Infection: A Rebuttal

To the Editor—The article by Eckmanns et al. [1] on the use of high-efficiency particulate air (HEPA) filtration on fungal infection was of interest to us, because we have been involved in infection prophylaxis for patients with acute leukemia since the 1960s [2]. As effective therapy became available for these patients, it was recognized that infectious complications not only were a major cause of death but also caused delays in the administration and dosage reductions of chemotherapy, thus reducing its efficacy. Protected environment–prophylactic antibiotic (PEPA) programs were developed to attempt to reduce the risk of infection during periods of neutropenia after chemotherapy. These PEPA programs included isolation units with HEPA filtration, strict patient isolation, special water-purification systems, special handling of patient wastes, and food restrictions.

The first type of isolation unit consisted of a bed enclosed within a plastic tent and a HEPA filtration unit. Subsequently, laminar airflow (LAF) rooms were designed in which one entire wall consisted of a HEPA filtration unit. The airflow in these units is laminar in distribution (although not completely), and the number of air exchanges is much higher than that obtained with a simple HEPA unit. The first LAF unit for patient occupancy was installed at our institution in 1968 [2]. The first LAF facility (a 20-bed unit) incorporated into the original design and construction of a hospital was opened here in 1977 and was in continuous operation until 2000 [3]. We have published >40 papers related to PEPA studies, varying from microbiological assessments to chemotherapy dosage escalation studies, and >2000 patients have been treated [4, 5].

Unfortunately, the review conducted by Eckmanns et al. [1] suffers from several methodological flaws. The clinical trials that they examined were designed to evaluate the entire PEPA program and not just air filtration. Most clinical trials of the PEPA program were mainly focused on the outcome of the chemotherapy—specifically whether it increased complete remission rates, the duration of remission, and survival. The focus on infection was whether it occurred and not the infecting organism and site of infection. Hence, most studies of the PEPA program were not designed to evaluate their impact specifically on fungal infections. The authors claim a “bias” because “studies that showed a small effect and no influence of ventilation on fungal infection are missing” (p. 1413), which is an erroneous conclusion for the reason cited above.

The most serious flaw of the analysis by Eckmanns et al. [1] is that the authors used all fungal infections in evaluating the impact of air filtration. Although mold spores are dispersed into the air and are usually respiratory pathogens, air is not the usual mode of transmission of *Candida* species, which have been the most common cause of fungal infection in these patients. HEPA filtration would not be expected to have a major impact on *Candida* infections. In an analysis of 102 treatment episodes in protected-environment (PE) units at our institution, 17 patients developed *Candida* infection, and only 1 developed aspergillosis [6]. Although *Candida* species can be cultured from various environmental sites, in that study, all of the infected patients had *Candida* species recovered from body sites before entry that persisted until the time of infection, despite antifungal prophylaxis.

The authors mention as a limitation “that none of the studies was blinded” (p. 1414). They state that “no studies involved the appropriate control subjects, who should have been situated in rooms with air conditioning but without HEPA filters” (p. 1414). Much effort is put forth during the installation of HEPA filters in LAF rooms to ensure that there is a tight seal between components. The HEPA filters cannot be installed and removed at will without damaging these seals. Also, for patients in groups to be comparable except for air filtration would require that all other prophylactic measures be followed in all patients. We recognized the practical impossibility of conducting a blinded study. A statistician with extensive experience in clinical trials was involved in the design and analysis of our studies.

The authors cite one of our studies that they discredited because “it did not contain valid data” (p. 1410), without specifying what was invalid [1, 7]. Presumably, this refers to a comment they made in the following paragraph referring to “a contradiction between the text and a figure” (p. 1410). We have carefully reviewed the article, and we can find no such contradiction.

The authors state that our second study suffered from a “severe methodological flaw in randomization” (p. 1410) [1, 8]. “Patients were only randomized to a PE unit when a unit was available” (p. 1410). The small number of PE units and the economic consequences would not permit us to always have an empty PE unit available. To enter patients in the study only when a PE unit was available would have prolonged the study beyond the period of our grant support. Referral of patients to our institution for therapy was a random event, and patients nearly always required
immediate therapy, which prevented any manipulations of entry in the study.

We have conducted many studies related to the PEPA program, including 6 prospective, randomized, controlled clinical trials. In the majority of these studies, patients in the PEPA program had fewer infections than did the control patients. In several studies, this permitted the administration of higher doses of chemotherapy [5]. Over the course of >30 years, we have repeatedly confirmed the value of the PEPA program as an adjuvant in improving the efficacy of antileukemic therapy and its long-term outcome. In multivariate analyses of several therapeutic trials, the PEPA program consistently emerged as a significantly independent variable for a favorable outcome [9, 10].

The preponderance of evidence indicates that the PEPA program in its entirety reduces the frequency of infection. There are insufficient data to evaluate the efficacy of air filtration on the frequency of mold infections. However, our environmental studies found low levels (if any) of molds in air, floor, and settling-plate samples [4]. We believe that infection prophylaxis, especially of fungal infections in immunocompromised patients, remains a focus for continuing research. It may be that the availability of effective new antifungal agents will minimize the need for air filtration in the future.

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References

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Reply to Bodey and Freireich
To the Editor—In their letter, Bodey and Freireich [1] criticize our systematic review [2] as suffering from several methodological flaws. First, they do not accept our conclusion that there might be a publication bias concerning studies with fungal infection as a study outcome. In general, studies that show statistically significant effects of treatment are more likely to be published [3]. Our Forrest plot suggested that, in studies when fungal infections are the outcome, there are no small studies showing no influence of ventila-

tion on the outcome (figure 3B in [2]). There could be several different reasons for this—one could be publication bias.

Bodey and Freireich state incorrectly that we used all fungal infections in evaluating the impact of air filtration. However, in the Methods section, we clearly defined a fungal infection as invasive aspergillosis and non-Candida fungal infection [2]. This definition applied throughout the article. Bodey and Freireich criticized our statement that none of the studies that we considered were blinded. We agree with Bodey and Freireich that it is almost impossible to conduct a blinded study to address the study question. Nevertheless, it is important to note that no study was blinded when interpreting the results of the studies, because of the lack of blinding might result in bias [4].

We mentioned in our article a study by Bodey et al. [5] that was excluded from the systematic review. That study contains a contradiction between the text on page 147 and figure 5 on page 147. Figure 5 shows a survival analysis in which the “Total Control Patients” line reaches zero at its end, which implies that all patients died by the time of analysis. The text states that 4 patients in the “Total Control Patients” group were still alive at the time of analysis. Because of this contradiction, it was impossible for us to identify the number of study participants in the study, hence its exclusion.

Bodey and Freireich disputed our statement regarding a methodological flaw in randomization in the study by Rodriguez et al. [6]. In our review, we considered the study by Rodriguez et al. [6] to be a non-randomized study. For randomization, an unpredictable allocation sequence must first be generated. Then this sequence must be concealed from investigators enrolling patients [7]. As Bodey and Freireich describe in their letter, this was not done in the study by Rodriguez et al. [6], which is why that study was considered to be a nonrandomized study.

The purpose of systematic reviews is to allow for a more objective appraisal of the theoretical experiments.