsies of 2 patients confirmed residual staphylococcal infection, and, interestingly, both survivors developed recurrent disease. All patients were homosexual men. One of the patients significantly improved after receiving commercial iv gammaglobulin, which contains staphylococcal toxin antibody [3]. Indeed, the HIV-1–infected patient treated by Andrews et al. [1] also responded favorably to iv gammaglobulin.

We suggested that the recalcitrant, erythematous desquamative disorder was related to defective chemotaxis [4], but observed that a lack of staphylococcal toxin antibody formation could also play a role. Therefore, the disorder—the characteristics of which have subsequently been confirmed [5, 6]—may have an immunologic relationship to recurrent nonmenstrual toxic shock syndrome in patients infected with HIV-1; patients with these disorders likely lack staphylococcal toxin antibody production. The absence of toxin antibody may be due to the “superantigen” molecular behavior of staphylococcal toxins.

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Antifungal Prophylaxis and the Rate of Bacteremia among Neutropenic Patients

Str.—We recently published an article in Clinical Infectious Diseases that explored the possible association between antifungal prophylaxis and the rate of documented bacteremia among febrile neutropenic patients with cancer [1]. This
Some studies have suggested the existence of a relative increase in the rate of bacteremia documented as the cause of primary fevers among neutropenic patients with cancer who are receiving antifungal prophylaxis (not empiric therapy, as apparently misinterpreted by Wenzel et al. [2]). For this reason, we decided to undertake a study of a large patient population (>3000 patients) to explore the possible association between the rate of documentation of primary bacteremia (not breakthrough bacteremia, as misinterpreted by Wenzel et al. [2]) and the administration of antifungal prophylaxis before the onset of fever. We studied patients who had had a febrile neutropenic episode and who were randomly allocated to receive empiric antibacterial treatment (not a prophylactic antibiotic regimen, as mentioned several times by Wenzel et al. [2]).

Before fever develops, neutropenic patients may or may not receive antifungal or antibacterial prophylaxis, depending mainly on the type of underlying disease and the expected duration of neutropenia [6]. When fever develops during neutropenia, patients receive empiric antibacterial therapy. Finally, persistently febrile and neutropenic patients who do not respond to initial empiric antibacterial therapy may receive empiric antifungal therapy, on the basis of the assumption that they might harbor an occult fungal infection that is the cause of their fever. This therapeutic strategy is usually called “empiric,” not “preemptive,” antifungal therapy, because it is not based on any formal clinical prediction rule or laboratory method that is able to identify patients in whom a fungal infection is likely to develop or is already incubating [7, 8].

Some studies have suggested the existence of a relative increase in the rate of bacteremia documented as the cause of primary fevers among neutropenic patients, because it is not based on any clinical prediction rule or laboratory method that is able to identify patients who might have evolved differently over time. We studied patients who had had a febrile neutropenic episode and who were randomly allocated to receive empiric antibacterial treatment (not a prophylactic antibiotic regimen, as mentioned several times by Wenzel et al. [2]). We tried to assess, at the time the patients presented with fever, which variable was associated with a diagnosis of documented bacteremia. The status of antifungal prophylaxis was one of the variables we took into account, because some of these patients were receiving antifungal agents and others were not. Our results confirmed that antifungal prophylaxis—at least with absorbable agents—is independently associated with the outcome of documented bacteremia.

Although we adjusted for other covariates that have a significant predictive value on the outcome (i.e., documentation of bacteremia), our retrospective study was essentially exploratory. As clearly stated in our article [1], we are well aware that our results are not based on a randomized comparison and cannot provide a definitive answer to the question. Of course, we agree with Wenzel and colleagues that we have not established a causal relationship. Actually, we never drew that conclusion. As Wenzel and colleagues point out, there might have been biases due to the nonrandomized design of our study [2]. For instance, patient profiles, as well as the strategy for giving a patient antifungal prophylaxis, might have evolved differently over time. This was discussed at length in our paper. However, the time frame in which the study was conducted was included as a covariate, but was not identified as a prognostic factor for the outcome. Furthermore, patient eligibility criteria were quite similar for the 4 trials.

Although we adjusted our analysis for several covariates, confounding might have occurred. It should be pointed out that we did not have to stratify our analysis for the randomly allocated empiric antibiotic treatment. Indeed, in no way can this regimen be considered a confounding variable, because the blood samples used to document the infection were obtained before empiric treatment was started; moreover, there is no possible link between antifungal prophylaxis and the empiric antibiotic treatment, because the allocation to receive empiric antibacterial treatment was made by means of a randomization mechanism. Clearly, there seems to be some general misunderstanding by Wenzel et al. [2] about the clinical setting in which the study was performed and about methods and definitions.

Admittedly, the magnitude of the impact of absorbable agents (OR, 1.49) is not particularly impressive from a clinical point of view, and the attributable risk discussed in the commentary is quite small. Once again, however, let us remember that the purpose of our analysis was purely exploratory.

There are points in the commentary of Wenzel et al. [2] that are difficult to understand. For example, they speak about “elements of cause and effect”; however, as we have said, we never claimed the existence of a causal relationship, and the effect of antifungal prophylaxis might simply be a marker for confounders not recorded in our data base.

In conclusion, we are grateful to Wenzel and colleagues for giving us the chance to briefly review some clinical issues in the field of febrile neutropenia. Indeed, it is likely that some of their comments simply stem from a lack of familiarity with the clinical setting of the study.
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Origins of Tuberculosis in North America

Sir—Rothschild and colleagues deserve congratulations for their elegant study of tuberculosis in a 17,000-year-old North American bison [1]. They are especially to be commended for the care they took to prevent contamination of their paleologic DNA samples. Their work is consistent with the hypothesis of Sreevatsan et al. [2] concerning the origins of modern species of mycobacteria, and it suggests that a prehistoric precursor of Mycobacterium tuberculosis was globally distributed.

A remaining issue of interest is which species of mycobacteria infected humans in the pre-Columbian Americas [3, 4]. Because the Bering Strait became open water >9000 years ago, one must suppose that the early mycobacterial species that caused human disease in the Western Hemisphere were established and geographically isolated by that time. It could have been either Mycobacterium bovis or M. tuberculosis; I have argued that it was most likely the latter [4]. It is unlikely to have been the organism present in the prehistoric bison, because that organism did not persist in the Americas.

One may speculate concerning where and when modern mycobacterial species evolved from early precursors, such as the organism that infected the prehistoric bison. However, it is not reasonable to assume that a modern species evolved from this precursor separately in the Western and Eastern hemispheres.

One may hope that future investigators who isolate DNA from specimens of paleologic human remains in the Americas will use the spoligotyping method used by Rothschild et al. [1] and will exercise similar care to prevent contamination of their samples. Only thus will the etiology of pre-Columbian tuberculosis in the Americas be established.

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