Editorial Response: Catheters and Candidemia

In the previous article, Blumberg and Reboli describe a curious event. In five separate instances, candidemia developed in a patient with a hematologic malignancy following at least 3 days of therapy with amphotericin B at a minimum dosage of 0.6 mg/(kg·d). While a similar pattern has been noted in a small number of patients in two prior reports [1, 2], the cases in this report provide additional details that are instructive in light of current concepts regarding the pathogenesis of candidal bloodstream infections. The explanation for the breakthrough candidemia in these five cases is not immediately clear. The blood cultures do not appear to have been contaminated: two of the patients had multiple positive blood cultures and the other three were febrile and appeared acutely ill in association with a single positive blood culture. Lack of amphotericin B might be suggested, but the patients had received an average of 1.6 g (range, 0.2–3.9 g) at an average dosage of slightly more than 50 mg/d prior to the episode of candidemia.

Were the organisms resistant to amphotericin B? This question is not easily answered. Such resistance has been described for most Candida species, including the two species infecting these patients [2–7]. With the exception of Candida lusitaniae [8], resistance is thought to be rare and usually is associated with substantial prior use of polyene antibiotics. We are not told the precise details of antifungal therapy given to the patients in the distant past, but at least two of the patients had previously had fungal infections and all were of course receiving amphotericin B at the time of the onset of breakthrough candidemia.

Although performance and interpretation of susceptibility testing of fungi is still an area of active debate and development [9], the authors partially addressed this issue with in vitro susceptibility data. Testing of the Candida albicans isolates from two of the patients (the Candida krusei isolates from the other three patients were apparently unavailable) by the now standardized M27P method [10] yielded an MIC well below the 1–2 μg/mL serum levels that could be expected for this dosage of amphotericin B [11]. Unfortunately, such a result only suggests, but does not prove, susceptibility.

Simple predictions of appropriate interpretive breakpoints by reference to achievable serum drug levels are made perilous by the arbitrary nature of susceptibility testing (MICs can be made to vary many-fold merely by changing test conditions), by in vivo effects of factors such as protein binding, by the uncertain relevance of serum levels (as opposed, for example, to tissue levels), by the inability of the M27P method to consistently detect resistance to amphotericin B, and most important, by the inability of any in vitro system to account for the impact of host factors on the course of infection [9, 12, 13]. However, improved methods for detection of in vitro resistance to amphotericin B have recently been developed and validated against Candida isolates that are known to be resistant in animal models [14, 15].

While Blumberg and Reboli did not use these newer methods, isolates with M27P-determined MICs as low as those reported in their article are quite unlikely to be found resistant by comparison with isolates known to be amphotericin B–resistant, even when tested by these improved methods. Thus, frank resistance to amphotericin B, at least for two of the cases, does not seem a viable explanation. As for the three untested C. krusei isolates, all that can be said is that C. krusei isolates in general tend to have slightly higher MICs than do C. albicans isolates and may require somewhat higher doses of amphotericin B for optimal therapy [1, 15, 16]. This MIC increase is usually modest, however, and does not place the MIC into a range that would suggest complete resistance to amphotericin B.

Looking further, the patients’ clinical scenarios do not immediately appear unusual. All had leukemia, all were profoundly neutropenic, and diarrhea and mucositis were common. Prior infections of other types were noted in all of the patients. One factor that did seem to distinguish the patients with breakthrough candidemia from a control group of patients with nonbreakthrough candidemia was a greater average duration of neutropenia prior to onset of candidemia: 59 days vs. 14 days (P = .07). While these results are limited by the small sample sizes involved, comparison with other studies suggests that this duration of neutropenia prior to onset of breakthrough candidemia is indeed unusually high, with more typical intervals being 12–20 days [2, 17]. Neutropenia is clearly a powerful risk factor for both development and persistence of fungal infections [18, 19], but it is not clear that this alone is a complete explanation for the development of a fungal infection in the face of what is usually adequate antifungal therapy.

Last, but not least, we come to the issue of the source of the candidemia. The best-recognized possibilities are the gut and intravascular catheters. The gut would seem a likely source, especially in patients with mucositis [20, 21]. The presence of oropharyngeal candidiasis is sometimes thought to suggest overgrowth elsewhere in the gut and thus to be a prelude to dissemination from the gut [20], but this finding was not noted in these patients. Rather, in these patients there was clinical evidence that an intravascular catheter was the source of the candidemia. While it is difficult to prove causation, clearance
of the bloodstream and resolution of fever seemed to follow catheter removal in each case. Even though the results were not corroborated with catheter-tip cultures, the overall pattern is supported by (1) the failure of ongoing amphotericin B therapy to prevent development of the infection, (2) the ability of continued amphotericin B therapy to resolve the infection after catheter removal, and (3) the resolution of candidemia in some of the patients despite continued neutropenia.

The importance of catheters in the development of candidemia is clear. Numerous studies have identified intravascular catheters (primarily central venous catheters) as risk factors for the development [18, 19, 22, 23] and persistence [19] of candidal bloodstream infections. While catheters can serve as the nidus for formation of a septic thrombus, they can also become infected themselves via several routes [24]. Most commonly, any type of catheter may become contaminated as a result of manipulation of the hub, with subsequent migration of bacteria along the internal surface of the catheter. Short-term nontunneled catheters may become involved by migration of bacteria along the intercutaneous tract to the distal vascular segment. Much less commonly, catheters may become infected as a result of hematogenous seeding or contamination of the infusion.

In any event, Candida species appear to have two mechanisms that would support firm adherence to a catheter. First, they have surface receptors that allow adherence to the thrombin biofilm that forms on the catheter, and coagulase production by Candida species may contribute further to formation of this biofilm [24, 25]. Second, hydrophobic interactions between Candida surface proteins and the plastic itself may also promote adherence [25, 26]. Adherent candidal biofilms, like bacterial biofilms, exhibit substantial resistance to the action of antimicrobial agents [27]. Taken together, these data suggest a plausible mechanism for the development of candidemia in the face of ongoing antifungal therapy: once the catheter is contaminated, the infecting Candida isolate need not actually be resistant by the usual measures in order to survive and grow in the relatively protected environment of the catheter’s biofilm.

This pathogenic mechanism would predict that it would be difficult to clear catheter-related candidemia. Several investigators have presented data to this effect [21, 28, 29]. Most recently, my colleagues and I analyzed the effect of catheter exchange on duration of candidemia, using data from a multicenter trial comparing fluconazole with amphotericin B as therapy for candidemia [30, 31]. The study group consisted entirely of nonneutropenic patients, and a post hoc classification suggested that a catheter was the likely source of candidemia in most of the patients. If a complete catheter exchange was defined as removal and replacement of all catheters on a single day, without use of a guide wire to make the exchange from a preexisting catheter, performance of a complete catheter exchange on or before the first day of therapy was associated with a reduction in the subsequent average duration of candidemia from 5.6 to 2.6 days ($P < .001$). It must be noted that the strength of this conclusion is limited by the lack of random assignment of patients to no-exchange and exchange groups, and the no-exchange group did have both a slightly higher APACHE II score (16.9 vs. 14.5; $P = .03$) and a larger number of vascular catheters in place (1.8 vs. 1.2; $P < .001$).

With that caveat stated, the overall pattern is still consistent with the idea that the catheter is a persistent focus of infection. In further support of this concept, redefinition of complete catheter exchange to include exchanges performed over a guide wire significantly lessened the beneficial effect of catheter exchange on the duration of candidemia. While it is difficult to estimate the impact of the more prolonged candidemia in the no-exchange group, a previously unpublished analysis of these data found that the no-exchange group had a higher overall mortality (38/76 [50%] vs. 29/97 [30%]; $P < .01$ by Fisher’s exact test).

Catheter-related candidemia has been noted to be associated with a lower morbidity than that associated with catheter-unrelated candidemia [32, 33], and the experience reported by Blumberg and Reboli is consistent with this concept. However, several authors have emphasized that this finding does not make catheter-related candidemia benign [21, 32]. For example, a recent review of 155 episodes of central venous catheter-associated fungemia in cancer patients found that even a single positive blood culture specimen obtained through a central venous catheter was associated with a substantial frequency of disseminated disease [21].

While these overall results strongly suggest that removal of catheters infected with a Candida species should be seriously considered, problems remain. First, the strength of the above data is limited: none of the results are from prospective trials designed specifically to address this issue. It is noteworthy that investigators studying this issue with regard to patients with cancer have not consistently found that catheter exchanges were necessary [34–36], perhaps because the impact of neutropenia and alternative sources of fungemia may have overwhelmed any beneficial effect of catheter exchange. More systematic work to clarify these issues obviously would be welcome.

Second, even if one decides to regularly remove infected catheters, there are only a limited number of tools that can help one decide if any given catheter is actually infected. As was the case for the patients described by Blumberg and Reboli, there is nothing characteristic about the age or type of the involved catheters. Differential quantitative blood cultures have been reported to identify catheter-related candidemia when greater numbers of organisms are found in the specimen obtained via the catheter rather than in a blood specimen obtained percutaneously [37], but the accuracy of this method is open to debate [38]. This method also requires several days for growth of the cultures. Exchange over a guide wire, with culture of the tip of the removed catheter, might also be contemplated, but this solution is only applicable for temporary catheters. Patients with permanent tunneled catheters present a difficult problem because of the substantial costs associated with place-
ment of a new catheter following removal of the old one. Unfortunately, no better solutions are known.

In my practice, I strongly recommend prompt removal of all intravascular catheters unless another source of candidemia is evident. The only exception I make to this rule is for the patient who is mildly ill and has a tunneled or subcutaneous-port central venous catheter. Given the lower rates of infection for such catheters, especially for those accessed via a subcutaneous port [35], one can rationally argue for cautious observation over 1–3 days in this scenario. If the patient’s condition improves, then the catheter may be salvageable or may never have been involved. On the other hand, if improvement is not evident, the catheter should be removed promptly. Recent data on the use of thrombolytic agents to clear infected catheters [39] and the possible implications of different types of plastic in the catheter [24] are intriguing, but the implications of these observations are as yet incompletely understood.

In conclusion, the data on the five patients described by Blumberg and Reboli serve as a timely reminder both of the importance of intravascular catheters in the pathogenesis of candidemia and of the fact that catheter-related candidemia may develop despite adequate antifungal therapy. While prolonged neutropenia may be an additional risk factor for breakthrough candidemia, these cases clearly demonstrate that catheters are often both part of the cause and the cure of candidal bloodstream infections.

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Note Added in Proof

The ideas presented by Blumberg and Reboli have also been supported by Girmenia and Martino [40], who recently described a small series of cases of catheter-related breakthrough fungemia due to fluconazole-susceptible *Candida* in fluconazole-treated patients, and by Nguyen et al. [41], who presented additional data supporting the importance of catheter exchange in the management of patients with candidemia.

References