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What Types of *Candida* Infections Should Be Included When Evaluating Breakthrough Infections during Posaconazole Prophylaxis?

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In the November issue of *Antimicrobial Agents and Chemotherapy*, Dolton et al. published findings from a retrospective multicenter study of posaconazole therapeutic drug monitoring (1). They found that among 72 patients taking posaconazole for prophylaxis against invasive fungal infections, 12 (17%) patients developed breakthrough fungal infection. Median posaconazole concentrations in patients with a breakthrough fungal infection were significantly lower than in patients that did not develop fungal infection. Those authors concluded that low posaconazole concentrations are associated with breakthrough fungal infections and propose monitoring posaconazole concentrations to ensure optimal systemic exposure. However, we think that the criteria used for inclusion of patients have to be further discussed.

The lack of a standard set of definitions for fungal infections used to be a major obstacle in clinical research, making it difficult to compare different clinical trials. As a result, defining criteria were published in 2002 by the European Organization for Research and Treatment of Cancer (EORTC) Group/National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) Consensus Group (2). These criteria were revised in 2008 and are used as standards in clinical research involving invasive fungal infections (3). The infections are classified as proven, probable, or possible. Briefly, proven mold infection requires demonstration of fungal elements in diseased tissue (i.e., biopsy specimens). A proven invasive yeast infection requires recovery of a yeast isolate by culture of a sample obtained by a sterile procedure from a normally sterile site, usually blood. To reach the level of probable fungal infection, a combination of a susceptible host, clinical signs compatible with fungal infection, and mycological evidence must be present. Possible infection requires only a susceptible host and clinical signs compatible with a fungal infection, the most frequent being dense lesions visible on a chest computed tomography (CT) scan indicative of a mold infection (3).

In the study by Dolton et al. it is stated in the Materials and Methods section that breakthrough infections were classified according to the 2008 guidelines (1). However, of the 12 cases of breakthrough infections listed in Table 2, case 1 is classified as a probable *Candida* infection in the lungs, a questionable entity according to the EORTC/MSG criteria except for cases with hematogenous spread to the lungs. Case 4 is classified as oral candidiasis, which cannot be classified as a proven, probable, or possible infection according to the EORTC/MSG criteria due to the lack of fulfillment of both clinical and mycological criteria. The same is true for case 7 (urinary tract infection with *Candida glabrata*). Case 8 is classified as presumed fungal endophtalmitis, a category not included in the EORTC/MSG criteria. This leaves us with one case of proven candida infection (candidemia) and seven cases with possible fungal lung infections.

The conclusion that low posaconazole concentrations are associated with risk of breakthrough fungal infections and that posaconazole concentration should be monitored to ensure optimal systemic exposure may well be true and, if so, is important. However, it may bring on considerable costs. It is therefore important to use clearly stated and internationally accepted definitions of invasive *Candida* infection.

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