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Geographic variation in the frequency of isolation and fluconazole and voriconazole susceptibilities of *Candida glabrata*: an assessment from the ARTEMIS DISK Global Antifungal Surveillance Program

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Abstract

Geographic differences in frequency and azole resistance among *Candida glabrata* may impact empiric antifungal therapy choice. We examined geographic variation in isolation and azole susceptibility of *C. glabrata*. We examined 23 305 clinical isolates of *C. glabrata* during ARTEMIS DISK global surveillance. Susceptibility testing to fluconazole and voriconazole was assessed by disk diffusion, and the results were grouped by geographic location: North America (NA) (2470 isolates), Latin America (LA) (2039), Europe (EU) (12 439), Africa and the Middle

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East (AME) (728), and Asia-Pacific (AP) (5629). Overall, *C. glabrata* accounted for 11.6% of 201 653 isolates of *Candida* and varied as a proportion of all *Candida* isolated from 7.4% in LA to 21.1% in NA. Decreased susceptibility (S) to fluconazole was observed in all geographic regions and ranged from 62.8% in AME to 76.7% in LA. Variation in fluconazole susceptibility was observed within each region: AP (range, 50–100% S), AME (48–86.9%), EU (44.8–88%), LA (43–92%), and NA (74.5–91.6%). Voriconazole was more active than fluconazole (range, 82.3–84.2% S) with similar regional variation. Among 22 sentinel sites participating in ARTEMIS from 2001 through 2007 (84 140 total isolates, 8163 *C. glabrata*), the frequency of *C. glabrata* isolation increased in 14 sites and the frequency of fluconazole resistance (R) increased in 11 sites over the 7-year period of study. The sites with the highest cumulative rates of fluconazole R were in Poland (22% R), the Czech Republic (27% R), Venezuela (27% R), and Greece (33% R). *C. glabrata* was most often isolated from blood, normally sterile body fluids and urine. There is substantial geographic and institutional variation in both frequency of isolation and azole resistance among *C. glabrata*. Prompt species identification and fluconazole susceptibility testing are necessary to optimize therapy for invasive candidiasis.

Keywords: *Candida glabrata*; Azoles; Surveillance

1. Introduction

Fluconazole is a mainstay for prophylaxis and empiric and directed therapy for invasive candidiasis (IC) (Baddley et al., 2008; Bilgen et al., 1995; Marr et al., 2000; Pappas, 2008; Pappas et al., 2009; Perlroth et al., 2007; Pfaller and Diekema, 2007a; Riddell and Kauffman, 2008; Spellberg et al., 2006; Wilson et al., 2005). Unfortunately, the use of this agent has been impacted by the emergence of *Candida* spp. with reduced susceptibility/resistance to this agent (Alexander et al., 2005; Arendrup et al., 2008; Armstrong-James, 2007; Baddley et al., 2001; Boschman et al., 1998; Hachem et al., 2008; Magill et al., 2006; Nguyen et al., 1996; Panackal et al., 2006; Pappas et al., 2009; Pasqualotto et al., 2008; Spanakis et al., 2006). Foremost among those species of *Candida* with decreased susceptibility to fluconazole is *Candida glabrata* (Abi-Said et al., 1997; Alexander et al., 2005; Arendrup et al., 2008; Hachem et al., 2008; Horn et al., 2009; Lee et al., 2009; Li et al., 2007; Malani et al., 2005; Nguyen et al., 1996; Pasqualotto et al., 2008; Pfaller and Diekema, 2007a; Pfaller et al., 2003, 2004a; Ruan et al., 2008; Trick et al., 2002; Wilson et al., 2005). The Infectious Diseases Society of America guidelines for the treatment of IC suggest that although infection due to *C. glabrata* may be treated with fluconazole using a dosing regimen of ≥12 mg/kg a day, such therapy should be guided by antifungal susceptibility testing whenever possible given the variable frequency of resistance seen with this species (Pappas et al., 2004, 2009). Although the echinocandins may provide reliable empiric coverage of *C. glabrata* (Pfaller et al., 2008), such agents are much more expensive than fluconazole, and deescalation from initial echinocandin coverage to the more economical fluconazole is encouraged whenever possible (Collins et al., 2007; Lichtenstein et al., 2008; Pappas et al., 2009).

Several studies have attempted to identify clinical parameters that would allow clinicians to identify those patients who are likely to become infected with *C. glabrata* versus *Candida albicans* as a means of providing appropriate early therapy (Chow et al., 2008; Guery et al., 2009; Hedderwick et al., 1998; Lee et al., 2009; Magill et al., 2006; Parkins et al., 2007; Shorr et al., 2007). Unfortunately, no consensus has come of such studies, and thus, the most common recommendation is that early empiric therapy be guided by the local epidemiology concerning the frequency of *C. glabrata* as a cause of IC and the institutional antifungal susceptibility profile of this species (Alexander et al., 2005; Collins et al., 2007; Lichtenstein et al., 2008; Magill et al., 2006; Morrell et al., 2005; Pappas et al., 2009; Parkins et al., 2007; Riddell and Kauffman, 2008; Wilson et al., 2005).

Both large antifungal surveys as well as more localized reports from individual institutions, cities, or countries have documented the variable occurrence of *C. glabrata* infection, including the susceptibility of this species to fluconazole (Alexander et al., 2005; Almirante et al., 2005; Arendrup et al., 2008; Asmundsdottir et al., 2002; Baddley et al., 2001; Chen et al., 2003; Cheng et al., 2004; Gonzalez et al., 2008; Hachem et al., 2008; Hajjeh et al., 2004; Laupland et al., 2005; Magill et al., 2006; Malani et al., 2005; Ostrosky-Zeichner et al., 2003; Pfaller and Diekema, 2004, 2007a; Pfaller et al., 2003, 2004a; Poikonen et al., 2003; Sandven et al., 2006; Sendid et al., 2006; Tan et al., 2008; Tortorano et al., 2006; Xess et al., 2007; Yang et al., 2006). Although *C. glabrata* appears to be most frequently encountered in the United States (Hajjeh et al., 2004; Malani et al., 2005; Ostrosky-Zeichner et al., 2003; Pfaller and Diekema, 2007a; Pfaller et al., 2003, 2004a), reports from other countries vary as to both the frequency of isolation and of resistance to fluconazole (Arendrup et al., 2008; Asmundsdottir et al., 2002; Chen et al., 2003; Gonzalez et al., 2008; Laupland et al., 2005; Sandven et al., 2006).

Previously, we have reported broad geographic trends in the isolation of *C. glabrata* from clinical specimens and the accompanying rates of fluconazole resistance both in the United States and internationally (Pfaller et al., 2003, 2004a). We now update this information using the extensive database of the ARTEMIS Antifungal Surveillance Program for the years 2001 through 2007 to include results for 23 305 isolates of *C. glabrata* obtained from 133 institutions in 38 countries. In addition to broad trends for countries and geographic regions, we will examine temporal trends in prevalence and fluconazole resistance for 22 individual institutions that have provided data for each of the 7 years of study. The latter analysis is to emphasize the importance of local versus regional epidemiologic data and its potential impact on empiric azole therapy.