Has Antifungal Susceptibility Testing Come of Age?

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The in vitro susceptibility of an infecting organism to the antimicrobial agent selected for therapy is one of several factors that influence the likelihood that therapy for an infection will be successful. To appreciate the value of antifungal susceptibility testing, it is helpful to review the overall predictive utility of antibacterial susceptibility testing. After >30 years of study, in vitro susceptibility can be said to predict the response of bacterial infections with an accuracy that is well summarized as the “90-60 rule”: infections due to susceptible isolates respond to therapy ~90% of the time, whereas infections due to resistant isolates respond ~60% of the time. On the basis of a growing body of knowledge, standardized susceptibility testing for selected organism-drug combinations (most notably, Candida species and the azole antifungal agents) has been shown to have similar predictive utility. Antifungal susceptibility testing is now increasingly and appropriately used as a routine adjunct to the treatment of fungal infections.
example, Lorian and Burns [10] correlated outcome with susceptibility testing results for 298 episodes of infection (∼25% due to Staphylococcus species and ∼75% due to gram-negative rods). These investigators observed a rate of response to therapy of 81% (219 of 271 episodes) for cases in which the infecting organisms were judged to be susceptible to the selected antibiotics, but a response rate of only 4% (1 of 27 episodes) for cases in which the infected organisms were resistant to the antibiotics selected for therapy.

More often, however, studies show that susceptibility testing results have value but far less impact than in the study just cited. For example, Weinstein et al. [11] reported that appropriate antimicrobial therapy was associated with an increase in the survival rate from 48% (10 of 21 patients) to 73% (224 of 309 patients). When multiple reports of the correlation of therapeutic outcome with in vitro susceptibility are examined (table 1), a pattern that we refer to as the “90-60 rule” emerges. Stated broadly, the 90-60 rule observes that infections due to susceptible isolates respond to appropriate therapy ∼90% of the time, whereas infections due to resistant isolates (or infections treated with inappropriate antibiotics) respond ∼60% of the time. What is intriguing about this rule is that it is relatively robust. Although there is a range of responses, the rule holds whether the outcome measurement is clinical response, bacteriological response, or mortality. The rule also holds whether the in vitro prediction tool is a true MIC, an inhibition-zone diameter, or a more sophisticated measurement, such as the ratio of the area under the concentration-time curve (AUC) to the MIC.

In reviewing table 1, it is important to note that some of the articles [18, 19] report the results of investigations designed to identify the microbiological variable that most closely predicted outcome. For example, Forrest et al. [18] correlated a variety of pharmacodynamic parameters to outcome. They observed that the AUC/MIC ratio seemed to be most important to outcome. They observed that the AUC/MIC ratio seemed to be most important to outcome. They observed that the AUC/MIC ratio seemed to be most important to outcome. They observed that the AUC/MIC ratio seemed to be most important to outcome.

Table 1. The “90-60 rule”: the range of correlations between susceptibility and outcome in studies of bacterial infections.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type(s) of infection</th>
<th>Drug(s) administered</th>
<th>Outcome measurement</th>
<th>Measurement used to determine susceptibility</th>
<th>Cases with successful outcome, % (no. of cases/total no. of cases), by susceptibility class</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11]</td>
<td>Bacteremia and fungemia</td>
<td>Various</td>
<td>Mortality</td>
<td>MICb</td>
<td>73 (224/309)</td>
<td>48 (10/21)</td>
</tr>
<tr>
<td>[12]</td>
<td>Bacteremia and fungemia</td>
<td>Various</td>
<td>Mortality</td>
<td>MICb</td>
<td>89 (594/665)</td>
<td>77 (97/126)</td>
</tr>
<tr>
<td>[10]</td>
<td>Serious bacterial infections</td>
<td>Various</td>
<td>Clinical response</td>
<td>MIC</td>
<td>81 (219/271)</td>
<td>4 (1/27)</td>
</tr>
<tr>
<td>[13]</td>
<td>Pneumococcal otitis media</td>
<td>Amoxicillin/clavulanic acid</td>
<td>Clinical response</td>
<td>MIC</td>
<td>80 (149/186)</td>
<td>68 (15/23)</td>
</tr>
<tr>
<td>[14]</td>
<td>Pneumococcal otitis media</td>
<td>Cefuroxime</td>
<td>Clinical response</td>
<td>MIC</td>
<td>94 (44/47)</td>
<td>78 (29/37)</td>
</tr>
<tr>
<td>[15]</td>
<td>Pneumococcal otitis media</td>
<td>Cefaclor or cefuroxime</td>
<td>Bacteriologic response</td>
<td>MIC</td>
<td>95 (55/58)</td>
<td>49 (9/20)</td>
</tr>
<tr>
<td>[16]</td>
<td>Pneumococcal otitis media</td>
<td>Cefaclor or azithromycin</td>
<td>Bacteriologic response</td>
<td>MIC</td>
<td>89 (23/26)</td>
<td>24 (6/25)</td>
</tr>
<tr>
<td>[17]</td>
<td>Bacteroides bacteremia</td>
<td>Various</td>
<td>Bacteriologic response</td>
<td>MIC</td>
<td>88 (60/68)</td>
<td>57 (4/7)</td>
</tr>
<tr>
<td>[18]</td>
<td>Moderate-to-severe bacterial infections</td>
<td>Ciprofloxacin</td>
<td>Bacteriologic response</td>
<td>MIC</td>
<td>82 (37/45)</td>
<td>26 (5/19)</td>
</tr>
<tr>
<td>[19]</td>
<td>Bacterial infections</td>
<td>Aminoglycosides</td>
<td>Clinical response</td>
<td>Peak/MIC ratio</td>
<td>∼90d</td>
<td>∼55d</td>
</tr>
<tr>
<td>[3]</td>
<td>Bacterial infections</td>
<td>Cefotaxime</td>
<td>Bacteriologic response</td>
<td>Zone diameter</td>
<td>92 (1464/1591)</td>
<td>63 (31/49)</td>
</tr>
<tr>
<td>[3]</td>
<td>Bacterial infections</td>
<td>Ciprofloxacin</td>
<td>Bacteriologic response</td>
<td>Zone diameter</td>
<td>91 (1652/1815)</td>
<td>62 (8/13)</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>89 (452/5081)</td>
<td>59 (215/368)</td>
</tr>
</tbody>
</table>

NOTE. If a study offered multiple correlations (e.g., [3, 15]), representative data were chosen, and unequivocal end points (bacteriologic response and mortality) were given preference over clinical response. P values were determined by Fisher’s exact test. AUC, area under the concentration-time curve; peak/MIC, ratio of the peak concentration to the MIC; zone diameter, diameter of the inhibition zone by disk diffusion testing.

a The definitions of “susceptible” and “resistant” were not the same in all the reports. In some cases, the designations “susceptible” and “resistant” referred to a post hoc classification of likelihood of response based on selection of the variable that seemed most closely linked with response. For further discussion, see the section What Is the Expected Degree of Correlation between In Vitro and In Vivo Data? The “90-60 Rule.”

b A combination of susceptibility testing and clinical judgement was used to categorize therapy as appropriate or inappropriate.

c Data on Haemophilus influenzae were also presented, but the authors concluded that the breakpoints they used were incorrect.

d This study does not indicate the number of patients in the groups with higher and lower peak/MIC ratios, but it did show a clear trend favoring higher ratios.

The reported success rates are for the groups with the highest (>12) and lowest (<2) peak/MIC ratios and were obtained by estimation from a figure in the article.

e Taken from data submitted to the National Committee for Clinical Laboratory Standards for establishing interpretive breakpoints [3].

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the response rate reached a plateau at an average of 82%. Among patients with a lower AUC/MIC ratio, the response rate was only 26%. The correlation shown is thus an example of “best fit to response.” This type of analysis provides strong support for the underlying assumptions of the 90-60 rule: some infections will not be cleared by increasing the dose of a drug, whereas others are cleared by seemingly small doses of the drug and, perhaps, largely by host defenses.

Once this pattern is observed, the next puzzle is the discrepancy between MIC and outcome. Stated simply, why does response follow the 90-60 rule rather than a 100-0 rule? Two possibilities exist. First, the susceptibility result might just be wrong in some way and, therefore, subject to correction by use of a different testing method or a different interpretive breakpoint. Alternatively, the problem might lie not with the susceptibility test but with the patient. Although examples of technical issues confounding correct testing certainly exist [15, 20], such issues are easily corrected, when discovered, and experienced clinicians quickly gravitate towards the second possibility as the more fundamental of the two. Factors such as drug pharmacokinetics, drug delivery to the site of infection, treatment of the site of infection, (lack of) host response, and production of toxins [2, 5, 21, 22] are well known, and it is clear how one or more of these factors might outweigh the impact of a susceptibility test result. A current and topical example that illustrates this observation is inhalational anthrax, the principal consequences of which are mediated not by the infecting organism itself but by its toxins [23]. Even though the infecting isolate of Bacillus anthracis may be highly susceptible to many drugs, antibacterial therapy has little impact on the course of disease once the organism has released a significant amount of toxin.

Thus, susceptibility testing should be seen as part of the process of predicting whether a given patient will respond to therapy. In this context, the rationale behind suggestions that susceptibility testing should be referred to as “resistance testing” [2] become exceedingly clear—testing only has value to the extent it can identify drugs that are less likely to succeed in eradicating infection. By avoiding use of such drugs, and thereby placing the patient towards the 90% end of the 90-60 rule, the physician has taken the first of many possible steps towards ensuring a good outcome.

WHY DO THE RESULTS OF INDIVIDUAL CLINICAL TRIALS SOMETIMES FAIL TO CLEARLY SUPPORT BREAKPOINTS?

Although some studies demonstrate a correlation between susceptibility testing results and response to therapy, results of individual clinical trials sometimes fail to demonstrate otherwise well-supported correlations. Unless the susceptibility testing method is seriously flawed, the usual explanation for this observation is that the study sample did not include enough drug-resistant isolates.

A recent example from the literature on antifungal agents [24] illustrates this problem well. In this study, a correlation between the response of candidemia to fluconazole (400 mg/day) was sought for 104 isolates from 68 fluconazole-treated patients. No clear correlation was seen between MICs and outcomes. However, only 2 of the 104 isolates were judged resistant at this dosage of fluconazole (MIC, ≥64 µg/mL [8]), and both of the episodes of disease caused by these isolates responded to therapy. In contrast, the episodes for which therapy failed were caused by isolates with MICs of fluconazole distributed across the observed range, and the majority of the treatment failures occurred for episodes caused by isolates with the most-common MIC values. Because the small MICs typical for susceptible isolates were the most common, it is perhaps not surprising that logistic regression analysis found that lower MICs correlated with a greater likelihood of treatment failure. A similar example of this can also be seen in a recent attempt to correlate MICs of fluconazole for Cryptococcus neoformans with outcome [25]. All isolates appeared to be similarly susceptible, and an MIC-response curve was not seen.

The principal lesson to be learned from these analyses is that small sample sizes and lack of drug-resistant isolates in a study population can lead to confusing results. Although there is a great deal of experimental and pharmacodynamic support for the currently recommended fluconazole breakpoints [26, 27], the results of the 2 studies mentioned previously [24, 25] do not clearly indicate a useful interpretive breakpoint. In the context, however, of other support for the proposed interpretive breakpoints, the lack of correlation across groups of mostly susceptible isolates indicates what the breakpoint is not.

HOW GOOD ARE THE CORRELATIONS FOR ANTIFUNGAL SUSCEPTIBILITY TESTING RESULTS?

With that background, just how useful is antifungal susceptibility testing? The NCCLS has proposed standardized testing methods for yeast (i.e., M27-A [8]) and filamentous fungi (i.e., M38-P [9]), and this review will focus on data generated by those methods. The methods themselves have been reviewed in detail elsewhere [26]. At present, there are adequate data to support the use of only a few organism-drug combinations; these are listed in Table 2. Each will be discussed briefly in turn. For further details, the interested reader is referred to the recent review [26] from which Table 2 is taken.

**Candida species andazole antifungal agents.** Testing of Candida species against fluconazole is both feasible and associated with predictive value that approximates the 90-60 rule (Table 3). This is true for both mucosal and invasive disease, although the supportive data are stronger for mucosal disease. On the basis
of these data, the NCCLS has proposed interpretive breakpoints [8] that use the standard categories “susceptible” and “resistant” along with the novel category “susceptibility that is dose- or delivery-dependent” (S-DD). The S-DD category is in many ways analogous to the category “moderately susceptible” that is used for bacterial breakpoints [51], but the designation “S-DD” emphasizes the need to maximize drug dose and delivery. The breakpoints are also supported by the findings of detailed pharmacodynamic studies [26, 27]. The situation for itraconazole breakpoints is similar to that for fluconazole, although the data are limited to mucosal disease. The situation for ketoconazole is less well defined; general correlations are evident from the literature, but breakpoints have not been proposed.

**C. neoforms and the azole antifungal agents.** No definitive interpretive methods or end points have been proposed. However, a modification of the M27-A method has shown an encouraging correlation with outcome (table 2).

**Yeasts and flucytosine.** The available data are limited. On the basis of a combination of historical data and in vivo data, interpretive breakpoints have been proposed for *Candida* species but not for *C. neoforms* (table 2).

**Yeasts and amphotericin B.** Technical issues limit the data. For *Candida* species, methods based on minimum lethal concentrations may be preferred [43]. Fortunately, resistance appears to be rare among the major *Candida* species [44]. Correlations for *C. neoforms* have been reported, but meaningful testing is technically difficult.

**Molds.** The correlations are very poorly defined for all agents. Suggestive data exist for individual organism-drug combinations, but are limited to work from a very small number of laboratories. Acquired resistance appears to be uncommon. For discussion, see [26] and [50].

### Table 2. Recommended susceptibility test methods and conditions for antifungal susceptibility testing.

<table>
<thead>
<tr>
<th>Organism, drug</th>
<th>Methods</th>
<th>Interpretation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida species</td>
<td>M27-A and methods that give concordant results</td>
<td>Susceptible, ≤8 μg/mL; susceptible-DD, &gt;8 μg/mL and ≤32 μg/mL; resistant, &gt;32 μg/mL. Results are best supported by data for mucosal disease, but the results also appear to hold for invasive disease. Administration of an adequate drug dose is critical as the MIC rises. <em>Candida krusei</em> is assumed to be intrinsically resistant and should not be tested.</td>
<td>[5, 8, 28–33]</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>M27-A and methods that give concordant results</td>
<td>Susceptible, ≤0.125 μg/mL; susceptible-DD, &gt;0.125 μg/mL and ≤0.5 μg/mL; resistant, &gt;0.5 μg/mL. Data apply only to mucosal disease. Ensuring adequate absorption by use of the solution is often critical to drug efficacy.</td>
<td>[5, 8]</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>M27-A and methods that give concordant results</td>
<td>No specific breakpoints proposed. However, aggregate data suggest that isolates with an MIC greater than ~0.125 μg/mL by use of the M27-A method are less likely to respond to therapy.</td>
<td>[30, 32–36]</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>M27-A and methods that give concordant results</td>
<td>Susceptible, ≤4 μg/mL; intermediate susceptibility, &gt;4 μg/mL and ≤16 μg/mL; resistant, &gt;16 μg/mL. These breakpoints are based largely on historical data and animal models, but they appear rational on the basis of the available clinical and pharmacokinetic data.</td>
<td>[8, 37–39]</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>M27-A–like methods that use AM3 broth, E-test, or MFC methods</td>
<td>Significant controversy and difficulty. Agar-based methods appear to have the most potential, in general, and isolates for which MICs of amphotericin B are greater than ~0.5 μg/mL are probably resistant. However, specific breakpoints have not been proposed, and intralaboratory variation makes use of reference isolates with known resistance mandatory. Fortunately, resistance appears uncommon among the 4 most common species.</td>
<td>[40–44]</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Modified M27-A (with use of YNB broth and a higher inoculum)</td>
<td>No specific breakpoints proposed. Data are limited, but consistent. MICs of &gt;2–4 μg/mL by this method appear to predict a greater chance of treatment failure, which definitely appears to be more likely if the MIC reaches 16 μg/mL.</td>
<td>[25, 45, 46]</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>M27-A–like methods</td>
<td>No specific breakpoints proposed. However, breakpoints similar to those for <em>Candida</em> species (see above) would appear rational.</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>M27-A–like methods that use AM3 broth or E-test</td>
<td>Significant controversy and difficulty. In general, agar-based methods have the most potential. Measurement of fungicidal concentrations may have value. No specific breakpoints proposed; testing should include reference isolates with known levels of resistance.</td>
<td>[47–49]</td>
</tr>
<tr>
<td>Mold fungi, any drug</td>
<td>Unknown</td>
<td>M38B-like methods have been shown to correlate for the combination of itraconazole and <em>Aspergillus fumigatus</em>. Correlations for amphotericin B are poorly defined.</td>
<td>[50]</td>
</tr>
</tbody>
</table>

**NOTE.** This table is reprinted and updated with permission from a similar table published in [26]. Useful methods for drugs (e.g., the echinocandins) and fungi that are not listed in this table are not defined. AM3, Antibiotic Medium 3; MFC, minimum fungicidal concentration; susceptible-DD, susceptibility that is dose- or delivery-dependent and requires maximization of drug delivery [5]; YNB, yeast nitrogen base broth.
A stepwise approach to the use of fungal identification and antifungal susceptibility testing in the selection of antifungal therapy

1. Identify the isolate at least to the genus level, if not to the species level.

2. For the organism-drug combinations of Candida species from sterile sites and fluconazole or flucytosine, routinely perform susceptibility testing. Testing these drugs by use of the M27-A method (see below for alternative methods) is useful as a guide to treatment of invasive disease. Although isolates from cases of mucosal infection may be usefully tested against fluconazole and itraconazole, the ease of judging the response and the non–life-threatening nature of mucosal disease usually renders such testing unnecessary. However, testing is a useful adjunct when determining whether clinical failure is more likely due to microbiological resistance or problems with drug delivery (e.g., enhanced drug clearance due to rifampin therapy).

3. For the following organism-drug combinations, consider performance of susceptibility testing as an adjunct to treatment for patients with invasive disease who experience clinical failure of initial therapy: (1) Candida species and amphotericin B; (2) C. neoformans and fluconazole, flucytosine, or amphotericin B; (3) C. neoformans and flucytosine; (4) C. neoformans and amphotericin B.

**Table 3. Range of correlations of susceptibility testing with outcome for fungal infections**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type(s) of infection</th>
<th>Drug administered, dosage in mg/day</th>
<th>Outcome measurement</th>
<th>MIC used to determine susceptibility, μg/mL</th>
<th>Cases with successful outcome, % (no. of cases/total no. of cases), by susceptibility class</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5]</td>
<td>Candidiasis, mostly mucosal</td>
<td>Fluconazole, 100</td>
<td>Clinical response</td>
<td>≤8</td>
<td>98 (248/253) 76 (37/49) .001</td>
</tr>
<tr>
<td>[31]</td>
<td>Mucosal candidiasis</td>
<td>Fluconazole, 100–200</td>
<td>Clinical response</td>
<td>≤8</td>
<td>80 (28/35) 46 (16/13) .034</td>
</tr>
<tr>
<td>[32]</td>
<td>Mucosal candidiasis</td>
<td>Fluconazole, 100</td>
<td>Clinical response</td>
<td>≤8</td>
<td>96 (49/51) 0 (0/15) .001</td>
</tr>
<tr>
<td>[33]</td>
<td>Mucosal candidiasis</td>
<td>Fluconazole, 100–400</td>
<td>Clinical response</td>
<td>≤32</td>
<td>88 (14/16) 0 (0/5) .001</td>
</tr>
<tr>
<td>[5]</td>
<td>Mucosal candidiasis</td>
<td>Itraconazole, 200</td>
<td>Clinical response</td>
<td>&lt;0.125</td>
<td>88 (162/184) 59 (47/80) .001</td>
</tr>
<tr>
<td>[32]</td>
<td>Mucosal candidiasis</td>
<td>Itraconazole, 200</td>
<td>Clinical response</td>
<td>&lt;0.05</td>
<td>98 (48/49) 6 (1/17) .001</td>
</tr>
<tr>
<td>[32]</td>
<td>Mucosal candidiasis</td>
<td>Ketoconazole, 400</td>
<td>Clinical response</td>
<td>&lt;0.125</td>
<td>94 (46/49) 11 (2/18) .001</td>
</tr>
<tr>
<td>[33]</td>
<td>Mucosal candidiasis</td>
<td>Ketoconazole, &gt;400</td>
<td>Clinical response</td>
<td>&lt;0.06</td>
<td>94 (17/18) 0 (0/3) .003</td>
</tr>
<tr>
<td>[5]</td>
<td>Candidiasis, mostly invasive</td>
<td>Fluconazole, &gt;100; median, 400</td>
<td>Clinical response</td>
<td>≤32</td>
<td>82 (146/178) 46 (18/39) .001</td>
</tr>
<tr>
<td>[28]</td>
<td>Invasive candidal infections</td>
<td>Fluconazole, 400</td>
<td>Clinical response</td>
<td>≤32</td>
<td>77 (23/30) 0 (0/2) .073</td>
</tr>
<tr>
<td>[29]</td>
<td>Candidemia</td>
<td>Fluconazole, mostly 100–200</td>
<td>Clinical response</td>
<td>≤8</td>
<td>52b &lt;14a .03</td>
</tr>
<tr>
<td>[46]</td>
<td>Cryptococcal meningitis</td>
<td>Fluconazole, &gt;400</td>
<td>Clinical response</td>
<td>≤16</td>
<td>91 (21/23) 0 (0/5) .001</td>
</tr>
<tr>
<td>[52]</td>
<td>Disseminated histoplasmosis</td>
<td>Fluconazole, 600–800</td>
<td>Clinical response</td>
<td>≤5</td>
<td>97 (36/37) 71 (20/28) .004</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>91 (838/923) 48 (131/274) .001</td>
</tr>
</tbody>
</table>

NOTE. All MICs were determined by NCCLS M27-A [8] or a closely related variant of that method. P values determined by Fisher’s exact test.

* Published data do not provide additional detail.

**ACKNOWLEDGMENT**

We thank Dr. Sevtap Arikan, Hacettepe University, Ankara, Turkey, for her critique of the manuscript.
lates that appear to be highly resistant to therapy is desirable for infection with iso-
spond to therapy. In general, alternative infected with resistant isolates will re-
cated by the 90-60 rule, some patients the best approach is not clear. As indi-
with an isolate later found to be resistant,
respond well to therapy for an infection with
molds (e.g., posaconazole appears to be
agents may have dissimilar activity against
the newer generation of azole antifungal
combination in question. Be aware that
susceptibility testing should be done, if possible (table A1).

5. For all other organism-drug
combinations, susceptibility testing is unlikely to
usefully influence the selection of therapy. Instead, select therapy based on gen-
eral guidance (e.g., Infectious Disease So-
ciety of America guidelines [63] or other
similar guidelines) and a review of spe-
cific survey data on the organism-drug
combination in question. Be aware that
the newer generation ofazole antifungal
agents may have dissimilar activity against
molds (e.g., posaconazole appears to be
more active than voriconazole against the
agents of zygomycosis [64, 65]).

6. For treatment of patients who re-
spond to therapy despite being infected
with an isolate later found to be resistant,
the best approach is not clear. As indi-
cated by the 90-60 rule, some patients
infected with resistant isolates will re-
spond to therapy. In general, alternative
therapy is desirable for infection with iso-
lates that appear to be highly resistant to
the therapy selected. However, as with the
parallel situation for bacterial infections, the physician should consider the follow-
ing factors: (1) the severity of the infec-
tion, (2) the patient’s immune status, (3)
the ability of the drug to reach adequate
levels at the target location, (4) the ease
of documentation of (lack of) response,
(5) the ability to identify and control the
primary site of infection, (6) the speed
of response, (7) the consequences of re-
currence of infection, (8) the magnitude
of the resistance, and (9) the ability to
increase the dose of the selected antifun-
gal agent in response to an elevated MIC.
For example, a nonneutropenic patient
(i.e., one with good immune status) who
has candidemia (i.e., a condition whose
course is easily followed) that clears im-
mediately after catheter removal (i.e.,
the probable primary site of infection is iden-
tified and controlled) is more likely to
respond well to therapy for an infection with
a marginally susceptible isolate than is a
leukopenic patient with multiple-organ
involvement and candidemia that persists
despite catheter removal. The limited
range of alternative antifungal agents and
the significant toxicity and/or the require-
ment for parenteral administration of
some drugs can make decisions to con-
tinue successful therapy in the face of re-
duced susceptibility entirely appropriate.

7. With respect to the selection of a
susceptibility testing method, convincing
correlation data with use of standardized
methods are limited to those obtained

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Drug(s) to which there is a high frequency of resistance</th>
<th>Class of resistance</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus terreus</td>
<td>Amphotericin B</td>
<td>Intrinsic</td>
<td>[53–55]</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>Azoles</td>
<td>Intrinsic and acquired</td>
<td>[56]</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>Azoles</td>
<td>Intrinsic</td>
<td>[56]</td>
</tr>
<tr>
<td>Candida lusitaniae</td>
<td>Amphotericin B</td>
<td>Intrinsic and acquired</td>
<td>[57, 58]</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>Fluconazole</td>
<td>Acquired</td>
<td>[52]</td>
</tr>
<tr>
<td>Scedosporium apiospermum</td>
<td>Amphotericin B</td>
<td>Intrinsic</td>
<td>[58, 60]</td>
</tr>
<tr>
<td>Scedosporium prolificans</td>
<td>Amphotericin B</td>
<td>Intrinsic</td>
<td>[61]</td>
</tr>
<tr>
<td>Trichosporon beigelii</td>
<td>Amphotericin B</td>
<td>Intrinsic</td>
<td>[62]</td>
</tr>
</tbody>
</table>

Table A1. Species with high rates of resistance to antifungal agents.

B; and (3) H. capsulatum and flucona-
zole. Optimal methods are under study
(see tables 2 and 3 for current data). Con-
sultation with an experienced microbi-
ologist is recommended.

4. Isolates of species with high rates
of intrinsic resistance need not be tested,
and alternative agents should be used. If
the selected therapy is associated with a
significant rate of acquired resistance, the
patient should be observed closely for
signs of clinical failure of treatment, and
susceptibility testing should be done, if possible (table A1).

5. For all other organism-drug
combinations, susceptibility testing is unlikely to
usefully influence the selection of therapy. Instead, select therapy based on gen-
eral guidance (e.g., Infectious Disease So-
ciety of America guidelines [63] or other
similar guidelines) and a review of spe-
cific survey data on the organism-drug
combination in question. Be aware that
the newer generation ofazole antifungal
agents may have dissimilar activity against
molds (e.g., posaconazole appears to be
more active than voriconazole against the
agents of zygomycosis [64, 65]).

6. For treatment of patients who re-
spond to therapy despite being infected
with an isolate later found to be resistant,
the best approach is not clear. As indi-
cated by the 90-60 rule, some patients
infected with resistant isolates will re-
spond to therapy. In general, alternative
therapy is desirable for infection with iso-
lates that appear to be highly resistant to
the therapy selected. However, as with the
parallel situation for bacterial infections, the physician should consider the follow-
ing factors: (1) the severity of the infec-
tion, (2) the patient’s immune status, (3)
the ability of the drug to reach adequate
levels at the target location, (4) the ease
of documentation of (lack of) response,
(5) the ability to identify and control the
primary site of infection, (6) the speed
of response, (7) the consequences of re-
currence of infection, (8) the magnitude
of the resistance, and (9) the ability to
increase the dose of the selected antifun-
gal agent in response to an elevated MIC.
For example, a nonneutropenic patient
(i.e., one with good immune status) who
has candidemia (i.e., a condition whose
course is easily followed) that clears im-
mediately after catheter removal (i.e.,
the probable primary site of infection is iden-
tified and controlled) is more likely to
respond well to therapy for an infection with
a marginally susceptible isolate than is a
leukopenic patient with multiple-organ
involvement and candidemia that persists
despite catheter removal. The limited
range of alternative antifungal agents and
the significant toxicity and/or the require-
ment for parenteral administration of
some drugs can make decisions to con-
tinue successful therapy in the face of re-
duced susceptibility entirely appropriate.

7. With respect to the selection of a
susceptibility testing method, convincing
correlation data with use of standardized
methods are limited to those obtained

with the M27-A method (table 2). Meth-
ods that produce results similar to M27-
A method can be developed, but their use
is often just as technically demanding as
is the primary method. A variety of such
methods have been proposed [26], and
one (Sensititre YeastOne; Trek Diagnostic
Systems) has recently been licensed for
use in the United States. Users of alter-
native methods that lack regulatory ap-
proval should carefully validate their re-
results by simultaneous testing with use of
M27-A. Incorporation of known drug-
resistant isolates into the testing proce-
dure is also of value.

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