Antifungal Antibiotics and Breakthrough Bacteremias

Richard P. Wenzel, Chris Gennings, and Michael B. Edmond
Departments of Internal Medicine and Biostatistics, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia

(See the article by Viscoli et al. on pages 1532–7)

Patients with fever and neutropenia are at high risk for infection (~50%) and bacteremia (~20%). As a result, most are treated with antibacterial prophylaxis until their absolute neutrophil count exceeds 500 cells/mm³ and their temperature returns to normal. The 1997 guidelines of the Infectious Diseases Society of America suggested 1 of 3 regimens: vancomycin plus ceftazidime, monotherapy with ceftazidime or imipenem (possibly cefepime or meropenem), or dual therapy with an aminoglycoside plus an antipseudomonal β-lactam [1].

If patients with fever and neutropenia have treatment failure after 3–5 days of empirical antibacterial therapy, they have an ~20% rate of acquiring an invasive fungal infection, and preemptive antifungal therapy has been shown to reduce the attack rate. Recently, the Infectious Diseases Society of America recommended adding amphotericin B or lipid-associated amphotericin B after 4–6 days of persistent fever to treatment regimens for patients with neutropenia [2].

Because candidemia is an important nosocomial problem in immunosuppressed patients [3], concerned clinicians over the past decade have frequently added initial prophylaxis with antifungal agents plus antibacterial antibiotics to the regimen for patients with fever and neutropenia. Some data have shown reduced rates of subsequent bloodstream infection with Candida species. Curiously, other small studies have suggested that antifungal prophylaxis for such patients may be associated with increased rates of subsequent bacterial bloodstream infections. In this issue of Clinical Infectious Diseases, Viscoli et al. [4] attempt to clarify the risk by examining the relationship between documented bacteremias and antifungal therapy among patients previously enrolled in 4 clinical trials of the European Organization for Research and Treatment of Cancer. All patients had been randomized to receive 1 of several regimens of prophylactic antibacterial antibiotics at the onset of fever and neutropenia. Some co-incidentally had received either poorly absorbable or absorbable antifungal prophylaxis, but these drugs were not delivered in a randomized or blinded fashion. The rates of bacteremia were 20% for patients who were receiving no antifungal agents versus 26% and 27% for those who were receiving poorly absorbable or absorbable drugs, respectively. The authors suggest that antifungal prophylaxis adversely influenced the rate of bacteremia in a clinically and statistically important fashion [4].

TRUE RELATIONSHIP OR ERROR

Because the outcome of interest of the study had a P value <.05, we suggest an examination of the differential diagnosis of the significant P value. There are 4 possibilities: that a true difference exists, and antifungal drugs caused an increase in the rate of recorded bacteremias; that no difference exists in fact, but a random (chance) error occurred, the probability for which was defined by the P value; that no difference exists, but a systematic error (bias) occurred, for which no correction is possible; no difference exists, but an error occurred because of failure to control for a confounding variable.

Of the 3 possible errors, we should particularly address bias and confounding. Could bias have caused an error? The answer is “yes.” For example, if most of the patients who received antifungal prophylaxis did so in the late years of the study and most of the placebo recipients were involved in the early years of the study, important changes in patient profiles, specific therapy, general supportive care, or institutional risk could have been linked to the outcome of bacteremia.

With respect to confounding, failure to correct for specific antibiotic regimens could explain the current results. For example, if 1 of the 8 antibiotic regimens was especially ineffective in preventing breakthrough bacteremias, and if more antifungal prophylaxis was linked to that
regimen than to others, an error related to confounding could have occurred. This error, unlike bias, can be corrected by performing stratified analyses or modeling the outcome.

**IF A TRUE RELATIONSHIP, WHAT IS THE CLINICAL IMPACT?**

If there is a true causal relationship between antifungal prophylaxis and increased rates of bacteremia, what is the magnitude of the clinical impact? The significance of parameter estimates based on a sample size of 2500 may be misleading and is certainly not guaranteed to distinguish clinically important variables. A useful addition to Viscoli et al. [4] would have been a table showing the proportions of bacteremias caused by the variables considered. With such data, the reader could judge the size of the proportions that were being compared and claimed as significant. Even if the antifungal agents caused higher rates of bacteremia, we do not know whether this finding was offset with effective prevention of rates of candidemia. Additionally, it might be useful to examine the attributable risk [5]—the estimate of the reduction in bacteremias should the risk factor of interest be eliminated [6, 7]. In this case, what is the attributable risk for absorbable antifungal drugs? Consider table 1.

The attributable risk, defined as \((a - b)/(1 - b)\) [6], is estimated to be 6.8% (95% asymmetrical approximate CI, 0%–85%). This relatively low attributable risk suggests that important factors other than use of absorbable antifungal agents contribute to bacteremia. Using the same approach, if we define the attributable risk as the proportion of bacteremia rates resulting from any antifungal agent (absorbable or poorly absorbable), it is 19.6% (CI, 0%–97%).

**ELEMENTS OF CAUSE AND EFFECT**

Finally, what elements of cause and effect are satisfied? We first examine biological plausibility: Why would an antifungal drug lead to an increase in bacteremia? We are aware of no animal models to support this relationship, and it seems unlikely that a reduced burden of *Candida* in stool would lead to breakthrough bacteremia. Therefore, the element of biological plausibility is not satisfied. Second, what is the magnitude of the effect? In fact, the estimated risk ratio is only 1.4 and, therefore, not very large. This too does not strongly support a causal relationship. Third, we are not shown a dose-response relationship, that is, whether more frequent use of antifungal drugs led to higher rates of bacteremia. Fourth, we are not provided any evidence of specificity. For example, if almost all bacterial organisms found in cultures from the blood of patients who were receiving antifungal antibiotics were *Escherichia coli*, this would support cause and effect. However, if a broad mixture of gram-positive and gram-negative organisms and aerobes as well as anaerobes were recovered, no specificity would have been demonstrated, and a causal relationship would be unlikely. In the current paper [4], these data are not supplied. Therefore, the last 2 elements of cause and effect are also missing.

**CONCLUSIONS**

One must admire any team of serious investigators who examine data to try to find relationships between drug use and outcomes. Recall that they were testing a hypothesis that others had previously raised. Certainly, we are grateful for the authors’ work and respectful of their efforts. However, how does one interpret the provocative paper by Viscoli et al. [4]? This is a difficult issue, and we have outlined the potential pitfalls of accepting a true causal relationship. We agree with the authors that rigorous prospective studies involving a standard antibacterial regimen in which all patients are randomized to antifungal drugs versus placebo will be needed to clarify the hypothesis raised. For the time being, we think that the possibilities of errors of chance, bias, or confounding are important considerations in interpreting the current study [4].

**REFERENCES**