Candidemia occurs in up to 10% of the patients in intensive care units (ICU), leading to prolonged use of mechanical ventilation and duration of hospital stay (5, 7, 8, 14, 16). As the choice of antifungals for treating candidemia in critically ill patients depends on knowledge of the local epidemiology, this study reviews the susceptibility of ICU candidemia strains isolated from 1997 to 2007 and archived in the UOA/HCPF1 collection (World Data Centre of Microorganisms, WDCM929 [http://wdcm.nig.ac.jp/hpccl.html]).

A total of 135 baseline Candida species from patients with ICU-acquired candidemia were tested. Isolates were identified to the species level by morphological and biochemical analyses and, where necessary, by sequencing of the internal transcribed spacer region and/or the D1/D2 domain, as described previously (4, 11, 12). MICs of pure compounds were determined with the AFST-EUCAST reference procedure (22). We tested standard compounds of fluconazole (Pfizer, Sandwich, Kent, UK), amphotericin B (Sigma, St. Louis, MO), itraconazole (Janssen, Beerse, Belgium), and fluconazole (Sigma, St Louis, MO), voriconazole (Pfizer, Sandwich, Kent, United Kingdom), caspofungin (AS MedCare, Lexington, KY), and posaconazole (Schering Plough Research Institute, Kenilworth, NJ). Newer echinocandins, micafungin (Astellas Pharma Inc., Osaka, Japan) and anidulafungin (Pfizer, Groton, CT), were also tested. Quality control was performed for every testing occasion by using the designated quality control strains, C. krusei ATCC 6258 and C. parapsilosis ATCC 22019, which were within the MIC range given for the EUCAST-evaluated drugs (22). The quality control MIC range for anidulafungin was 0.25 to 0.5 μg/ml and 0.5 to 1 μg/ml for micafungin and caspofungin. For ATCC 22019, anidulafungin and micafungin MIC ranges were 0.5 to 2 μg/ml, and the MIC range for caspofungin was 2 to 4 μg/ml.

Inclusion of outbreak strains in this study may have constrained the accuracy of Candida species ranking order, but it revealed the predominant causes of point source ICU outbreaks of candidemia during the study period. In that respect, C. lusitaniae (1), C. krusei, and C. parapsilosis (data not shown) were causes of verified ICU outbreaks according to the related case definitions and descriptive and molecular epidemiology parameters. Therefore, a higher percentage (66.6%) of non-C. albicans isolates is reported than the 42% recorded for Europe in the SENTRY study (17). Despite C. parapsilosis being reported as the most frequent non-C. albicans ICU candidemia agent in Europe, geographical and possibly time-associated variations are highlighted in certain European studies in which C. glabrata is the second most frequently reported ICU candidemia agent (10, 13). Temporal variation was shown in a recent study in which, in 2002, C. parapsilosis reached 51% of the total isolation rates yet without reference to ICU outbreaks, while the absence of C. tropicalis was noted in the years 2000 to 2001 (3). Our study indicates that in the past 10 years, C. glabrata and C. tropicalis were always isolated at fluctuating isolation rates, whereas C. dubliniensis, known for its potential to acquire fluconazole resistance (2, 20), comprised 8.8% of the C. albicans isolates and was isolated only in the first 5 years of the study.

Our results show that drugs traditionally used in the ICU as standard treatments, such as fluconazole and amphotericin B, generally demonstrate low MICs, in agreement with previous observations (9, 19). However, high amphotericin B MICs were noted in two outbreak-unrelated C. krusei strains, the outbreak strain C. lusitaniae (MIC, 4 μg/ml) (Table 1), and 3/10 C. tropicalis strains (MIC, 2 μg/ml). Interestingly, high fluconazole MICs (32 μg/ml) were recorded for 6/45 C. albicans isolates (MIC, ≥64 μg/ml), compared with 3/19 C. krusei isolates, 2/18 C. lusitaniae isolates, 1/2 C. rugosa isolates, and a C. intermedia isolate. Besides C. glabrata and C. krusei resistance to fluconazole, only 4/18 outbreak-unrelated C. parapsilosis isolates demonstrated resistance (MIC, 32 μg/ml) (21). Nonetheless, fluconazole resistance associated with ICU fluconazole usage over the study period was not documented. Overall, posaconazole and voriconazole displayed potent antifungal activities against most ICU candidemia isolates. Yet, voriconazole resistance was identified in 8/19 C. krusei and 2/10 C. tropicalis isolates in accordance with their increased itracon-
azole MICs. Elevated posaconazole MICs were recorded for the same C. albicans, C. krusei, C. glabrata, and C. tropicalis strains, which displayed high itraconazole MICs and resistance to fluconazole and voriconazole, indicating azole cross-resistance.

Elevated echinocandin MICs were recorded for some C. parapsilosis, C. guilliermondii, and C. rugosa isolates, for a single C. kefyr isolate, and for some C. tropicalis isolates. The overall MICso for anidulafungin and caspofungin against the six most frequently found Candida isolates was 0.5 μg/ml and for micafungin was 0.03 μg/ml, whereas 92% of the 121 isolates frequently found (Table 1) were inhibited at anidulafungin and caspofungin MICs of ≤2 μg/ml, as recorded previously (6, 19). Overall, the MICso of echinocandins against C. parapsilosis (2 μg/ml) was conspicuously higher (18) than those recorded for the common Candida species, such as C. albicans (MIC range, 0.06 to 0.25 μg/ml), C. glabrata (MIC range, 0.12 to 1 μg/ml), and C. tropicalis (MIC range, 0.12 to 0.25 μg/ml).

The majority of Candida species demonstrated limited species-related and echinocandin-specific trailing and paradoxical (14) (Eagle) phenomena. With anidulafungin, C. albicans trailing was limited to 7/45 isolates. Paradoxical phenomena occurred in only 10/45 C. albicans isolates, 1/18 C. lusitaniae isolates, and 1/4 C. dubliniensis isolates, while these phenomena occurred with micafungin (15) in only 4/45 C. albicans and only 1/4 C. dubliniensis isolates.

Data for the relative isolation rates and the recognition of outbreak-associated Candida species, including isolate susceptibility to nine established and recently licensed antifungal agents from Greek ICU, are reviewed for the first time. Indigenous ICU isolate susceptibility trends show that decreased susceptibility to all antifungals has a sporadic distribution among all isolates.

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REFERENCES


7. Dimopoulos, G., F. Ntziora, G. Rachiotis, A. Armaganidis, and M. E. Fal-