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Clinical Correlates of Antifungal Macrodilution Susceptibility Test Results for Non-AIDS Patients with Severe *Candida* Infections Treated with Fluconazole

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Although the clinical correlates of the reference antifungal susceptibility test results in hematogenous and deep-seated *Candida* infection are still controversial, we evaluated the clinical correlates of this test in deep-seated *Candida* infections in non-AIDS patients. Thirty-two non-AIDS patients with hematogenous or deep-seated *Candida* infections were treated with intravenous fluconazole (400 mg a day), and the clinical outcomes were evaluated. Coexisting bacterial infections were treated with appropriate antibiotics, superinfection or reinfection was excluded, inadequate fluconazole therapy was avoided, and essential surgical intervention was performed. The MICs of fluconazole for these 32 *Candida* isolates were determined according to the M27-A procedure approved by the National Committee on Clinical Laboratory Standards. MICs were interpreted as susceptible (≤8 μg/ml), dose-dependent susceptible (16 to 32 μg/ml), and resistant (≥64 μg/ml) according to the criteria of the M27-A standard. The success rates were 79% (19 of 24; 95% confidence interval [CI], 59 to 93%) in the susceptible category, 66% (4 of 6; 95% CI, 19 to 95%) in the dose-dependent susceptible category, and 0% (0 of 2; 95% CI, 0 to 84%) in the resistant category. We conclude that the clinical correlation of the reference antifungal susceptibility test results is high in hematogenous and deep-seated *Candida* infections.

Although the macrodilution antifungal susceptibility test M27-A was recently approved by the National Committee on Clinical Laboratory Standards (NCCLS), good correlations between the clinical response and MICs were reported only in oropharyngeal *Candida* infections in AIDS patients (5, 6, 12, 14–17, 22, 23). The clinical correlates of MICs in hematogenous and deep-seated *Candida* infections are still controversial, according to recent studies (18, 19). Because severe *Candida* infections usually occur in immunodeficient or debilitated patients and coexisting severe bacterial infections are common in these patients, evaluation of the clinical response to antifungal agents is complicated (1, 3, 7). We evaluated 32 non-AIDS patients with severe *Candida* infections treated with fluconazole according to the criteria of prior studies and correlated the clinical outcomes with the fluconazole susceptibility test results for these 32 *Candida* isolates according to M27-A methods.

MATERIALS AND METHODS

Patient enrollment. All patients with severe *Candida* infections who consulted the Infectious Disease Department of Chang Gung Memorial Hospital, Keelung, Taiwan, between January 1998 and December 1998 were treated with fluconazole and analyzed. Severe *Candida* infections included candidemia, peritonitis, pyelonephritis, pyothorax, pneumonia, and infective endocarditis. Diagnosis of these infections was made according to the criteria set by the Centers for Disease Control (9). The *Candida* isolates were stored for fluconazole susceptibility study.

Treatment regime. In patients with serum creatinine levels below 3 mg/dl, 200 mg of fluconazole was administered intravenously twice daily for 1 to 4 weeks, depending on the clinical response (10). In patients with serum creatinine levels above 3 mg/dl, 200 mg of fluconazole was administered intravenously once daily (10). In uremic patients with peritonitis due to chronic ambulatory peritoneal dialysis and without candidemia, 256 mg of fluconazole in 2,000 ml of dialysate was given intraperitoneally four times a day for 2 to 3 weeks (10). Coexisting bacterial infections were treated with appropriate antibiotics according to antimicrobial susceptibility (3). Surgery was done if necessary in order to eradicate the infection if the patient agreed.

Evaluation criteria. Follow-up evaluations were performed every day after the start of treatment. Standard clinical laboratory evaluations (blood chemistry, urinalysis, complete blood count, blood bacterial and fungal culture, and chest roentgenogram) were performed before, during, and after treatment as medically indicated. Interpretation of the clinical and microbiological responses was done according to the following criteria. Clinical cure was indicated by resolution of clinical signs and symptoms of infection due to the original *Candida* species without signs of relapse of infection caused by the original *Candida* species within 3 months after fluconazole was discontinued and repeated posttherapy culture became negative for the original *Candida* species (19). Any coexisting bacterial infection was treated with appropriate antibiotics. Superinfection or reinfection due to *Candida* species different from the original *Candida* species were excluded prior to evaluation. Inadequate duration of therapy with fluconazole was avoided. Surgical intervention essential to the eradication of infection was performed before evaluation. Clinical failure was indicated by an absence of clinical response to fluconazole therapy after at least 1 week of therapy, with persistence of positive culture or development of unacceptable drug toxicity (19).

In vitro susceptibility test. MICs were determined and interpreted for the 32 *Candida* isolates causing 32 severe *Candida* infections according to the procedure of the approved macrodilution reference method of antifungal susceptibility testing (M27-A) of the NCCLS (8, 20). Both 24- and 48-h MICs were determined. The control strains *Candida albicans* ATCC 90028 and *Candida krusei* ATCC 6258 were used in all tests (8). Briefly, *Candida* isolates at a final concentration of 0.5×10^3 to 2.5×10^3 cells per ml were incubated in air at 35°C for 48 h with twofold dilutions from 0.125 to 128 μg/ml. The MIC was defined as the concentration of drug that produced 80% reduction of turbidity by comparison to the drug-free control. RPM1 1640 buffered to pH 7.0 with 0.165 M MOPS (morpholinepropanesulfonic acid) was used (8).

RESULTS

The mean age of the 32 patients was 60.8 years (range, 16 to 85 years), with 21 men and 11 women. The most frequent underlying disease was malignancy (13 patients). Other underlying diseases included neutropenia (two patients), end-stage

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TABLE 1. Basic clinical data for severe *Candida* infections with fluconazole therapy[a]

Parameter	No. (%) of patients	Mean duration (range) of therapy (days)	No. (%) cured
Total	32		
Sex ratio (male/female)	21/11		
Site of *Candida* infection (source of isolation)			
Candidemia (blood)	21	15.3 (7–28)	15 (71.4)
Peritonitis, non-CAPD (ascites fluid)	1	14	1 (100)
Peritonitis, CAPD (peritoneal dialysate)	3	19 (15–25)	2 (66.6)
Pyelonephritis (nephrostomy and catheterized urine)	4	11.5 (8–14)	4 (100)
Pyothorax (pleural effusion)	1	10	1 (100)
Pneumonia (bronchoalveolar lavage fluid [bacterial count, $>10^3$/ml])	1	14	1 (100)
Definite infective endocarditis (blood)	1	16	0 (0)
Coexisting bacterial infections			
Severe pneumonia and respiratory failure	11		
Pneumonia without respiratory failure	5		
Septicemia	4		
Peritonitis	5		
Biliary tract infection	3		
Pyelonephritis	3		
Soft tissue infection	1		
Pyothorax	1		
Liver abscess	1		
Total with coexisting bacterial infections	24 (75)		

[a] Age of patients (mean ± standard deviation), 60.8 ± 16.28 years; range, 16 to 85 years.

renal disease (five patients), obstructive uropathy with nephrostomy (two patients), common bile duct stones and choledocholithotomy (three patients), perforated peptic ulcer and peritonitis (one patient), necrotizing and posttraumatic pancreatitis (three patients), diabetes mellitus and neurogenic bladder (five patients), cerebrovascular disease (two patients), motor neuron disease (one patient), hypovolemic shock (one patient), and benign prostate hypertrophy after transurethral resection (one patient). There were no rapidly fatal underlying diseases according to McCabe and Jackson's definition (13). Twenty-one patients had candidemia, one had postoperative peritonitis, three had peritonitis due to chronic ambulatory peritoneal dialysis (CAPD), four had pyelonephritis, one had pneumonia, one had pyothorax, and one had infective endocarditis (Table 1). In the case of *Candida* pneumonia, the patient had lung carcinoma and did not respond to broad-spectrum antimicrobial therapy. Culture of purulent bronchoalveolar lavage fluid produced only *C. albicans*, with colony counts of $>10^3$/ml. Twenty-four patients had coexisting severe bacterial infections, and pneumonia was the most common. Gram-negative bacilli were the most frequent pathogens in the coexisting bacterial infections, including 13 nonfermentative gram-negative bacillus isolates, 11 enteric bacilli, 1 *Stenotrophomonas maltophilia* isolate, 1 *Haemophilus influenzae* isolate, 5 *Staphylococcus aureus* isolates, 2 *Staphylococcus epidermidis* isolates, 7 *Enterococcus faecalis* isolates, 1 group B *Streptococcus* isolate, 1 *Gardnerella vaginalis* isolate, 1 *Bacteroides fragilis* isolate, and 1 atypical mycobacterium.

The duration range of fluconazole therapy was 7 to 28 days, with a mean of 15.3 days. A clinical response to fluconazole was obtained within 7 days of the start of therapy in 25 of 32 patients (78.1%), of whom 23 showed complete clearance and 2 had signs of relapse of clinical infection. Two candidemic patients had no clinical response to fluconazole after 7 days of therapy, with persistence of candidemia. In 4 of the 32 patients, coexisting severe bacterial infections due to multiresistant gram-negative bacilli were not controlled by appropriate antimicrobial therapy, and the patients died during fluconazole therapy. In one patient with infective endocarditis, which was confirmed by vegetations on a cardiac echogram, and persistent candidemia, surgical intervention was recommended, but the patient and her family refused. The patient died during fluconazole therapy. A case of pyelonephritis due to *C. albicans* in a patient with obstructive uropathy and nephrostomy was treated with 2 weeks of fluconazole therapy. Fever and pyuria subsided after fluconazole therapy. However, 3 days after fluconazole was stopped, mild fever developed again. Both blood culture and urine culture from nephrostomy were repeated, and both produced *Candida tropicalis*.

Of the 32 clinically significant *Candida* isolates, 17 were *C. albicans* and 15 were non-*albicans* (see Table 3). The 24-h MIC results (range, 0.125 to 64 μg/ml; geometric mean, 4.81 μg/ml) were calculated to be three to four times lower than the 48-h MICs by the macrodilution method. Because the correlation between 48-h MIC results and clinical-response results was significantly superior to that of the 24-h MIC results when NCCLS breakpoints of susceptibility were utilized according to the methods of prior studies (5, 6, 12, 14–17, 22, 23), 48-h MICs obtained by a macrodilution method may be adequate predictors of clinical outcome (Table 2). The 48-h MICs of these 32 isolates are shown in Table 3. *C. albicans* showed a wide range of MICs, from 0.25 to >64 μg/ml, with a geometric mean of 10.1 μg/ml. The MIC results of the reference strains ATCC 90028 and ATCC 6258 were all within the standard acceptable range of MICs. The MICs of 24 isolates in 24 cases were ≤8 μg/ml, and 19 of these cases were cured clinically. The clinical success rate was 19 of 24 (79%; 95% confidence interval [CI], 56 to 93%) for susceptible isolates interpreted according to the criteria of NCCLS standard M27-A (Table 2). The MICs of another six isolates from six patients were 16 to 32

TABLE 2. In vitro and in vivo correlation for fluconazole in severe *Candida* infections

Outcome	No. of cases			
	Susceptible[a]	Dose-dependent susceptible[b]	Resistant[c]	Total
Clinical cure	19	4	0	23
Clinical failure	5	2	2	9
Total	24	6	2	32

[a] Fluconazole 48-h MIC, ≤8 μg/ml (candidemia [14] success/failure, 11/3; peritonitis [4], 3/1; pyelonephritis [3], 3/0; pyothorax [1], 1/0; pneumonia [1], 1/0; infective endocarditis [1], 0/1).
[b] Fluconazole 48-h MIC, 16 to 32 μg/ml (candidemia [5] success/failure, 3/2; pyelonephritis [1], 1/0).
[c] Fluconazole 48-h MIC, ≥64 μg/ml (candidemia [2] success/failure, 0/2).

μg/ml, and four of these cases were cured clinically. The clinical success rate was four of six (66%; 95% CI, 19 to 95%) for dose-dependent isolates. The MICs in the remaining two nonneutropenic evaluable cases were ≥64 μg/ml. The patients with these two candidemia cases, one due to *C. albicans* and one due to *Candida guilliermondii*, had underlying esophageal carcinoma after chemotherapy and radiotherapy and were not neutropenic and they failed to respond clinically. The success rate in this category was zero of two (0%; 95% CI, 0 to 84%) for resistant isolates (Table 2). In clinically cured patients, the range of 24-h MICs were 0.125 to 2.0 μg/ml, with a mean of 0.94 μg/ml. In cases of clinical failure, the range of 24-h MICs was 0.15 to 64 μg/ml, with a mean of 14.72 μg/ml.

DISCUSSION

In nine studies of oropharyngeal candidiasis in patients with AIDS, clinical correlation of the results of the NCCLS antifungal susceptibility test M27-A was high, ranging from 73 to 98% (5, 6, 13, 14–17, 22, 23). However, MIC data in deep-seated or hematogenous *Candida* infection is still infrequently reported (12, 15), except in animal studies (2, 4, 11, 21). Rex et al. recently reported an inverse correlation of MICs in patients with nonneutropenic candidemia, which is inconsistent with prior studies (18, 19). However, a majority of our cases of candidemia and deep-seated *Candida* infections in non-AIDS patients did not reveal inverse clinical correlation of MICs obtained by the same method. In the Rex study, 36 (from 19 patients) of the 100 isolates from 64 fully evaluable fluconazole-treated patients for which the fluconazole MICs were ≤16 μg/ml were associated with failure (18, 19). Four isolates for which the fluconazole MICs were ≥32 μg/ml were obtained from four patients who responded to initial fluconazole therapy (18, 19). The inverse clinical correlation of MICs in the Rex report may be due to some pitfalls in evaluation. Clinical failure in cases with MICs of ≤16 μg/ml may be due to failure to control coexisting bacterial infections, which are common and which are often not discovered in immunocompromised or debilitated patients with candidemia. Seventy-five percent of our patients had severe coexisting bacterial infections. Coexisting bacterial infections should be controlled with appropriate antibiotics before or during fluconazole therapy. In four of our patients, coexisting severe bacterial infections due to multiresistant gram-negative bacilli were not controlled by appropriate antibiotics, and the patients died during fluconazole therapy. These four cases were evaluated as clinical failures according to the criteria of prior studies. An inadequate duration of fluconazole therapy might also result in clinical failure, even with MICs of ≤16 μg/ml. Two weeks of fluconazole therapy for candidemia might not be adequate, even with MICs in the susceptible range, if the candidemia arises from peritonitis or intraperitoneal abscess secondary to intestinal perforation. Of the 21 patients with candidemia in our study, 2 had MICs of ≤8 μg/ml which arose from peritonitis and intraperitoneal abscess due to intestinal perforation. After 2 weeks of fluconazole therapy and appropriate antibiotics for coexisting mixed bacterial infections, fever subsided, repeated blood cultures became negative, and intraperitoneal abscess size diminished. Repeated cultures of peritoneal discharge from the intra-abdominal abscesses were still positive for the same *Candida* species. Thus, we believed this was due to inadequate fluconazole therapy and continued fluconazole for about two more weeks combined with appropriate antibiotics. Repeated cultures of discharge drained from the abscess site after another 2 weeks of fluconazole therapy became negative for *Candida* species. Repeated computerized tomograms of the abdomen later revealed complete resolution of the intraperitoneal abscesses. Two to 4 weeks of fluconazole therapy, depending on the origin of the candidemia, would be more reasonable for candidemia and would result in good correlation with the MICs.

Superinfection or reinfection by *Candida* species other than the initial *Candida* species is different from clinical failure for the initial *Candida* infection. In our study, we had a case of pyelonephritis due to *C. albicans* in a patient with obstructive uropathy and nephrostomy that was treated with 2 weeks of fluconazole therapy, and the patient developed reinfection due to *C. tropicalis* 3 days after fluconazole was stopped. This case should be considered a clinical cure for the original infection due to *C. albicans*, although it was complicated by reinfection by *C. tropicalis*.

Candidemia due to susceptible *Candida* isolates can be com-

TABLE 3. Mycological data and susceptibility to fluconazole

Candida species (no. of cases)	24-h MIC[b]		48-h MIC[b]		
	Range (μg/ml)	Geometric mean (μg/ml)	Range (μg/ml)	Geometric mean (μg/ml)	No. (%) of clinical cures
C. albicans (16)	0.25–64	4.84	0.25–>64	10.10	11 (68.7)
C. glabrata (5)	0.125–2.0	0.92	0.125–16	6.72	4 (80)
C. parasilosis (4)	0.125–1.0	0.4	0.125–2.0	0.9	4 (100)
C. guilliermondii (4)	0.125–64	17.03	1.0–>64	42.25	3 (75)
C. tropicalis (1)	0.125	0.125	0.125	0.12	1 (100)
C. intermedia (1)	2.0	2.0	16	16	0 (0)
C. famata (1)	0.125	0.125	16	16	0 (0)

[a] Reference strains, *C. albicans* ATCC 90028 (MIC = 0.25 to 1.0 μg/ml) and *C. krusei* ATCC 6258 (MIC = 16 to 64 μg/ml).
[b] MIC determined by macrodilution according to NCCLS standard M27A.

plicated with infective endocarditis requiring surgical intervention, but it may not be detected before death. In our study, we had a patient with peritonitis due to intestinal perforation with candidemia due to *Candida glabrata* secondary to central venous catheter infection. The catheter was removed, and the fever subsided before the culture result was known, and an antifungal agent was not given. However, 4 weeks later, fever and candidemia recurred due to infection by *C. glabrata* with a fluconazole MIC of ≤0.125 μg/ml. Candidemia persisted, and a cardiac echogram revealed prominent vegetations diagnostic of infective endocarditis. Intravenous fluconazole was given, and surgical intervention was recommended. However, the patient and her family refused surgery. The patient finally died during fluconazole therapy. This case was regarded as clinical failure according to the criteria of a prior study (19).

Although the incidence of coexisting bacterial infections is high in severe *Candida* infections, coexisting bacterial infection should not exclude clinical evaluation of antifungal agents, because increasingly potent antibiotics have become available in recent years which can control many severe bacterial infections. The clinical correlation of dose-dependent sensitive MICs of 16 to 32 μg/ml in our study was four of six (66.6%). In one case of *Candida famata* candidemia with a dose-dependent sensitive MIC (16 μg/ml), fever subsided after 3 days of parenteral fluconazole therapy, and 400 mg of fluconazole a day was given for a total of 20 days. However, 10 days later fever recurred, and the blood culture remained positive for *C. famata*. Thus, this case was evaluated as clinical failure according to the criteria of a prior study (19).

Of the 32 cases, two isolates from two nonneutropenic cases with MICs of ≥64 μg/ml failed to respond clinically and microbiologically. The clinical success rate of resistant isolates with MICs of ≥64 μg/ml was zero of two (0%; 95% CI, 0 to 84%). Although there was a lack of high-MIC isolates, the results were consistent and supportive of the NCCLS interpretive breakpoints. In summary, our data suggest that the 48-h MICs obtained by the macrodilution reference method of the NCCLS correlate well with the clinical response in candidemia and deep-seated *Candida* infections treated with 400 mg of fluconazole per day.

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