Isavuconazole is the active component of the new azole antifungal agent BAL8557, which is entering phase III clinical development. This study was conducted to compare the in vitro activities of isavuconazole and five other antifungal agents against 296 *Candida* isolates that were recovered consecutively from blood cultures between 1995 and 2004 at a tertiary care university hospital. Microdilution testing was done in accordance with CLSI (formerly NCCLS) guideline M27-A2 in RPMI-1640 MOPS (morpholinepropanesulfonic acid) broth. The antifungal agents tested were amphotericin B, fluconazole, itraconazole, voriconazole, and isavuconazole. *C. albicans* was the most common species, representing 57.1% of all isolates. There was no trend found in favor of non-*Candida albicans* species over time. In terms of MICs, isavuconazole was more active (0.004 mg/liter) than amphotericin B (0.5 mg/liter), itraconazole (0.008 mg/liter), voriconazole (0.03 mg/liter), and fluconazole (8 mg/liter). For isavuconazole, MICs of 0.002 to 0.004 mg/liter for *C. albicans* to 0.25 to 0.5 mg/liter for *C. glabrata*. Two percent of isolates (46 isolates), isavuconazole isolates, and the MICs were 2 and 4 mg/liter, respectively. In conclusion, isavuconazole is highly active against Candida bloodstream isolates, including fluconazole-resistant strains. It was more active than itraconazole and voriconazole against *C. albicans* and *C. glabrata* and appears to be a promising agent against systemic *Candida* infections.

**MATERIALS AND METHODS**

**Organisms.** A total of 296 bloodstream isolates of *Candida* spp. obtained consecutively at a single university center over a 10-year period between 1995 and 2004 were selected for testing. The collection included *C. albicans* (166 isolates), *C. glabrata* (46 isolates), *C. krusei* (11 isolates), *C. parapsilosis* (23 isolates), *C. tropicalis* (25 isolates), and other *Candida* spp. (25 isolates, including 6 isolates of *C. lusitaniae*, 4 of *C. guilliermondii*, 4 of *C. kefyr*, 3 of *C. dubliniensis*, 2 each of *C. famata* and *C. pulcherrima*, and 1 each of *C. cattenuata*, *C. inconspicua*, *C. lipolytica*, and *C. rugosa*) (Table 1). All isolates were identified to the species level by CHROMagar *Candida* (Mast Diagnostica GmbH, Reinfelden, Germany) and with the VITEK 2 automated identification system (bioMérieux, Marcy l’Etoile, France) using VITEK 2 YST cards in accordance with the guidelines of the manufacturers. Identification of rare species was confirmed by API Candida (bioMérieux). Prior to testing, each isolate was subcultured at least twice on Sabouraud dextrose agar plates to ensure purity and optimal growth.

**Antifungal susceptibility testing.** Broth microdilution was performed by the reference method described by the NCCLS (formerly National Committee for Clinical Laboratory Standards) in accordance with guideline M27-A2 (5), with a final inoculum concentration of 0.5 x 10^8 to 2.5 x 10^8 cells per ml and RPMI 1640 medium (Sigma, Steinheim, Germany) buffered to pH 7.0 with 0.165 M MOPS (morpholinepropanesulfonic acid) buffer (Merck, Darmstadt, Germany). Microtiter plates containing dehydrated antifungal agents were provided by Merlin Diagnostica (Bornheim-Hersel, Germany). The antifungal agents and concentration ranges tested in twofold steps were as follows: amphotericin B, 0.03 to 32 mg/liter; clotrimazole, 0.03 to 64 mg/liter; fluconazole, 0.06 to 128 mg/liter; itraconazole, 0.004 to 8 mg/liter; voriconazole, 0.004 to 8 mg/liter; and isavuconazole, 0.00025 to 8 mg/liter. Plates were incubated in air at 35°C for 24 to 48 h. Plates were observed for the presence or absence of growth at 24 h and reexamined at 48 h if sufficient growth was not obtained at 24 h. The MIC was determined visually as the lowest concentration of drug showing no growth for amphotericin B and a prominent reduction of growth (≥50%) for fluconazole and the azoles compared to the drug-free growth control. *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were used as quality control strains.

Interpretative criteria for susceptibility to amphotericin B (MIC, ≤1 mg/liter), fluconazole (MIC, ≤4 mg/liter), fluconazole (MIC, ≤8 mg/liter), and itraconazole (MIC, ≤0.125 mg/liter) were those published by Rex et al. (9) and CLSI (5).

**RESULTS AND DISCUSSION**

The number of *Candida* bloodstream infections at our hospital remained stable from 1995 to 2002, ranging from 20 to 29 episodes per year; it increased, however, to 49 and 47 episodes over the past two decades, the incidence of *Candida* bloodstream infections has increased dramatically (3, 15), primarily due to the increase in the number of at-risk patients. Mortality rates associated with systemic *Candida* infections remain high (1, 4). Several *Candida* spp., such as *C. glabrata* and *C. krusei*, exhibit reduced susceptibility to fluconazole, the first available triazole antifungal agent (8). Recently, a new generation of triazoles, including posaconazole, voriconazole, ravuconazole, and isavuconazole, has been developed. As a prodrug, BAL8557 is the water-soluble triazole precursor suitable for clinical development. This study was conducted to compare the in vitro activities of isavuconazole and five other antifungal agents against 296 *Candida* isolates that were recovered consecutively from blood cultures between 1995 and 2004 at a tertiary care university hospital. Microdilution testing was done in accordance with CLSI (formerly NCCLS) guideline M27-A2 in RPMI-1640 MOPS (morpholinepropanesulfonic acid) broth. The antifungal agents tested were amphotericin B, fluconazole, itraconazole, voriconazole, and isavuconazole. *C. albicans* was the most common species, representing 57.1% of all isolates. There was no trend found in favor of non-*Candida albicans* species over time. In terms of MICs, isavuconazole was more active (0.004 mg/liter) than amphotericin B (0.5 mg/liter), itraconazole (0.008 mg/liter), voriconazole (0.03 mg/liter), and fluconazole (8 mg/liter). For isavuconazole, MICs of 0.002 to 0.004 mg/liter for *C. albicans* to 0.25 to 0.5 mg/liter for *C. glabrata*. Two percent of isolates (46 isolates), isavuconazole isolates, and the MICs were 2 and 4 mg/liter, respectively. In conclusion, isavuconazole is highly active against *Candida* bloodstream isolates, including fluconazole-resistant strains. It was more active than itraconazole and voriconazole against *C. albicans* and *C. glabrata* and appears to be a promising agent against systemic *Candida* infections.
in 2003 and 2004, respectively. The species distribution is illustrated in Fig. 1. C. albicans was the most common species, with 56.1% of all isolates; followed by C. glabrata, accounting for 15.5% of isolates; C. tropicalis (8.4%); and C. parapsilosis (7.8%). These data are in agreement with previously reported findings (6, 7).

Table 1 summarizes the MIC distributions and in vitro susceptibilities of 296 bloodstream isolates of Candida spp. to isavuconazole in comparison to other azole antifungal agents, amphotericin B, and flucytosine. Isavuconazole showed good activity against all Candida spp., including those species that are inherently less susceptible to fluconazole (e.g., C. glabrata and C. krusei). Overall, on the basis of MIC_{90}, isavuconazole was as active as amphotericin B, itraconazole, and voriconazole (each at 0.5 mg/liter) and more active than flucytosine (2 mg/liter) and fluconazole (8 mg/liter). In terms of MIC_{50}, isavuconazole was more active (0.004 mg/liter) than amphotericin B (0.5 mg/liter), itraconazole (0.008 mg/liter), voriconazole (0.03 mg/liter), fluconazole (0.125 mg/liter), and fluconazole (8 mg/liter). For isavuconazole, MIC_{50}/MIC_{90} ranged from 0.002/0.004 mg/liter for C. albicans to 0.25/0.5 mg/liter for C. glabrata. Using tentative breakpoints, all isolates were susceptible to amphotericin B, whereas 92.6% of isolates were susceptible to flucytosine. Nonsusceptibility to flucytosine was noted for 0.6%
isolates. Limitations of our study include the fact that the number of isolates was small and represents only a single medical center. Larger studies are needed to confirm the potent activity of the drug against fluconazole-resistant strains.

In conclusion, isavuconazole exhibited good activity against 296 Candida bloodstream isolates obtained over a period of 10 years. Isavuconazole was more potent than fluconazole against all organisms tested and often more potent than itraconazole, voriconazole, amphotericin B, and fluconazol, confirming its potential as a useful agent for patients with serious systemic Candida infections.

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**REFERENCES**


