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.

The challenges that beset attempts to correlate in vitro drug-susceptibility testing results with response to therapy in vivo have been the subject of many thoughtful review articles. Articles that have discussed this topic with respect to testing of antibacterial agents [1–3] have provided an outstanding framework for investigators in other disciplines. Although it is important to remain aware that “criteria for susceptibility testing have frequently resulted from a blend of science, faith, and business” [4, p. 492], some consistently important principles have emerged during the >30 years of active work in the field of susceptibility testing. Along with our colleagues from the National Committee for Clinical Laboratory Standards (NCCLS) Subcommittee on Antifungal Susceptibility Testing, we summarized the key principles in 1997 [5] as follows: (1) an MIC is not a physical or chemical measurement, (2) host factors are often more important than susceptibility test results in determining clinical outcome, (3) susceptibility of a microorganism in vitro does not predict successful therapy, and (4) resistance in vitro should often predict therapeutic failure. These principles continue to be sound but should be updated for 2002 because of the growing appreciation of the importance of pharmacodynamic analyses to the best interpretation of MIC values [6, 7].

It is our purpose here to place these theoretical ideas into a practical clinical context with respect to antifungal susceptibility, in general, and with respect to the standardized NCCLS susceptibility testing methods M27-A (for yeasts [8]) and M38-P (for filamentous fungi [9]), in particular. To this end, we will discuss the relevance of antifungal susceptibility testing by addressing 3 questions: (1) What is the expected degree of correlation between in vitro and in vivo data? (2) Why do the results of individual clinical trials sometimes fail to clearly support breakpoints? Finally, (3) How good are the correlations for antifungal susceptibility testing results?

WHAT IS THE EXPECTED DEGREE OF CORRELATION BETWEEN IN VITRO AND IN VIVO DATA? THE “90-60 RULE”

A clear understanding of the answer to this question provides the key insights required to use susceptibility testing results effectively. Sometimes, the degree of correlation can be quite impressive. For ex-
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>MIC(^b)</td>
<td>Susceptible 83 (224/309)</td>
<td>Resistant 48 (10/21)</td>
</tr>
<tr>
<td>[12]</td>
<td>Bacteremia and fungemia</td>
<td>Various</td>
<td>Mortality</td>
<td>MIC(^b)</td>
<td>Susceptible 89 (594/665)</td>
<td>Resistant 77 (97/126)</td>
</tr>
<tr>
<td>[13]</td>
<td>Pneumococcal otitis media</td>
<td>Amoxicillin/clavulanic acid</td>
<td>Clinical response</td>
<td>MIC</td>
<td>Susceptible 80 (149/186)</td>
<td>Resistant 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>Susceptible 94 (44/47)</td>
<td>Resistant 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>Susceptible 95 (55/58)</td>
<td>Resistant 45 (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>Susceptible 89 (23/26)</td>
<td>Resistant 24 (6/25)</td>
</tr>
<tr>
<td>[17]</td>
<td>Bacteroides bacteremia</td>
<td>Various</td>
<td>Bacteriologic response</td>
<td>MIC</td>
<td>Susceptible 88 (60/68)</td>
<td>Resistant 57 (4/7)</td>
</tr>
<tr>
<td>[18]</td>
<td>Moderate-to-severe bacterial infections</td>
<td>Ciprofloxacin</td>
<td>Bacteriologic response</td>
<td>AUC/MIC ratio</td>
<td>Susceptible 82 (37/45)</td>
<td>Resistant 26 (5/19)</td>
</tr>
<tr>
<td>[19]</td>
<td>Bacterial infections</td>
<td>Aminoglycosides</td>
<td>Bacteriologic response</td>
<td>Peak/MIC ratio ~90(^d)</td>
<td>Susceptible 92 (1464/1591)</td>
<td>Resistant 63 (31/49)</td>
</tr>
<tr>
<td>[3]</td>
<td>Bacterial infections</td>
<td>Cefotaxime</td>
<td>Bacteriologic response</td>
<td>Zone diameter</td>
<td>Susceptible 91 (1652/1815)</td>
<td>Resistant 62 (8/13)</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Susceptible 89 (4521/5081)</td>
<td>Resistant 59 (215/366)</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 (\(\geq 12\)) and lowest (\(< 12\)) 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].

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 and that patients for whom the ratio was ≥125 achieved the best response to therapy. Among patients with a ratio of ≥125,
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, $\geq 64 \mu g/mL$ [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 and azole 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
conazole, although the data are limited to azole breakpoints is similar to that for flu-
findings of detailed pharmacodynamic breakpoints are also supported by the na-
“moderately susceptible” that is used for isolates with an MIC greater than \(0.125 \mu g/mL\) by use of the M27-A method are less likely to respond to therapy.

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].

**Dimorphic fungi.** Application of the M27-A method to *Histoplasma capsulatum* (yeast phase) yielded a strong corre-
Antifungal susceptibility testing has indeed come of age as a useful clinical tool. There is still a need for more precise methodologies that might further extend its utility, and knowledge of how to apply susceptibility testing to the most recently licensed antifungal agents (caspofungin and voriconazole) is not yet available [26]. However, it is still fair to say that antifungal susceptibility testing is indeed come of age as a useful clinical tool.

Other fungi and drugs. For other organisms, meaningful amounts of convincing data obtained with use of standardized methods do not exist.

SUMMARY

Taken together, current data regarding the predictive utility of susceptibility testing for the fungi (table 3) are consistent with the 90-60 rule that we derived from our experience with antibacterial agents (table 1). The recent demonstrations that the principles outlined by the NCCLS process can be adapted to treat both C. neoformans [46] and H. capsulatum infections [52] are exciting next steps in the evolution of this area of research. When these principles can be combined with knowledge of the known patterns of primary resistance among the fungi, a logical approach to the use of antifungal susceptibility testing can be developed (see Appendix). There are, doubtless, further refinements to the technique of antifungal susceptibility testing that might further extend its utility, and knowledge of how to apply susceptibility testing to the most recently licensed antifungal agents (caspofungin and voriconazole) is not yet available [26]. However, it is still fair to say that antifungal susceptibility has indeed come of age as a useful clinical tool.

Acknowledgment

We thank Dr. Sevtap Arikan, Hacettepe University, Ankara, Turkey, for her critique of the manuscript.

APPENDIX

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.
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

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>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5]</td>
<td>Candidiasis, mostly mucosal</td>
<td>Fluconazole, 100</td>
<td>Clinical response</td>
<td>&lt;8</td>
<td>98 (248/253)</td>
<td>76 (37/49)</td>
</tr>
<tr>
<td>[31]</td>
<td>Mucosal candidiasis</td>
<td>Fluconazole, 100–200</td>
<td>Clinical response</td>
<td>&lt;8</td>
<td>80 (28/35)</td>
<td>46 (16/13)</td>
</tr>
<tr>
<td>[32]</td>
<td>Mucosal candidiasis</td>
<td>Fluconazole, 100</td>
<td>Clinical response</td>
<td>&lt;8</td>
<td>96 (49/51)</td>
<td>0 (0/15)</td>
</tr>
<tr>
<td>[33]</td>
<td>Mucosal candidiasis</td>
<td>Fluconazole, 100–400</td>
<td>Clinical response</td>
<td>&lt;32</td>
<td>88 (14/16)</td>
<td>0 (0/5)</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)</td>
<td>59 (47/80)</td>
</tr>
<tr>
<td>[32]</td>
<td>Mucosal candidiasis</td>
<td>Itraconazole, 200</td>
<td>Clinical response</td>
<td>&lt;0.5</td>
<td>98 (48/49)</td>
<td>6 (1/17)</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)</td>
<td>11 (2/18)</td>
</tr>
<tr>
<td>[33]</td>
<td>Mucosal candidiasis</td>
<td>Ketoconazole, &lt;400</td>
<td>Clinical response</td>
<td>&lt;0.06</td>
<td>94 (17/18)</td>
<td>0 (0/3)</td>
</tr>
<tr>
<td>[5]</td>
<td>Candidiasis, mostly invasive</td>
<td>Fluconazole, &gt;100; median, 400</td>
<td>Clinical response</td>
<td>&lt;32</td>
<td>82 (146/178)</td>
<td>46 (18/39)</td>
</tr>
<tr>
<td>[28]</td>
<td>Invasive candidal infections</td>
<td>Fluconazole, 400</td>
<td>Clinical response</td>
<td>&lt;32</td>
<td>77 (23/30)</td>
<td>0 (0/2)</td>
</tr>
<tr>
<td>[29]</td>
<td>Candidemia</td>
<td>Fluconazole, mostly 100–200</td>
<td>Clinical response</td>
<td>&lt;8</td>
<td>52</td>
<td>&lt;14</td>
</tr>
<tr>
<td>[46]</td>
<td>Cryptococcal meningitis</td>
<td>Fluconazole, &lt;400</td>
<td>Clinical response</td>
<td>&lt;16</td>
<td>91 (21/23)</td>
<td>0 (0/5)</td>
</tr>
<tr>
<td>[52]</td>
<td>Disseminated histoplasmosis</td>
<td>Fluconazole, 600–800</td>
<td>Clinical response</td>
<td>&lt;5</td>
<td>97 (36/37)</td>
<td>71 (20/28)</td>
</tr>
<tr>
<td>Total</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>91 (838/923)</td>
<td>48 (131/274)</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.
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-
the best approach is not clear. As indi-
spond to therapy despite being infected
with an isolate later found to be resistant,
more active than voriconazole against the
molds (e.g., posaconazole appears to be
the newer generation of azole antifungal
agents of zygomycosis [64, 65]).

5. For all other organism-drug combi-
nations, susceptibility testing is unlikely
to usefully influence the selection of ther-
apy. 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 of azole 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-
spend 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-
spend 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 following
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 rec-
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.

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

<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>[59, 60]</td>
</tr>
<tr>
<td>Scedosporium prolificans</td>
<td>Amphotericin B</td>
<td>Intrinsic</td>
<td>[61]</td>
</tr>
<tr>
<td>Trichosporon beigeli</td>
<td>Amphotericin B</td>
<td>Intrinsic</td>
<td>[62]</td>
</tr>
</tbody>
</table>

References

6. Craig WA. Pharmacokinetic/pharmacody-
7. Mouton JW, van Gogtop ML, Andes D, Craig WA. Use of pharmacodynamic indices to pre-