Correspondence

Garlic Supplements and Saquinavir

SIR—In their recent article, Piscitelli et al. [1] advise that "patients receiving saquinavir as their sole protease inhibitor should avoid using garlic supplements" [1, p. 238]. In their study, healthy volunteers who received the antiretroviral drug saquinavir and a garlic supplement exhibited a significant decline in plasma levels of saquinavir. As one reason for the decline in systemic levels of saquinavir, the authors suggest that the effect "may be caused by the induction of CYP450 [cytochrome P450] in the gut mucosa" by garlic supplements [1, p. 237].

This warning against taking garlic supplements, stated in the article and publicized in the media, is based on results with a single supplement, GarliPure Maximum Allicin Formula (Natrol), that is standardized with allicin, an unstable compound that is known to convert to polysulfides that induce the production of cytochrome P450. The study and its conclusions do not address the availability of garlic supplements that are not standardized with allicin. For example, Kyolic Aged Garlic Extract (Wakunaga), which is standardized by water soluble S-allyl cysteine, is devoid of allicin and does not induce the production of cytochrome P450.

Thus, a limited conclusion by Piscitelli and colleagues would have been more prudent—namely, that patients receiving saquinavir as their sole protease inhibitor should avoid taking the allicin-standardized garlic supplement they studied. Although additional clinical research is needed, use of a supplement that is not standardized with allicin, such as Kyolic Aged Garlic Extract, may be a safe option for people being treated with saquinavir.

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Reply

SIR—We agree with Dr. Borek [1] that, despite having data only on the interaction between a single garlic preparation and saquinavir, we drew a generalized conclusion regarding the need for patients to use caution if they combine garlic supplements with saquinavir when using that drug as the sole protease inhibitor [2]. Because we have no information to suggest which constituent (or excipient) in the garlic formulation is responsible for the drug interaction, we cannot speculate about the effects of other commercial products or dietary garlic on the pharmacokinetics of saquinavir or relate our findings to allicin concentrations. We provided data on the allicin (and allin) content of the supplement we studied solely because we considered the verification of product content to be important. Since publication of our article, we have had a study brought to our attention in which garlic supplements were tested for drug release in simulated gastrointestinal conditions: most supplements released far less allicin in such conditions than they did when crushed and suspended in water [3]. Thus, the supplement we used may well release little allicin in vivo. Given the risks associated with reduced antiretroviral concentrations, we consider our conservative interpretation to be appropriate for use in advising patients [4, 5].

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Prevention of Nosocomial Fungal Infection: The French Approach

SIR—We recently read with interest 3 articles in *Clinical Infectious Diseases* about

the environmental risk of invasive aspergillosis (IA) for immunocompromised patients [1–3]. IA is a major cause of death among neutropenic patients and patients who have undergone solid-organ transplantation. In the first article, Graybill [1] emphasized that prevention of IA should include both antifungal prophylaxis and the separation of patients from environmental sources of infection. With regard to potential environmental sources of *Aspergillus* conidia, Anaissie and Costa [2] suggested that nosocomial aspergillosis could be caused by airborne conidia that have a water source. Finally, Hajjeh and Warnock [3] emphasized the need for use of appropriate air-quality precautions during hospitalization but questioned their cost-effectiveness. They considered the fact that most cases of IA occurred outside of the hospital and that chemoprophylaxis, therefore, could be an interesting alternative to air-quality precautions. We would like to comment on several points raised by these authors.

The 3 articles discussed the risk of inhalation of conidia from environmental sources. In particular, the authors suggested that only a small proportion of cases of IA are acquired in the hospital, and they postulated that water is a major source of fungal infection. The authors also argued that environmental sampling is often performed only after new cases occur, and that data from phenotypic and/or genotypic comparisons between clinical and environmental isolates are difficult to interpret.

Two French study groups (The Mycologic Study Group of the French Society of Hematology and The Research Group on Fungal Infections [GRIF]) and 1 European study group (The European Group for Research on Biotypes and Genotypes of *Aspergillus* [EGBA] Network) have been conducting research on the environmental risk of IA and have developed preventive strategies. The salient points of these strategies are as follows:

1. Air-control measures remain crucial for the reduction of environmental dissemination of fungal conidia. We believe that the nosocomial origin of aspergillosis has been convincingly demonstrated in epidemic situations [4–6]. Moreover, Alberti et al. [7] recently showed that the concentration of *Aspergillus* species and other fungi in the air in a hematology unit correlated with the incidence of IA in nonepidemic situations. Thus, we strongly recommend that patients who are at high risk of infection benefit from the measures put forth by the Centers for Disease Control and Prevention [8]—that is, the use of high-efficiency particulate air (HEPA) filtration, use of laminar air flow (LAF) systems, high rates of room-air change, use of positive pressure, and use of well-sealed rooms [9–12].

2. Air-control efficiency must be monitored. Several years ago, we started regular monitoring of environmental fungal contamination (for *Aspergillus* and other airborne fungal species) with 2 major goals: to detect increases in conidia density and to assess air-control efficiency. From our point of view, environmental monitoring requires the following: (1) air sampling with an efficient biocollector [13]; (2) surface sampling with contact Petri dishes or swabs, which is a simple and efficient monitoring method that can detect minor contamination, even when concomitant air samples test negative for fungi [14]; (3) sampling of patient rooms that are equipped with HEPA filters, with or without LAF, and sampling of all parts of the ward that are provided with air filtration and positive pressure (particularly corridors); and (4) use of guidelines for patient management and cleaning procedures in protective environments, which should be adapted according to the results of monitoring [15, 16].

Determination of the baseline values of air and surface concentrations of *Aspergillus* species and other fungal conidia in our units is essential for valuable assessment of any further increase in fungal contamination. Given the genetic diversity of *Aspergillus fumigatus* isolates, and given the current limitations of molecular typing methods to localize the fungal source or to date the infection, environmental sampling is not, in our view, simply a means of comparing environmental isolates with clinical isolates [17–20].

3. The sources and routes of conidia transmission are unclear. Anaissie and Costa [2] suggested that aspergillosis is waterborne, and they postulated that nosocomial aspergillosis can be airborne from water sources in the hospital setting. However, our recent experience with sampling of water in French hospitals differs markedly from that reported in the literature [21–23]. Water was sampled from the taps in patients' rooms during a 1-year prospective study (750 water samples were obtained from 5 teaching hospitals), and *Aspergillus* species were recovered from <1% of samples, compared with 21% of water samples obtained by Anaissie et al. [23]. These differences may be related to the means of water collection and treatment. In a recent study from The Netherlands, Warris et al. [24] found that all 20 water samples that they had obtained were negative for *A. fumigatus,* and they confirmed that the nature of the water source had a significant impact on mold recovery from water. Thus, the environmental risk of IA linked to water should be interpreted according to the local situation—namely, the source of water (underground vs. surface water). In addition, because humidity favors fungal growth, high fungal densities near water sources may simply reflect the presence of conidia in the air or on surfaces and indicate the need for new cleaning procedures. Furthermore, the biotope of *A. fumigatus* differs from that of *Fusarium* and *Acremonium* species.

Alternative sources of conidia inhalation should not be neglected. These sources include the clothing of visitors and medical staff as well as personal and medical materials. Therefore, specific preventive measures may be appropriate. The

gastrointestinal route of infection is rarely considered; however, we have recently observed a high rate of food contamination by filamentous fungi, such as *Aspergillus* species and Zygomycetes [25], and we are currently assessing disinfection procedures [26]. The existence of isolated gastrointestinal filamentous fungal infection without pulmonary or disseminated infection supports the hypothesis that, in addition to the risk of conidia inhalation, contact with food or water can lead to conidia absorption.

Aspergillosis mainly occurs in neutropenic patients. Air-control measures are presently the most effective way of significantly reducing the incidence of nosocomial aspergillosis. Although they are expensive and only partially effective, these measures should not be called into question, as shown by their protective effect against early infections after bone marrow transplantation [27, 28]. However, the efficiency of air-control measures should be continuously monitored by regular measurement of environmental levels of fungal conidia. This approach is strongly recommended in French hospital units that use air-control measures, as are specific investigations of cases of *Aspergillus* infection [15]. However, there should be more investigation and control of alternative sources of contamination. Prevention of delayed acquired aspergillosis is even more difficult: control of environmental sources of contamination and follow-up of *Aspergillus* colonization are difficult outside of the hospital setting, and, until now, there has been no demonstration that any antifungal drug or cytokine can significantly prevent or reduce the risk of aspergillosis in patients who are at risk of infection.

Acknowledgment

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Reply

Sir—Gangneux et al. [1] agree with us that alternative hospital sources of *Aspergillus* conidia should be investigated and that air-quality precautions need to be strictly implemented to prevent airborne nosocomial aspergillosis.

We agree with the sampling sites recommended by Gangneux et al. [1], but we emphasize the importance of sampling water-related areas and structures, such as sinks and showers. We also agree that variation in ecological niches may account for potential differences among institutions with regard to the rate and type of fungal colonization in water. These differences could also be explained by other factors, such as the methods of collection and the timing of sampling (e.g., sampling the first liter of water from a source vs. sampling subsequent liters) [2]. As stated by Gangneux and colleagues, humidity may indeed favor fungal growth in water-related structures, such as bathrooms. As we have recently shown, cleaning the surfaces of such structures may decrease the risk of aerosolization of fungal conidia [3].

Gangneux et al. [1] also mention that we consider hospital water to be a major source of infection, a statement that we did not make. In the original article [4], we were asked to make the case for our hypothesis that hospital water was a potential source of *Aspergillus* conidia. We did so; however, we reiterated that this hypothesis needs to be considered in hospitals in which cases of nosocomial aspergillosis continue to occur despite the strict implementation of air-quality precautions. Gangneux and colleagues mention a study [5] that showed a correlation between airborne mold concentration and the incidence of invasive aspergillosis, which does not conflict with our hypothesis about waterborne mold. As discussed in our editorial, fungal conidia could have been "secondarily airborne" from a water source.

We thank Gangneux et al. [1] for raising these important questions, and we reiterate the need for continued implementation of air-quality precautions in high-risk hospital wards and for additional studies to determine the exact contribution of alternative sources (i.e., water and other sources) to nosocomial and community-acquired aspergillosis.

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Clinical Infectious Diseases 2002; 35:346

Role of Non-O157:H7 *Escherichia coli* in Hemolytic Uremic Syndrome

Sir—We read with interest the article by Dundas et al. [1] but were surprised that the authors neglected to look for other, non-O157:H7 verocytotoxigenic *Escherichia coli* (VTEC) or to test serum samples from the patients for antibodies to these microorganisms. We have shown, in our serological studies of serum samples collected during an outbreak of hemolytic uremic syndrome, that "multiple strain infection may be the rule rather than the exception" [2]. We have further shown that such multiple infections, involving a variety of VTEC, contributed significantly to the outbreak and that the greater the variety of infecting VTEC, the greater the possibility that clinical complications will occur [3]. In addition, Dundas et al. [1] report that culture of fecal samples for VTEC O157 yielded positive results in only 81% of cases, which strongly suggests that other VTEC serotypes were involved as well. Cases in which fecal cultures did not yield VTEC O157 (19% of the total) were included in the data analysis as "probable" cases. However, because culture-confirmed cases were not compared with probable cases, the complication rate among patients with probable cases cannot be determined from the data presented.

Meat has been shown to harbor VTEC of a great variety of serotypes; these microorganisms originate in the intestinal tracts of the animals at slaughter, and many of them, though not all, have been isolated from samples from infected humans [4]. We would be very surprised if the outbreak described by Dundas et al.

[1], which "originated in a retail source in which cooked meats were cross-contaminated" did not involve animal-derived VTEC with a number of such serotypes.

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Clinical Infectious Diseases 2002; 35:346–7

Reply

Sir—Goldwater and Bettelheim [1] make the important and relevant point that non-O157:H7 and non–lactose-fermenting verocytotoxigenic *Escherichia coli* (VTEC) O157 strains are important contributors to the etiology of both VTEC disease and HUS. However, the authors appear to have overlooked the fact that the Central Scotland outbreak occurred in 1996; their useful and relevant work has all been published since 2000. In addition, the Central Scotland outbreak had the features of a protracted, single-source–type outbreak: it centered on a single butcher's premises, and all cases of infection that occurred in patients who were included in the outbreak cohort fitted a clear case definition. In all cases in which a pathogen was identified (81% of the total), the infecting microorganism was confirmed to be the same strain (phage type 2; VT 2). Isolates from the butcher's premises, from meat, and from infected individuals were confirmed to be an identical strain by pulsed-field gel electrophoresis. Although it is conceivable that other strains were involved, it is highly unlikely, under the circumstances.

Goldwater and Bettelheim's letter [1] highlights an important difference in approach between investigation of a recognized outbreak of acute VTEC disease in which a predominant strain has been identified and retrospective investigation of cases of HUS. The role of non–lactose-fermenting and non-O157 VTEC cannot be underestimated, but such microorganisms were not thought to be relevant in the context of the Central Scotland outbreak.

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Clinical Infectious Diseases 2002; 35:347

Linezolid-Induced Pancytopenia

Sir— I read with interest the recent article "Thrombocytopenia Associated with Linezolid Therapy," by Attassi et al. [1]. I wish to report 2 cases of linezolid-induced pancytopenia.

Patient 1 was an 88-year-old woman with a vancomycin-resistant *Enterococcus faecium* infection associated with a prosthetic hip who refused prosthesis removal and was treated with suppressive linezolid therapy (600 mg twice daily). The patient had normal renal and hepatic function at baseline, was receiving no myelosuppressive medications, and was not receiving heparin. She developed mild nausea, vomiting, diarrhea, and progressive pancytopenia while receiving linezolid. On day 21 of linezolid therapy, the WBC count had decreased from 4.9×10^3 cells/μL at baseline to 2.5×10^3 cells/μL; the hemoglobin level had decreased from 11.5 to 7.9 g/dL; and the reticulocyte count was 0.55%. The platelet count had decreased from 298×10^3 to 160×10^3 platelets/μL by day 15 and continued to decrease progressively, to 99×10^3 platelets/μL on day 21. Linezolid therapy was stopped on day 21 after initiation of treatment. The patient's WBC count and platelet count reached nadir 2 days after administration of linezolid ceased (2.3×10^3 cells/μL and 93×10^3 platelets/μL, respectively) and increased spontaneously 5 days after the drug was discontinued; the anemia was initially treated with erythropoietin alfa but was not corrected, and transfusions were required. There were no hemorrhagic or new infectious complications.

Patient 2 was an 84-year-old man with a group B streptococcus infection associated with a prosthetic knee who was treated with oral linezolid (600 mg twice daily) after removal of the prosthesis. Linezolid was used because the patient had documented allergic reactions to penicillin, cefazolin, sulfamethoxazole, vancomycin, and clindamycin. This patient was taking warfarin sodium for atrial fibrillation and was receiving no myelosuppressive drugs. On day 7 of linezolid therapy, the complete blood count was at baseline (WBC count, 5.7×10^3 cells/μL; hemoglobin level, 11.7 g/dL; platelet count, 170×10^3 platelets/μL); on day 20, however, the WBC count had decreased to 4.6×10^3 cells/μL, the hemoglobin level to 10.7 g/dL, and the platelet count to 82×10^3 platelets/μL. Linezolid adminis-

tration was stopped on day 21. The WBC count and the platelet count reached nadir 4 days after discontinuation of linezolid (to 3.3×10^3 cells/μL and 55×10^3 platelets/μL, respectively); the platelet count returned to a level $>100 \times 10^3$ platelets/μL only 7 days after administration of the drug ceased. The hemoglobin level decreased to 7.9 g/dL 7 days after linezolid therapy was stopped; there was no evidence of bleeding, but the patient required blood transfusions. The patient completed a 6-week antibiotic course with oral azithromycin; his infection was cured.

These 2 cases illustrate the potential that administration of linezolid will result in serious myelosuppressive effects, necessitating serial, frequent laboratory follow-up and phlebotomy, as well as blood transfusions. In their report, Attassi et al. [1] focus on thrombocytopenia and emphasize that platelet counts $<100 \times 10^3$ platelets/μL occur in 32% of patients (6 of 19 patients) with no risk factors for thrombocytopenia after $\geqslant$10 days of linezolid therapy, which is a far greater frequency than the product label reports [2], and report several bleeding complications. Reversible anemia recently has been reported by others as well [3]. Our cases indicate that pancytopenia may also occur in patients who are receiving linezolid. My experience, although anecdotal, is disturbing, and reading the report by Attassi et al. [1] has heightened my concern. Infectious diseases physicians are well aware that there is a great need for alternative therapeutic options for treatment of infections caused by gram-positive organisms, whether because of drug resistance, patient intolerance to first-line antibiotics, or the need for good bioavailability. However, it seems that linezolid may not be an option for prolonged treatment in a substantial number of patients and that, if it is used, close monitoring of the blood count in all patients is necessary. Linezolid is an extremely expensive drug (the cost for administration of 600 mg of the oral formulation twice daily is $100 per day); in the end, this prohibitive cost may limit indiscriminate or prolonged use, which may be a saving grace for patients.

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Thrombocytopenia Secondary to Linezolid Administration: What Is the Risk?

Sir—Attassi et al. [1] raise concerns that the incidence of thrombocytopenia associated with administration of linezolid may be higher than the 3% incidence previously reported by the manufacturer [2]. In addition, the authors propose that the risk for thrombocytopenia may occur earlier than the 2-week time frame after which the manufacturer recommends monitoring of platelet counts in patients who do not have other risk factors for thrombocytopenia. We would like to describe our experience with treating patients with linezolid, because we have also seen a higher-than-reported incidence of thrombocytopenia.

Shands Hospital at the University of Florida is a 576-bed university teaching hospital in Gainesville. Since linezolid received US Food and Drug Administration approval, the use of this drug has been restricted at our institution, and all use requires prior approval of the Infectious Diseases Service. Linezolid use is limited to the treatment of serious infections caused by gram-positive organisms that are resistant to other therapies (e.g., vancomycin-resistant enterococci) and treatment of patients who are intolerant to other drugs (e.g., patients infected with methicillin-resistant *Staphylococcus aureus* who cannot tolerate vancomycin).

Since May 2000, a total of 71 patients at our institution have received linezolid for durations ranging from 1 to 44 days. Forty-eight patients received therapy for $\geqslant$5 days. Thrombocytopenia, defined as a decrease in platelet count of $\geqslant$30%, occurred in 23 (48%) of 48 patients, with a range of decrease of 32%–89%. This incidence of thrombocytopenia is similar to the 47% incidence reported by Attassi et al. [1]. In our patients, a decrease in platelet count to <100,000 cells/mm^3 occurred in 9 (19%) of 48 patients, compared with the 32% incidence reported by Attassi et al. [1].

In contrast to Attassi et al. [1], we have seen a similar median duration of therapy for patients who developed thrombocytopenia (median, 12 days; range, 5–34 days) and patients who did not develop thrombocytopenia (median, 12 days; range, 5–44 days). Attassi et al. [1] reported a longer duration of therapy for patients who developed thrombocytopenia (median, 19.1 days; range, 10–42 days) than for patients who did not develop thrombocytopenia (median, 7.7 days; range, 5–11 days).

It is clear that the incidence of thrombocytopenia associated with linezolid therapy is much higher than the 3% incidence found in clinical trials reported by the manufacturer in the product information [2]. It is likely that restricting the use of this agent has resulted in selection of a population of patients who are inherently sicker, and thus more prone to hematologic abnormalities, than those included in the clinical trials. Because thrombocytopenia has occurred with a median duration of therapy of <14 days, clinicians should begin monitoring platelet counts <14 days after initiation of treat-

ment. We recommend at least weekly monitoring of platelet counts in all patients receiving linezolid therapy. A thorough evaluation of the risk factors for thrombocytopenia associated with linezolid therapy should be performed, to determine whether select patient groups can be targeted for more- or less-intense monitoring of platelet counts.

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Safety of *Lactobacillus* Strains as Probiotic Agents

SIR—Although I agree with Sipsas et al. [1] that any report of organisms causing disease needs to be taken seriously, I disagree with many of the points they make in their letter. First of all, the original review that they cite [2], although laudable, included several important inaccuracies, starting with a definition for probiotics that the authors of the review appear to have made up. Probiotics should be defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [3, p. 2]. The original review [2] wrongly stated that probiotic products used in Europe differ from those used in the United States, because, for example, *Lactobacillus rhamnosus* GG is used on both continents. Furthermore, the authors of that review [2] and Sipsas et al. [1] missed a critical point: for a strain of *Lactobacillus* to be considered a probiotic, it first must have been shown to confer health benefits on the host [3]. Unfortunately, countless numbers of "probiotic" products on the market—and too many organisms cited in the literature as "probiotics"—have never been shown to confer any health benefits on the host. At best, there are a handful of strains for which there is evidence of an associated health benefit [4]. Yet, even with so many pseudoprobiotic products available, which often have unreliable contents [5], very few case reports of side effects have been reported [6].

The case report [7] cited by Sipsas et al. [1] lacks essential details necessary for useful conclusions to be made. The patient consumed "heavy daily" amounts of undisclosed dairy products that may or may not have contained a probiotic strain (probably they did not, given that few such strains are available). There is no mention of the patient being immunocompromised, as stated by Sipsas et al. [1]. The patient had constipation, but we do not know whether it resolved because the patient ate dairy products or whether it was caused by excessive eating. Did the patient sustain a microscopic intestinal lesion as a result of the constipation or colonoscopy? Did the laxative preparation given before colonoscopy include an antibiotic? Either way, the intestinal flora was disrupted. Because the isolates did not undergo molecular identification, and because no attempt was made to determine whether they were the same as the strains in the yogurt ingested by the patient, it is a stretch to say there is any evidence of a correlation between the endocarditis and the patient's diet, never mind the ingestion of a true probiotic.

It is difficult to determine how many people use probiotics safely on a daily basis. The manufacturer of the product Yakult, which contains *Lactobacillus casei* strain Shirota, claims sales of >9 billion bottles per year. Sales by Danone, Valio, and other manufacturers of products that contain probiotics for which there is evidence of health benefit likely increase that figure to >20 billion doses per year. To raise fears of endocarditis on the basis of 4 cases (yogurt is not a probiotic, so I have discounted 6 of the cases mentioned by Sipsas et al. [1]) that have occurred in 10 years, after perhaps 200 billion doses of probiotic products have been ingested around the globe, is to exaggerate and misrepresent the true risks of probiotic therapy.

With respect to safety, credible scientists in the field of probiotics have long cautioned that use of any therapy, including administration of lactobacilli, foods, or pharmaceuticals, should take into account the condition of the patient or end user. For some immunocompromised patients and patients with intestinal bleeding, probiotic ingestion may or may not have beneficial results. Because probiotic products are readily available over the counter, there is an onus on the consumer to understand what they are buying.

Sipsas and colleagues, citing a 2001 study [8] in which the infecting organism could not be correlated with that isolated from yogurt ingested by the patient, have failed to show an "increasing number of reports that suggest a pathogenic role for the lactobacilli used as probiotic agents" [1, p. 1284]. Rather, they have raised false alarms on the basis of personal perceptions. If they describe pathogenic virulence factors produced by well-proven probiotic organisms in highly reliable product formulations and then show that these are expressed in patients with disease, then we will gladly take notice. Until then, there is good evidence that properly tested probiotics have an enormous potential to prevent disease and, in some cases, treat it. Until this message is taken seriously by health care professionals, governments, and industry, rumormongering is not constructive. Pick up any pharmaceutical compendium and you will find many reasons why we should be more concerned

with the side effects of drugs than with the safety of probiotics.

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