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# *Candida rugosa*, an Emerging Fungal Pathogen with Resistance to Azoles: Geographic and Temporal Trends from the ARTEMIS DISK Antifungal Surveillance Program

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***Candida rugosa* is a fungus that appears to be emerging as a cause of infection in some geographic regions. We utilized the extensive database of the ARTEMIS DISK Antifungal Surveillance Program to describe the geographic and temporal trends in the isolation of *C. rugosa* from clinical specimens and the in vitro susceptibilities of 452 isolates to fluconazole and voriconazole. *C. rugosa* accounted for 0.4% of 134,715 isolates of *Candida*, and the frequency of isolation increased from 0.03% to 0.4% over the 6.5-year study period (1997 to 2003). *C. rugosa* was most common in the Latin American region (2.7% versus 0.1 to 0.4%). Decreased susceptibility to fluconazole (40.5% susceptible) was observed in all geographic regions; however, isolates from Europe and North America were much more susceptible (97 to 100%) to voriconazole than those from other geographic regions (55.8 to 58.8%). *C. rugosa* was most often isolated from blood and urine in patients hospitalized at the Medical and Surgical inpatient services. Notably, bloodstream isolates were the least susceptible to both fluconazole and voriconazole. *C. rugosa* should be considered, along with the established pathogens *Candida krusei* and *Candida glabrata*, as a species of *Candida* with reduced susceptibility to the azole antifungal agents.**

Although quite rare as a cause of invasive fungal infections (9), *Candida rugosa* has recently been cited as a possible "emerging" fungal pathogen (6). Fungemia due to this species of *Candida* was unrecognized prior to 1985, when catheter-related fungemia was reported in two different institutions in the United States (15, 21). Subsequently, Dube et al. (3) reported 15 episodes of candidemia due to *C. rugosa* in burn patients receiving topical nystatin treatment in a U.S. hospital. No obvious source of the infections was found; however, the isolates were shown to be resistant to nystatin and to have reduced susceptibility to both amphotericin B and fluconazole. More recently, a cluster of six episodes of candidemia caused by *C. rugosa* was reported in Brazil (2). Two of the episodes represented breakthrough infections in patients receiving amphotericin B treatment, and all four patients treated with this agent died. Follow-up surveillance revealed that *C. rugosa* was a frequent colonizer of high-risk patients and accounted for 44% of 32 consecutive episodes of fungemia at one Brazilian tertiary care center (17). Those reports suggest that *C. rugosa* may exhibit decreased susceptibility to both polyenes and fluconazole, may cause catheter-related fungemia in seriously ill patients, may be transmitted from patient to patient in the hospital setting, and may be endemic in certain institutions (6).

Aside from these few observations, there is a paucity of information regarding the epidemiology, frequency of occurrence, and antifungal susceptibility profile of this uncommon species of *Candida* (9). In the present study, we have taken advantage of the extensive database compiled by the ARTEMIS DISK Antifungal Surveillance Program (11) to describe the geographic and temporal trends in the isolation of *C. rugosa* from clinical specimens collected from 127 medical centers between 1997 and 2003, the types of specimens and clinical services in which *C. rugosa* infections are recognized, and the in vitro susceptibilities of 452 clinical isolates, including 74 bloodstream infection (BSI) isolates, of this species to both fluconazole and voriconazole as determined by standardized disk diffusion testing. This report will serve as the largest study of *C. rugosa* isolates to date.

## MATERIALS AND METHODS

**Organisms and test sites.** A total of 134,715 isolates of *Candida* spp. from 127 different medical centers in Asia (23 sites), Latin America (16 sites), Europe (74 sites), the Middle East (2 sites), and North America (12 sites) were isolated and identified between June 1997 and December 2003. All *Candida* spp. considered pathogens by the respective attending physicians from all body sites (e.g., blood, normally sterile body fluids, deep-tissue biopsy, genital tract, gastrointestinal tract, respiratory tract, skin, and soft tissue) and isolates from all in-hospital and outpatient locations during the study period were tested. Data for *C. rugosa* were stratified by year of isolation, geographic region, clinical service (hospital location), and specimen type. *Candida* spp. considered by the local-site investigator to be colonizers, that is, not associated with clinical infection, were excluded, as were duplicate isolates (the same species and the same susceptible-resistant biotype profile within any 7-day period). Identification of isolates was performed in accordance with each site's routine methods.

**Susceptibility test methods.** Disk diffusion testing of fluconazole and voriconazole was performed as described previously (10–12) and in accordance with Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS) document M44-A (5). Agar plates (150-mm diameter) containing Mueller-Hinton agar (obtained locally at all sites) supplemented with 2% glucose and 0.5 μg of methylene blue per ml at a depth of 4.0 mm were used. The agar surface was

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TABLE 1. Variation in the frequency of *Candida rugosa* by geographic region[a]

| Region | Total no. of *Candida* species isolates | Total no. (%) of *C. rugosa* isolates |
|---|---|---|
| Asia-Pacific | 17,183 | 83 (0.4) |
| Europe | 41,187 | 54 (0.1) |
| Latin America | 11,280 | 311 (2.7) |
| North America | 6,111 | 4 (0.1) |
| Total | 75,761 | 452 (0.6) |

[a] Data were obtained from the ARTEMIS DISK Global Antifungal Surveillance Program from 2001 to 2003. Isolates represent all incident isolates from all sites of infection.

inoculated by using a swab dipped in a cell suspension adjusted to the turbidity of a 0.5 McFarland standard. Fluconazole (25-μg) and voriconazole (1-μg) disks (Becton Dickinson, Sparks, Md.) were placed onto the surfaces of the plates, and the plates were incubated in air at 35 to 37°C and read at 18 to 24 h. Zone diameter endpoints were read at 80% growth inhibition by using the BIOMIC image analysis plate reader system (version 5.9; Giles Scientific, Santa Barbara, Calif.) (4, 10–12).

The interpretive criteria for the fluconazole and voriconazole disk diffusion tests were those of the CLSI (5, 13, 14) and are as follows: susceptible (S), zone diameters of ≥19 mm (fluconazole) and ≥17 mm (voriconazole); susceptible-dose dependent (SDD), zone diameters of 15 to 18 mm (fluconazole) and 14 to 16 mm (voriconazole); and resistant (R), zone diameters of ≤14 mm (fluconazole) and ≤13 mm (voriconazole). The corresponding MIC breakpoints (5, 13, 14) are as follows: S, MIC of ≤8 μg/ml (fluconazole) and ≤1 μg/ml (voriconazole); SDD, MIC of 16 to 32 μg/ml (fluconazole) and 2 μg/ml (voriconazole); R, MIC of ≥64 μg/ml (fluconazole) and ≥4 μg/ml (voriconazole).

**QC.** Quality control (QC) was performed in accordance with CLSI document M44-A (5) by using *Candida albicans* ATCC 90029 and *Candida parapsilosis* ATCC 22019. A total of 5,865 and 5,484 QC results were obtained for fluconazole and voriconazole, respectively, more than 99% of which were within the acceptable limits. External quality assurance was performed by testing more than 2,900 isolates from blood and normally sterile-site infections against both fluconazole and voriconazole by ARTEMIS participating laboratories and by the central reference laboratory (10, 12). Excellent agreement was seen between participating and reference laboratories, ensuring the accuracy of the ARTEMIS data.

**Analysis of results.** All disk zone diameters were read by electronic image analysis and interpreted and recorded with a BIOMIC Plate Reader system (Giles Scientific). Test results were sent by e-mail to Giles Scientific for analysis. The zone diameter susceptibility categories (S, SDD, or R) and QC test results were all recorded electronically. Patient and doctor names, duplicate test results (the same patient, the same species, and same biotype result), and uncontrolled results were automatically eliminated by the BIOMIC system prior to analysis.

## RESULTS

**Isolation of *C. rugosa* over time and by geographic region.** A total of 134,715 isolates of *Candida* spp. were isolated and identified at 127 study sites between June 1997 and December 2003 (11). *C. rugosa* ranked ninth among more than 16 species of *Candida*, accounting for approximately 0.4% of all isolates (11). The frequency of isolation of *C. rugosa* increased by more than 10-fold over the course of the study (0.03% to 0.4%) (11).

Data for the various sites contributing isolate results to the study were available for the time period of 2001 through 2003 (Table 1). *C. rugosa* represented 0.6% of the 75,761 isolates collected during this time period and was most common in the Latin American region (Table 1).

**Geographic variation in susceptibility of *C. rugosa* to fluconazole and voriconazole.** Table 2 presents the in vitro susceptibilities of *C. rugosa* to fluconazole and voriconazole, stratified by geographic region of origin, as determined by CLSI disk diffusion testing. These isolates were obtained from 115 institutions in 35 countries. Overall, it is evident that *C. rugosa* exhibits decreased susceptibility to both fluconazole and voriconazole, with only 40.5% and 61.4% of isolates, respectively, showing susceptibility to these two triazole antifungal agents. Susceptibilities to fluconazole were lowest (<40%) in the Asia-Pacific (34.9%) and Latin American (35.7%) regions and highest in Europe (75.9%).

TABLE 2. Geographic variation in susceptibilities of *Candida rugosa* to fluconazole and voriconazole

| Region | Antifungal agent | No. of isolates tested | % of isolates[a] | | |
|---|---|---|---|---|---|
| | | | S | SDD | R |
| Asia-Pacific | Fluconazole | 83 | 34.9 | 8.4 | 56.7 |
| | Voriconazole | 34 | 58.8 | 23.5 | 17.7 |
| Europe | Fluconazole | 54 | 75.9 | 13.0 | 11.1 |
| | Voriconazole | 46 | 97.8 | | 2.2 |
| Latin America | Fluconazole | 311 | 35.7 | 8.4 | 55.9 |
| | Voriconazole | 310 | 55.8 | 12.9 | 31.3 |
| North America | Fluconazole | 4 | 50.0 | 25.0 | 25.0 |
| | Voriconazole | 4 | 100.0 | | |
| Total | Fluconazole | 452 | 40.5 | 9.1 | 50.4 |
| | Voriconazole | 394 | 61.4 | 12.2 | 26.4 |

[a] All isolates were tested by disk diffusion performed in accordance with CLSI standard M44-A. S, susceptible, with zone diameters of ≥19 mm for fluconazole and ≥17 mm for voriconazole; R, resistant, with zone diameters of ≤14 mm for fluconazole and ≤13 mm for voriconazole; SDD, susceptible-dose dependent, with zone diameters of 15 to 18 mm for fluconazole and 14 to 16 mm for voriconazole.

Although voriconazole was always more active against *C. rugosa* than fluconazole, irrespective of geographic region, the lowest susceptibilities to this agent (55.8 to 58.8%) were also observed in the regions with the lowest susceptibilities to fluconazole (Table 2). In contrast, 97% to 100% of *C. rugosa* isolates from Europe (97.6%) and North America (100%) were susceptible to voriconazole. These extremes in voriconazole susceptibility among isolates of *C. rugosa* are important to recognize, especially given previous suggestions (based on very limited data) that this species was highly susceptible to voriconazole (6, 9).

**Trends in resistance to fluconazole and voriconazole among *C. rugosa* isolates over time.** Although resistance to fluconazole among isolates of *C. rugosa* tested in 2001 was already quite high (31.7%) (Table 3), more resistance was observed in 2002 and 2003, where 66.0% and 61.2% of isolates, respectively,

TABLE 3. Trends in in vitro resistance to fluconazole and voriconazole among *C. rugosa* isolates as determined by CLSI disk diffusion testing over time[a]

| Antifungal agent | Resistance during yr[b]: | | | | | |
|---|---|---|---|---|---|---|
| | 2001 | | 2002 | | 2003 | |
| | No. of isolates | %R | No. of isolates | %R | No. of isolates | %R |
| Fluconazole | 186 | 31.7 | 150 | 66.0 | 116 | 61.2 |
| Voriconazole | 129 | 3.1 | 149 | 38.0 | 116 | 38.0 |

[a] Data were obtained from the ARTEMIS DISK Surveillance Program, 2001 to 2003.

[b] Zone (≤14 mm [fluconazole] or ≤13 mm [voriconazole]) disk diffusion testing was performed in accordance with CLSI standard M44-A.

TABLE 4. Susceptibility of *Candida rugosa* to fluconazole and voriconazole by clinical service

| Clinical service (total no. of isolates)[a] | Antifungal agent | No. of isolates tested (%)[b] | % of isolates from service[c] | % of isolates | | |
|---|---|---|---|---|---|---|
| | | | | S | SDD | R |
| Hematology-oncology (4,635) | Fluconazole | 14 (3.1) | 0.3 | 71.4 | 21.4 | 7.1 |
| | Voriconazole | 11 (2.8) | | 90.0 | | 9.1 |
| Medical (17,408) | Fluconazole | 179 (39.6) | 1.0 | 31.8 | 3.9 | 64.2 |
| | Voriconazole | 158 (40.1) | | 44.9 | 19.0 | 36.1 |
| Surgical (5,126) | Fluconazole | 145 (32.1) | 2.8 | 40.0 | 9.7 | 50.3 |
| | Voriconazole | 140 (35.5) | | 67.1 | 10.0 | 22.9 |
| ICU (10,052) | Fluconazole | 24 (5.3) | 0.2 | 41.7 | 12.5 | 45.8 |
| | Voriconazole | 10 (2.5) | | 80.0 | 10.0 | 10.0 |
| Outpatient (6,414) | Fluconazole | 17 (3.8) | 0.3 | 70.6 | 17.6 | 11.8 |
| | Voriconazole | 17 (4.3) | | 88.2 | 5.9 | 5.9 |
| Other, NOS (32,136) | Fluconazole | 73 (16.1) | 0.2 | 49.3 | 15.1 | 36.6 |
| | Voriconazole | 58 (14.8) | | 75.9 | 3.4 | 20.7 |

[a] Total number of *Candida* isolates from each service.
[b] Percentage of all *C. rugosa* isolates tested.
[c] *C. rugosa* as a percentage of all isolates from that clinical service.

were resistant to fluconazole. Likewise, resistance to voriconazole was low in 2001 (3.1%) and was 10-fold higher (38.0%) in both 2002 and 2003.

**Variation in the frequency of isolation and antifungal susceptibility profile of *C. rugosa* by clinical service.** The clinical services reporting the isolation of *C. rugosa* from patient specimens included the hematology-oncology service, the medical and surgical services, intensive care units (ICUs) (medical, surgical, and neonatal), and the outpatient service (Table 4). Those isolates from services with only a few isolates and those for which a clinical service was not specified were included in the category "other, not otherwise specified" (NOS).

*C. rugosa* was isolated most frequently from hospitalized patients from the medical and surgical services and was less common from the hematology-oncology, ICU, and outpatient services. Likewise, isolates from the medical and surgical services were the least susceptible to both fluconazole (31.8% and 40.0%, respectively) and voriconazole (44.9% and 67.1%, respectively), whereas the isolates that were the most susceptible to both agents were seen in the hematology-oncology and outpatient services (Table 4).

**Variation in the frequency of isolation and antifungal susceptibility profile of *C. rugosa* by clinical specimen type.** The major specimen types yielding *C. rugosa* as a putative pathogen included blood, urine, respiratory, skin, soft tissue, and genital specimens (Table 5). Those isolates from uncommon specimen types and those for which a specimen type was not recorded were grouped under "miscellaneous (Misc.), NOS."

Aside from the Misc., NOS category, more *C. rugosa* isolates were found in blood and urine specimens than in respiratory, skin, soft tissue, and genital specimens (Table 5). Thus, *C. rugosa* most often causes infection in sites common to other *Candida* spp. Importantly, isolates of *C. rugosa* from blood were considerably less susceptible to both fluconazole (28.4%) and voriconazole (35.6%) than those from any other specimen type (Table 5).

## DISCUSSION

The results from this large study of *C. rugosa* both confirm previous observations regarding this species and refute others (6, 9). First of all, it does appear, as suggested previously by

TABLE 5. Susceptibility of *Candida rugosa* to fluconazole and voriconazole by specimen type

| Specimen type/site (total no. of isolates)[a] | Antifungal agent | No. of isolates tested (%)[b] | % of isolates from site[c] | % of isolates | | |
|---|---|---|---|---|---|---|
| | | | | S | SDD | R |
| Blood (8,256) | Fluconazole | 74 (16.4) | 0.9 | 28.4 | 6.8 | 64.9 |
| | Voriconazole | 59 (15.0) | | 35.6 | 20.3 | 44.1 |
| Urine (9,722) | Fluconazole | 99 (21.9) | 1.0 | 39.4 | 6.1 | 54.5 |
| | Voriconazole | 83 (21.1) | | 61.4 | 15.7 | 22.9 |
| Respiratory (20,274) | Fluconazole | 41 (9.1) | 0.2 | 46.3 | 12.2 | 41.5 |
| | Voriconazole | 36 (9.1) | | 63.9 | 2.8 | 33.3 |
| Skin/soft tissue (4,986) | Fluconazole | 23 (5.1) | 0.5 | 47.8 | 13.0 | 39.1 |
| | Voriconazole | 21 (5.3) | | 66.7 | 9.5 | 23.8 |
| Genital (15,831) | Fluconazole | 20 (4.4) | 0.1 | 75.0 | 10.0 | 15.0 |
| | Voriconazole | 12 (3.0) | | 100.0 | | |
| Misc., NOS (16,692) | Fluconazole | 195 (43.1) | 1.2 | 40.0 | 10.3 | 49.7 |
| | Voriconazole | 183 (46.5) | | 66.1 | 10.9 | 23.0 |

[a] Total number of *Candida* isolates from each specimen type.
[b] Percentage of all *C. rugosa* isolates tested.
[c] *C. rugosa* as a percentage of all isolates of that specimen type.

Colombo et al. (2) and Nucci and Marr (6), that the frequency of *C. rugosa* as a cause of candidal infections is increasing and that these infections are especially common in Latin America (Table 1). Although the apparent "emergence" of *C. rugosa* may simply reflect an increasing tendency for clinical laboratories to identify isolates of *Candida* species, one cannot discount the possibility that given the increased numbers of immunocompromised individuals worldwide, an ever-increasing number of previously rare species, such as *C. rugosa*, are truly emerging as opportunistic pathogens (6, 9). Furthermore, *C. rugosa* does appear to exhibit decreased susceptibility to fluconazole, and this pattern varies by geographic region (Table 2). Decreased susceptibility to both polyenes and fluconazole has been noted previously (1–3, 9), even though data were based on the testing of relatively few isolates.

Previously reported data regarding the susceptibility of *C. rugosa* to voriconazole suggested that this agent was very active against this species (6, 7, 9). Again, this conclusion was based on the testing of very small numbers of isolates obtained primarily from North America and Europe. The data presented herein indicate that *C. rugosa* should be considered to have decreased susceptibility to voriconazole as well as fluconazole (Table 2). This pattern of decreased susceptibility was most prominent in the Asia-Pacific and Latin American regions (Table 2). Voriconazole appeared to be considerably more active against *C. rugosa* isolates from Europe and North America. The reasons for these geographic differences in azole susceptibility are not known; however, the most conservative approach to dealing with infections caused by *C. rugosa* would be to assume decreased susceptibility (e.g., resistance) until proven otherwise by standardized antifungal susceptibility testing (16). Very few isolates of *C. rugosa* have been tested against the echinocandins (7, 9). The few isolates that have been tested all appear to be susceptible to these agents at clinically achievable concentrations (i.e., $<2$ μg/ml).

In addition to the apparent emergence of *C. rugosa* as a cause of clinical infection, there also seems to be a trend towards the emergence of resistance to fluconazole and voriconazole over time (Table 3) (11). Resistance to fluconazole increased from a baseline rate of ~30% to more than 60% over the course of the study (Table 3). Similarly, resistance to voriconazole increased from 3.1% in 2001 to 38.0% in 2002 and 2003 (Table 3). These parallel increases in resistance provide further support for a strong degree of cross-resistance among the azole class of antifungals. Although little is known about resistance mechanisms specific to *C. rugosa*, mechanisms described for other *Candida* species include the alteration of the 14-α-demethylase target (19) along with the induction of efflux pump mechanisms (18, 22).

As suggested previously by Colombo et al. (2) and by Rosas et al. (17), infections due to *C. rugosa* were most common among patients hospitalized in the medical and surgical services of the participating hospitals (Table 4). Likewise, resistance to both fluconazole and voriconazole was highest among isolates from these two services. Interestingly, the most susceptible isolates to both agents were found in the hematology and oncology services, where one might expect azole drug pressure to be greatest. Thus, the in vitro susceptibility of this species to the azole antifungals is not entirely predictable, suggesting that, as with *C. glabrata* (9), antifungal susceptibility testing may play a useful role in optimizing the antifungal therapy for this organism (8, 20).

Finally, it is important that *C. rugosa* is most often detected in bloodstream and urinary tract infections (Table 5). Furthermore, the isolates obtained from blood cultures demonstrated the highest level of resistance to both agents. This finding reinforces previously published opinions regarding the importance of identifying isolates of *Candida* obtained from blood and normally sterile-site infections to the species level (8, 9, 16, 20). It should be noted that although isolates of *C. rugosa* from blood are clearly pathogenic, the isolation of this or any other species of *Candida* from nonsterile sites (e.g., urine, respiratory, and genital specimens) may simply represent colonization rather than infection. We have included isolates of *C. rugosa* from sites other than blood based on the clinical assessment of the local-site investigators that the isolate was associated with clinical pathology in the respective patient.

In summary, we have used the extensive and validated database of the ARTEMIS DISK Antifungal Surveillance Program (11) to address several gaps in our knowledge of *C. rugosa* as an opportunistic pathogen. Our findings suggest that not only is this species emerging as an agent of invasive fungal infection, it also appears to be developing increased resistance to azole antifungal agents, especially in certain geographic regions. *C. rugosa* appears to fill the same clinical niche as other more common species of *Candida* in that it most often causes BSI and urinary tract infections in patients hospitalized in the medical and surgical inpatient services. Notably, BSI isolates of this species are the least susceptible to both fluconazole and voriconazole. Thus, *C. rugosa* joins the established pathogens *C. glabrata* and *C. krusei* as a species of *Candida* with reduced susceptibility to the azole antifungal agents. These data provide significant new information regarding a relatively uncommon cause of opportunistic fungal infection and underscore the value of longitudinal global surveillance studies such as ARTEMIS.

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