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MINIREVIEW

Susceptibility Testing of Fungi: Current Status of Correlation of In Vitro Data with Clinical Outcome

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INTRODUCTION

The recent explosion in the rates of opportunistic fungal infections (2, 5), combined with the increasing number of reports of resistance to all of the available antifungal agents (38, 45, 83, 94), has propelled interest in clinically relevant methods for antifungal susceptibility testing. In 1983, the National Committee for Clinical Laboratory Standards (NCCLS) responded by establishing a subcommittee to develop standardized antifungal susceptibility testing procedures. Initial studies demonstrated that MIC results could vary as much as 50,000-fold when a variety of disparate methods were compared (14, 29). While other strategies were possible (68), the NCCLS subcommittee elected to reduce the complexity of the standardization problem by focusing first on broth-based methodologies with defined media. Within this context, a number of investigators have since collaborated both independently (23, 34, 59, 80, 86) and in cooperation with the NCCLS subcommittee (24, 27, 56, 58) to examine the role of variables such as inoculum preparation, inoculum size, medium composition, incubation temperature, incubation time, and endpoint definition on interlaboratory variability. The end result of this process is NCCLS document M27, titled *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*. The initially proposed version (M27-P [49]) has recently been revised to the tentative level (M27-T [where the T represents tentative] [50]). The M27 method is summarized in Table 1 and is reviewed in detail elsewhere (28, 68). As currently configured, the interlaboratory agreement for the M27 method is comparable to that obtained for antibacterial testing (54).

The reproducibility of the M27 method facilitates clinical investigations designed to determine the ability of susceptibility testing to predict clinical response to *Candida*, *Torulopsis*, and *Cryptococcus neoformans* infections. To improve the utility of the M27 method for predicting clinical outcome, it is necessary to perform investigations aimed at the following two areas. First, the M27 method is a reference standard and was not intended as a practical procedure for routine use in a clinical laboratory. Early reports on efforts on the conversion of the M27 method to a microdilution format (24), of the use of colorimetric indicators (55, 84), and of the use of novel agar-based technologies (17, 90) are all promising and indicate that more convenient implementations of the M27 method will be feasible. The second issue is much more complex. While the M27 method and its derivatives are reproducible, this does not guarantee detection of clinically relevant differences in susceptibility between isolates. For example, in studies with cilofungin, a 16-fold difference in MICs (obtained by a macrodilution assay in *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid [HEPES]-buffered [pH 7.4] Synthetic Amino Acid Medium-Fungal) did not translate into an in vivo outcome difference in an animal model (44). Conversely, recent work has demonstrated that the M27 method has only a limited ability to identify amphotericin B-resistant isolates of *Candida* and *Cryptococcus* and that changes in test medium and/or test format may be required before relevant results can be consistently obtained with this drug (31, 66, 90). These studies serve as reminders that all susceptibility testing methods are arbitrary and are limited approximations of the in vivo situation and that substantial skepticism is appropriate before accepting any given method.

How, then, do we establish the clinical relevance of a given method and how should we determine interpretive breakpoints? This problem is especially complex because of the inherent variability of all in vivo systems and the fact that host factors (e.g., immune parameters such as leukocyte number, mechanical factors such as undrained abscesses, and penetration of the drug to the specific site of infection) can potentially have more influence on clinical outcome than intrinsic drug susceptibility. However, even though low MICs do not guarantee successful outcomes and high MICs do not guarantee failure, prediction of resistance, at least in the area of antibacterial agents, is far more reliable clinically than prediction of susceptibility (for a review, see reference 75). Early analysis of data correlating fluconazole susceptibility in vitro and clinical outcome with isolates from AIDS patients with oropharyngeal candidiasis seems to support this point (NCCLS subcommittee meeting, 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, Calif., 17 to 20 September 1995). The problem, then, is to determine the approximate relationship between the MIC and the likelihood of a successful outcome, despite these interfering factors. To date, only a limited number of studies have carefully related in vitro test results to clinical antifungal efficacy in humans. In

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TABLE 1. Summary of M27 methodology

Item	Implementation in the M27 method
Methodology	Broth macrodilution; final volume, 1 ml
Medium	RPMI-1640 containing 0.165 M MOPS (pH 7.0)
Fungal inoculum	0.5×10^3–2.5×10^3 organisms/ml
Incubation temperature	35°C
Incubation time	48 h (*Candida* spp.) or 72 h (*C. neoformans*)
Endpoint	Amphotericin B, optically clear tube; azoles and flucytosine: 80% reduction in turbidity by comparison with growth control

this minireview, we review these studies to define the current usefulness and limitations of susceptibility testing in the clinical laboratory. Although these initial studies leave many questions unanswered, they have begun a process that should accelerate in future years and that should make susceptibility testing increasingly useful.

STRATEGIES FOR CORRELATING IN VITRO RESULTS WITH IN VIVO OUTCOMES

The outcomes of three general groups of fungal infections might be correlated with in vitro results: animal models of infection, clinical studies of cutaneous and mucosal infections, and clinical studies of deep, invasive fungal infections. Each group has features that make it both attractive and unattractive. An alternative strategy, that of setting interpretive breakpoints directly in relation to achievable levels of antifungal agents in serum is not satisfactory since (i) the MICs of antifungal agents are greatly influenced by test conditions and (ii) the pharmacokinetics of certain antifungal agents (e.g., amphotericin B) are not fully understood. This problem has been reviewed elsewhere (68) and will not be further addressed in this minireview.

Experimental infections in animals. Studies with animals offer one solution to the problem of compensating for the effect of host factors. Ideally, infecting strains of fungi that differ only in their in vitro susceptibility to an antifungal agent are studied in parallel. The variable of greatest interest can thus be isolated and controlled to a much greater degree than is ethically possible in clinical trials. These studies permit (for example) clear demonstration of relationships between the MIC and the minimal effective dose (3, 87) or demonstrate that, at least for some fungi, the minimum lethal concentration may be a better predictor of outcome than the MIC (89). While a detailed examination of such studies is beyond the scope of this minireview, a recent review of 17 such studies found that 12 of the studies found coherent relationships between in vitro results and treatment efficacy for amphotericin B, flucytosine, and a variety of azoles (68). The principal limitation of these data is that animal models of fungal infection may be poor mimics of the infection in humans. Furthermore, differences in drug pharmacokinetics may make it difficult to translate dosing requirements. Nonetheless, such data are encouraging.

Cutaneous and mucosal infections. In the case of the fungi, the most abundant infections are those of the integument or mucous membranes: dermatophytosis, vaginitis, and oral or esophageal thrush. While these infections typically cause more morbidity than mortality, they are appealing targets of study for three reasons. First, since failure in treating these infections has less potential for adverse effects than failures of therapy of invasive infections, cutaneous infections readily lend themselves to new therapies whose efficacies are not yet established. Second, mucocutaneous infections are relatively more frequent than invasive fungal infections. Finally, and more importantly, the manifestations of these infections are relatively uniform, assessment of the response is straightforward, and samples for culture are easily obtained prior to, during, and following therapy. For all of these reasons, studies correlating susceptibility results with treatment response have been most numerous with these sorts of infections. On the downside, however, it is difficult to extrapolate results from these clinical trials to other more invasive fungal infections. First, with the notable exception of *Candida* species, fungal organisms causing invasive mycoses infrequently produce mucocutaneous infections. Second, the pharmacokinetics and bioavailability of antifungal drugs in body organs may differ markedly from those in the skin. Finally, the defects in host defenses that lead to invasive fungal infections are often different from the problems that lead to cutaneous fungal infections. These factors must be considered before results with mucosal or skin infections are applied to the treatment of invasive fungal infections.

Invasive fungal infections. Direct studies of patients with fungal infections that involve the viscera do not suffer from a lack of relevance. Such patients constitute the groups that would likely benefit the most from any aid in optimizing their therapy. However, these studies are difficult to design and their execution is slow for a variety of reasons. Patient enrollment is often slow because of the sporadic nature of almost all of the invasive fungal infections. For some invasive infections, the diagnosis is difficult and samples for culture subsequent to diagnosis cannot always be obtained. For other invasive infections, the manifestations of disease are quite varied, and this hampers a uniform analysis of the response. Finally, host factors may determine to a large extent the outcome of the infection. In short, despite the theoretical appeal of direct studies, practical issues often prevent the acquisition of clear-cut data and complicate the correlation of in vitro susceptibility with outcome.

CLINICAL STUDIES

For the reasons just discussed, the principal target for studies correlating the MIC with outcome has been *Candida* infections and, to a much smaller extent, infections caused by *C. neoformans*. Described in Table 2 is a series of studies which provided sufficient detail to permit interpretation. Table 2 excludes a number of other investigations for a variety of reasons, including (i) inclusion of small numbers of patients, (ii) use of inadequately described MIC measurement procedures, (iii) use of arbitrary interpretive breakpoints, (iv) lack of clinical data, and/or (v) failure to control for potential drug-drug interactions (1, 7, 9, 16, 18–20, 22, 25, 26, 32, 37, 39, 41, 42, 47, 48, 52, 53, 62, 78, 81, 88, 91–93). Also not included in Table 2 are (i) two small studies (nine patients total) demonstrating general correlations of ketoconazole and itraconazole MICs with outcome in oropharyngeal candidiasis (40, 82) and (ii) several clinical trials in which ketoconazole MICs failed to correlate with outcome for coccidioidomycosis, sporotrichosis, blastomycosis, histoplasmosis, and nonmeningeal cryptococcosis (15, 30, 79). These studies, while instructive, diverge from the main focus of this minireview and will not be further discussed.

In large part because of its substantial clinical utility in therapy of oropharyngeal candidiasis and cryptococcal meningitis, the largest number of studies correlating in vitro antifungal susceptibility testing with clinical outcome involve fluconazole and, to a lesser extent, amphotericin B. While several studies have specifically focused on ketoconazole and itracon-

TABLE 2. Correlation of outcome with in vitro susceptibility[a]

Infection	No. of strains	No. of patients	Drug	Method	Correlation	Reference
Oropharyngeal candidiasis with AIDS	2	2	Flu	NCCLS	Failure of 400 mg/day at MIC of ≥64 μg/ml	36
	4	4	Flu	NCCLS	Failure of 100–200 mg/day at MIC of ≥25 μg/ml	13
	29	26	Flu	NCCLS	Failure of 100–200 mg/day at MIC of ≥16 μg/ml	71
	62	28	Flu	NCCLS	Failure of 100–200 mg/day at MIC of ≥8 μg/ml	8
	121	29	Flu	NCCLS	Clear dose response, failure of 400–800 mg/day at MIC of ≥64 μg/ml	57, 63
	213	35	Flu	NCCLS	Failure of 800 mg/day at MIC of ≥64 μg/ml	77
	212	46	Flu	NCCLS	Failure of 200 mg/day at MIC of ≥16 μg/ml	35
	17	4	Flu	Broth/HR	100–200 mg/day begins to fail at MIC of 12.5 μg/ml	10
	11	8	Flu	Broth/HR	Up to 800 mg/day fails at MIC of ≥80 μg/ml	51
	50	44	Flu	Broth/HR	300–400 mg/day fails at MIC of ≥25 μg/ml	72
	46	45	Flu	Broth/HR	100 mg/day begins to fail at MIC of 12.5 μg/ml	4
	NS	45	Flu	Broth/HR	Up to 400 mg/day fails at MIC of ≥12.5 μg/ml	21
	201	65	Flu	Broth/HR	400 mg/day fails at MIC of ≥25 μg/ml	73
	65	25	Flu	Broth/YNB	Failure of 200–400 mg/day at MIC of 2–8 μg/ml	85
	65	25	Flu	Agar	Failure of 200–400 mg/day at zone diameter of 25 mm	85
	30	30	Flu	Agar	All at MIC of ≥6.25 μg/ml failed 50 mg/day	70
	224	180	Flu	Agar	100–200 mg/day fails at MIC of 8–16 μg/ml	76
Candidemia (without AIDS)	232	146	Flu	NCCLS	No correlation, although only a few isolates at highest MICs	67
	232	146	AmB	NCCLS	No correlation; MICs for all isolates were similar	67
	29	26	AmB	Broth	MIC of ≥0.8 μg/ml correlated strongly with failure	61
C. neoformans meningitis with AIDS	76	76	Flu	Broth	No correlation with NCCLS method, but use of alternative medium produced good correlation, especially if adjusted for host factors	95, 96
	4	1	AmB	Broth	Rise in MIC from 0.4 to 1.6 μg/ml correlated with failure	60

[a] Studies examining the correlation between MIC and outcome in humans. Abbreviations: NS, not stated; AmB, amphotericin B; Flu, fluconazole; HR, High-Resolution medium; YNB, yeast nitrogen base, NCCLS, NCCLS M27P methodology.

azole MICs (40, 82) and many others have reported them in passing (see, for example, references 4, 6, 13, and 35), this area has not been exhaustively pursued. Because of the potential for the development of resistance to flucytosine, it is now rarely used alone to treat patients, and well-studied cases correlating the MIC with outcome are not available.

Fluconazole. The extensive use of fluconazole has permitted the accumulation of a substantial amount of data on the relationship between the MIC and outcome, with the preponderance of the available studies focusing on oropharyngeal candidiasis in patients with AIDS. For this particular scenario, 16 studies are tallied in Table 2. Those studies used three main methods for MIC testing: the M27 method, other broth methods, or a variety of agar-based methods. The only studies with readily compared in vitro methodologies are those that use the standardized NCCLS broth macrodilution or broth microdilution procedures. Collectively, the seven NCCLS-compliant reports cover >600 isolates from >150 patients and demonstrate a consistent trend. For the typical fluconazole dosage of 100 mg/day, failures begin to be seen when the MIC reaches 8 μg/ml and become almost a certainty when the MIC reaches 16 μg/ml. Dosages of 400 to 800 mg/day are often efficacious unless the MIC is ≥64 μg/ml. The relapsing nature of oropharyngeal candidiasis in AIDS patients has made this pattern especially obvious. Such patients are often treated repeatedly with short courses of fluconazole, thus setting the stage for the induction of resistance and/or the selection of resistant strains in ~5% of such patients (see reference 69 for a review of this problem). When individual patients are carefully followed, the rise in MIC can be clearly correlated with a lessened clinical response to a given dose of fluconazole. A striking example of this phenomenon is found in the report by Redding et al. (63) (the patient described by Redding et al. [63] is also described elsewhere [57]). Over a 2-year period, the patient described by Redding et al. (63) experienced 15 relapses of oropharyngeal candidiasis, and each relapse was treated with fluconazole. During the first relapses, the MIC for the patient's infecting *C. albicans* isolate was ≤8 μg/ml, but the infection responded to 100 mg/day. Then, as the MIC for the isolates rose steadily toward 64 μg/ml, progressively greater doses of fluconazole were required to produce a clinical response and fluconazole was completely ineffective after the 14th relapse. This is shown graphically in Fig. 1, in which the minimum effective dose of fluconazole at each relapse is plotted against the MIC for the isolate from that episode. Of interest, the approximate breakpoints suggested by these data do correlate roughly with the achievable levels of fluconazole in blood: 100 mg/day produces peak levels of approximately 6 μg/ml, 400 mg/day produces peak levels of 20 to 30 μg/ml, and the linear pharmacokinetics of fluconazole would predict levels of 40 to 60 μg/ml at 800 mg/day (33). Analysis of the other studies done in this area is limited by a lack of a common ground for comparison of the reported MICs. However, those studies that use High-Resolution broth would be expected to yield results similar to those obtained by the M27 method (58), and indeed, this pattern is evident in Table 2. For the other studies, all that can be said is that a correlation was indeed evident.

In the area of invasive *Candida* infections, we are aware of only one study that has systematically tried to correlate the fluconazole MIC with the outcome. In that study, Rex et al. (67) performed in vitro susceptibility testing on 232 bloodstream *Candida* isolates collected during a clinical trial comparing 400 mg of fluconazole per day with 0.5 to 0.6 mg of amphotericin B per kg of body weight per day as therapy for candidemia in nonneutropenic adults. The MICs were determined by both the broth macrodilution and broth microdilu-

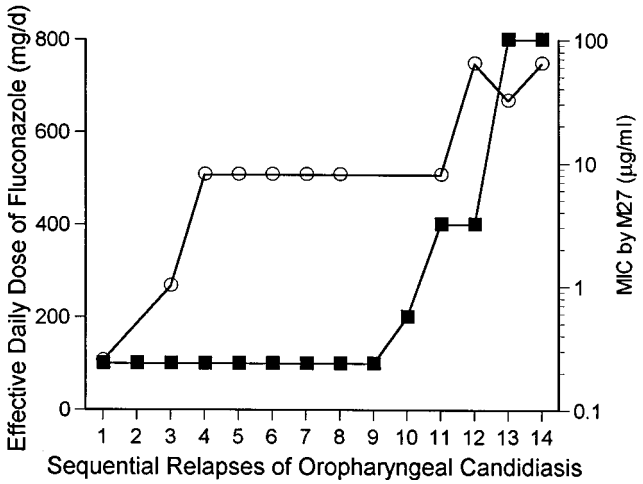

FIG. 1. Correlation between MIC and effective dose of fluconazole for oropharyngeal candidiasis. ■, effective daily dose of fluconazole; ○, the MIC for the *C. albicans* isolate from the clinical episode of oropharyngeal candidiasis. Data are adapted from previously published data (63) and are used by permission.

tion variations of the M27 method. Analysis of the correlation of the MICs obtained by the M27 method (by both the broth macrodilution and broth microdilution formats) with clinical outcome showed that of the 100 isolates from 64 fully evaluable fluconazole-treated patients for whose isolates fluconazole MICs were ≤16 μg/ml, 36 isolates (from 19 patients) were associated with treatment failure. Conversely, four isolates for which fluconazole MICs were ≥32 μg/ml were obtained from four patients who responded to initial fluconazole therapy. Interestingly, logistic regression analysis showed an inverse correlation with outcome: lower MICs correlated with failure rather than success ($P = 0.05$). The investigators suggest two possible related reasons for this lack of in vitro-in vivo correlation. First, although limited by the small number of isolates for which the MIC was high, one can hypothesize that the observed MICs of up to ~64 μg/ml are at or below the relevant interpretive breakpoint for isolates that cause this disease and a fluconazole dosage of 400 mg/day. Interestingly, this putative breakpoint corresponds to the putative breakpoint of 400 mg of fluconazole per day in the therapy of oropharyngeal candidiasis. Second, it appears likely that host factors played a significant role in the response, as suggested by the apparent correlation between intravascular catheter exchange and the time to the clearance of organisms from the bloodstream (64).

The final area in which a correlation between the fluconazole MIC and outcome has been sought is for AIDS-related *C. neoformans* meningitis. Here again, only a single large study has been conducted, but that study is very instructive. Witt et al. (95, 96) determined the MICs for *C. neoformans* isolates from 76 patients enrolled in two collaborative clinical trials. The first clinical trial was designed to evaluate the efficacy of 400 mg of fluconazole per day with flucytosine as therapy for meningitis (43), while the second trial examined the efficacy of fluconazole at dosages from 800 to 2,000 mg/day alone or in combination with flucytosine (46). When the MIC was correlated with the response, several interesting observations were made. First, MICs determined by the M27 method did not correlate with outcome ($P = 0.311$). While this may be due in part to the relatively poor growth of *C. neoformans* in the RPMI-1640 medium specified by the M27 method (31), determination of MICs by a variation of the M27 method (with morpholine propanesulfonic acid [MOPS]-buffered [pH 7.0] yeast nitrogen base medium supplemented with 0.5% [wt/vol] glucose, an inoculum of 10^4 yeasts per ml, and incubation at 35°C for 48 h) produced a significant ($P = 0.01$) correlation with outcome. Furthermore, upon multivariate analysis, it became clear that use of flucytosine and the presence of a positive blood culture at the time of entry into the study also had a significant impact on response. When the patients were subdivided into these four possible groups (did or did not receive flucytosine, did or did not have a positive blood culture), a distinct and strong correlation of the MIC with outcome became apparent. For example, the predicted probability of treatment failure of a patient who (i) did not receive flucytosine, (ii) had a negative blood culture, and (iii) was infected with an isolate for which the MIC was 16 μg/ml would be over 40%. This probability decreases to about 10% if the patient receives flucytosine.

Taken together, these data for fluconazole, *Candida* species, and *C. neoformans* make it clear that fluconazole MICs determined by M27 and related methods can correlate with outcome under certain circumstances. While the correlation is most apparent for oropharyngeal candidiasis, consistent data have been presented for invasive infections caused by both organisms. It is, however, important that the data for *Candida* species are mostly for *C. albicans*: the non-*C. albicans* species are present in lower numbers in patients in all of the studies reviewed here, and the correlation of the MIC with outcome for these species is less certain. The NCCLS Subcommittee for Antifungal Susceptibility Testing is currently reviewing in detail both these data and data from the drug's manufacturer. It is hoped that that review will result in interpretive breakpoints for at least some types of infections.

Amphotericin B. The situation for amphotericin B is even more complex than that for fluconazole. However, since amphotericin B is the other mainstay of therapy for infections caused by *Candida* species and *C. neoformans*, a review of the available data is warranted. First, a number of investigations have reported increases in amphotericin B MICs for isolates recovered during prolonged therapy with this agent that seemed to correlate with clinical failure (12, 20, 25, 52). Second, Powderly et al. (61) examined the in vitro susceptibility to amphotericin B of 29 *Candida* isolates causing fungemia in 26 patients undergoing allogeneic or autologous bone marrow transplantation and/or myelosuppressive chemotherapy. For isolates causing invasive disease, an MIC of ≥0.8 μg/ml was strongly correlated with therapeutic failure and death. While encouraging, these data have not been replicated by others. In particular, when the amphotericin B MICs for the isolates, determined by the M27 method, from the previously mentioned trial of fluconazole versus amphotericin B as therapy for candidemia were correlated with outcome, all of the MICs were clustered at ~0.5 μg/ml and did not correlate with outcome (67). As noted above, the M27 method appears to have difficulty identifying amphotericin B-resistant isolates, and use of antibiotic medium 3 or conversion to an agar-based testing format appears to be necessary for reliable results for both *Candida* species and *C. neoformans* (66, 74, 90). However, repeat testing of the *Candida* isolates from the previously mentioned trial with patients with candidemia by these alternative methods did not identify any isolates for which the MICs were high (66, 90). Thus, the lack of correlation of the MIC with outcome for these isolates appears likely because of both a lack of substantial resistance and the host factors discussed earlier.

For *C. neoformans* meningitis, we are aware of only a single study on the correlation of the amphotericin B MIC with outcome. In that study, Powderly et al. (60) tested four serial

isolates from a single patient. A distinct rise in the MIC from 0.4 to 1.6 μg/ml (determined with yeast extract broth) correlated with clinical relapse and failure. Less dramatic rises in the *C. neoformans* MIC during therapy have been reported by another investigator (11), but no attempt was made to correlate the MIC with outcome.

Taken together, the situation for the correlation of the amphotericin B MIC with outcome is far from clear-cut, but there does appear to be hope. The key problem at present is identification of a method which readily identifies isolates known to be resistant. Such a method appears to be close at hand, and with this it is hoped that the development of meaningful interpretive breakpoints can proceed.

SUMMARY AND FUTURE DIRECTIONS

In summary, it is clear that in vitro susceptibility testing can predict outcome in selected clinical situations. The clearest data are from the fluconazole-treated AIDS patients with oropharyngeal candidiasis. In this setting, the homogeneity of the underlying immune defect, combined with the ease of identification and monitoring of the infection, creates a near-perfect test situation. In more complex scenarios, such as the heterogeneous population of patients enrolled in a recent study of candidemia (65), no such clear-cut correlation was present. The importance of host factors in the correlation of the MIC with outcome cannot be overemphasized. Examples of these parameters include patient status (underlying disease, the presence of intravascular catheters, and $CD4^+$ T-cell number), drug pharmacokinetics (absorption and distribution), patient compliance, and drug-drug interactions. Identification of relevant factors can substantially improve the degree of the MIC-outcome correlation and thus improve the clinical utility of in vitro testing.

An important feature in this entire process is the role of standardized susceptibility testing procedures. While not without flaws, the proposed NCCLS reference method has been invaluable in allowing multiple investigators to contribute data that can be used to clarify the correlation between the fluconazole MIC and outcome. While the development of simplified second-generation methods is eagerly anticipated, the role of the reference method as a common touchstone is critical. Only by use of either the reference method itself or methods with a known relationship to the reference method can this broad collaborative process really proceed.

Current work is focusing on defining interpretive breakpoints for fluconazole and *Candida* species, refinement of the in vitro procedures used to measure susceptibility to amphotericin B, ketoconazole, and itraconazole, and the acquisition of a broad base of data on the relationship between the MIC and outcome for these three drugs. Although considerable work remains to be done, the available data suggest that solutions to each of these problems are possible and that routine susceptibility testing of fungi will become meaningful for clinical decision making in the foreseeable future.

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