Therapeutic Drug Monitoring of Antifungals: Pharmacokinetic and Pharmacodynamic Considerations

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Abstract: Therapeutic drug monitoring of any pharmacologic agent should be considered when there is both significant pharmacokinetic variability and strong, clinically relevant, exposure–effect relationships. Many antifungal drugs exhibit marked variability in drug concentration as a result of inconsistent absorption, metabolism, elimination, or interaction with concomitant medications. For each of the available antifungal drugs, both preclinical and clinical trials have exhibited a relationship between serum concentrations and treatment efficacy. For a smaller subset of compounds, a similar relationship has been identified for the toxicity. The kinetic variability among patients falls outside the therapeutic window for a group of four antifungal compounds. This review summarizes the current literature on therapeutic drug monitoring for these antifungal agents.

Key Words: therapeutic drug monitoring, antifungals, fluconazole, itraconazole, voriconazole, posaconazole

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INTRODUCTION

Invasive fungal infections are a serious and challenging clinical problem. As the population of at-risk immunocompromised patients increases, the incidence of invasive mycosis has risen in parallel.1–3 Despite recent advances in antifungal pharmacology, the morbidity and mortality resulting from invasive fungal infections remains unacceptably high. For the two most common invasive infections, aspergillosis and candidiasis, recent studies estimate that patient survival remains as low as 30% and 70%, respectively.1,2

Historically, the treatment of invasive fungal infections has been marked by few options for therapy because of the limited number of available agents, innate and acquired antifungal drug resistance, and marked drug toxicity. However, over the past 6 years, therapeutic options for invasive fungal diseases have nearly doubled with the development and approval of five new compounds. Study of the pharmacology of these new agents continues to evolve. Understanding of the pharmacokinetics and pharmacodynamics of these drugs will be important to optimize drug choice, dosing regimen design, and to guide therapeutic drug monitoring.

Several factors must be considered in determining the role of therapeutic drug monitoring in patient management. An accurate, rapid, and cost-effective drug assay must be readily available to the clinician. Two pharmacologic features then determine the relevance of drug concentration monitoring. The foremost variable is an unpredictable drug dose–exposure relationship that may be the result of a variety of factors, including erratic bioavailability, variation in drug metabolism or elimination, or interaction with a concomitant medication resulting from alteration of the antimicrobial compound pharmacokinetics. Pharmacokinetic variability is especially critical for drugs with a narrow therapeutic index. Next, there must be a clear relationship between drug concentration and either toxicity or treatment efficacy. Consideration of these pharmacologic variables for available antifungals compounds is the focus of this review.

Antifungal Drug Monitoring Assays

Validated assays have been developed for each of the commonly used antifungal drugs. These assays most often include either microbiologic or a high-performance liquid chromatography (HPLC) assay. The most commonly used method is HPLC resulting from enhanced sensitivity and the reduced time necessary to complete the assay. In most cases, both methods provide similar results. One exception to this rule is for the triazole antifungal, itraconazole. Microbiologic assay results for itraconazole are two to three times higher than those observed with HPLC. This discrepancy is the result of the enhanced microbiologic activity of the itraconazole metabolite (hydroxy-itraconazole) relative to the parent molecule. For all other available antifungals, there are no microbiologically active metabolites.

The cost of these assays is relatively small compared with the expense of the drugs themselves and the patient complications associated with inappropriate antifungal drug exposures. At present, there are only three or four specialized clinical laboratories in the United States that regularly perform these assays. Thus, the time between sample collection and a laboratory result may approach 1 week in some circumstances. The development of additional laboratories will be needed to improve this time lapse to allow therapeutic drug monitoring to more effectively impact on patient outcomes.

Specific Antifungal Drugs

Flucytosine

Flucytosine (5-FC) is a pyrimidine analog that was one of the first antifungal compounds developed. The drug has broad-spectrum activity against Candida species and
**Cryptococcus neoformans.** Clinical use of 5-FC is mainly limited to combination therapy with another antifungal, amphotericin B, for the treatment of cryptococcal meningitis as a result of the rapid selection of resistant isolates when used as monotherapy. The compound is available as an oral formulation that is reliably and nearly completely absorbed. However, wide inter- and intrapatient pharmacokinetic variability was recognized during initial drug development and recently confirmed in the report of a large clinical experience.4 The predominant variable accounting for these differences is variation in renal elimination of 5-FC. Much of this variation is the result of nephrotoxicity associated with administration of the polyene antifungal, amphotericin B. The timing of monitoring of this antifungal, which has a relatively rapid elimination half-life (3–6 hours), has been traditionally within 1 to 3 hours of administration. The drug dose is commonly weight-based (150 mg/kg per day) and administered in four divided doses. A recent report of more than 1000 5-FC serum concentrations in 233 patients with invasive fungal infections demonstrated this pharmacokinetic variability among patients.4 In this large cohort, monitoring identified “therapeutic” peak concentrations in only 20% of patients. 5-FC concentrations were considered subtherapeutic in 40% and undetectable in 5% of samples. Supratherapeutic concentrations were reported in 39% of the samples assayed of which 10% fell into a range considered to be toxic (>100 mg/L).4,5

Pharmacodynamic studies have demonstrated a strong relationship between 5-FC serum concentrations and both toxicity and efficacy. The strongest of these associations has been the toxicodynamic relationship for two relatively common adverse effects, bone marrow suppression and hepatic dysfunction. For example, in a study of 86 patients receiving 5-FC for cryptococcal meningitis, the incidence of both bone marrow suppression and hepatic toxicity was greater than 60% in patients with peak concentrations greater than 100 mg/L.5 Conversely, these toxicities were observed in only 30% of patients with 5-FC concentrations below 100 mg/L. Pharmacodynamic investigation of 5-FC relative to treatment effect has been primarily limited to preclinical infection models. Results from these models demonstrated a strong relationship among 5-FC concentrations in serum relative to the minimum inhibitory concentration (MIC) and treatment efficacy. Maximal organism killing was observed at concentrations just above the MIC and optimal outcomes were observed when serum concentrations exceeded the MIC for only 50% of the dosing interval [time above MIC (T >MIC) 50%].6 A search for similar relationships in clinical trials has not been sought. However, if one considers the MIC distribution for most Candida and Cryptococcal isolates and the pharmacokinetics of 5-FC in patients, it is possible that one could administer lower doses to achieve the pharmacodynamic target of 50% T > MIC.7

**Triazoles.** Four triazole compounds (fluconazole, itraconazole, voriconazole, and posaconazole) have been approved and are commonly used for the management of invasive fungal infections as a result of their relative safety, broad-spectrum activity, and the availability of both parenteral (except posaconazole) and oral preparations. Despite a similar mechanism of action, structural differences among this group of antifungal drugs results in distinct pharmacokinetic properties for each compound. The kinetic characteristics of three of these drugs (itraconazole, voriconazole, and posaconazole) meet the criteria suggesting the usefulness of therapeutic drug monitoring. The pharmacokinetics of fluconazole are predictable and studies have not demonstrated a need for concentration monitoring.

**Itraconazole.** Itraconazole is used in the therapy of a wide spectrum of invasive fungal infections, including Candida, Aspergillus, endemic fungi, and dermatophytes. Three itraconazole formulations are available, allowing both parenteral and oral administration. Pharmacokinetic studies in both healthy volunteers and population pharmacokinetic investigations have repeatedly identified wide interpatient kinetic variation.8 The variation in serum concentrations is largely the result of differences in absorption of the oral formulations. The degree of variation has been shown to vary among formulations.10-14 The most erratic absorption is observed with the tablet formulation compared with the liquid (cyclodextrin) preparation. In general, the cyclodextrin formulation is more readily absorbed than the tablets, resulting in roughly a 30% larger area under the curve than with the tablet preparation. Peak serum concentration at steady state after the oral solution at a dose of 200 mg every 12 hours ranged from 0.513 to 2.278 mg/L with a median concentration of 1.326 mg/L. In contrast, the peak serum concentration at steady state after administration of the capsule formulation at the same dose of 200 mg every 12 hours ranged from 0.297 to 1.609 mg/L with a median value of 0.741 mg/L.10 Factors that impact on the absorption of these preparations include gastric pH and food and are also specific to the formulation.10-14 The absorption from capsules is pH-dependent and requires an acidic environment for optimal absorption. Therefore, it is best absorbed when taken with a meal or cola. Many drugs that are intended to lower gastric pH have a deleterious impact on itraconazole drug absorption. In contrast, the absorption of the oral solution is enhanced when it is taken in a fasted state and has more predictable absorption. In addition, patient factors, including mucosal disease associated with chemotherapy, have also been shown to impact on pharmacokinetic variability.9 Thus, it is not surprising that variation in population kinetic studies is significantly larger than that observed in healthy volunteer studies (coefficient of variation 83–115% compared with 47%, respectively).8,9

Itraconazole has a long elimination half-life (24 hours), is administered once daily, and most monitoring studies have examined trough concentrations. Numerous itraconazole concentration–effect studies have been undertaken and each has demonstrated a strong link to drug efficacy.15-18 A similar relationship for toxicity has not been identified. The itraconazole pharmacodynamic efficacy investigations include both preclinical animal model and clinical trials. The disease states studied include a wide variety of invasive fungal diseases, including those resulting from Candida, Aspergillus, Cryptococcus, and Coccioidoides. In addition, the usefulness of monitoring has been examined using two treatment strategies, including prophylaxis, to prevent the development of an invasive fungal infection as well as treatment of documented
infections. In a preclinical study of animals with invasive aspergillosis, investigators examined the relationship between itraconazole trough concentrations using a microbiologic assay and treatment effect. Maximal reduction in the burden of aspergillus was observed in animals with trough concentrations greater than 6 mg/L. These results correlate well with findings from aspergillus treatment trials. For example, in a group of 21 patients with invasive aspergillosis, mean itraconazole concentration in responders was 6.5 mg/L and only 4.2 mg/L in nonresponders (again based on a microbiologic assay). A similar quantitative relationship was observed in a group of patients with coccidioidomycosis (nonlymphitis). Among this cohort of 39 patients, concentrations measured by bioassay were 6.5 ± 4.2 mg/L in the 28 patients who had a clinical response and only 4.0 ± 3.2 mg/L in 11 nonresponders. In another study, examination of treatment effect using an itraconazole HPLC assay was undertaken in a group of 25 patients with HIV and cryptococcal meningitis. In patients with trough concentrations exceeding 1 mg/L, 100% experienced a complete clinical response. In contrast, those patients with concentrations below 1 mg/L experienced only a partial response 66% of the time.

The largest database examining the relationship between itraconazole therapeutic drug monitoring and treatment efficacy is from a study of oral mucosal candidiasis. Data encompassing more than 250 patients from four trials examined the impact of both itraconazole trough concentration and Candida MIC. The trough concentration associated with the highest treatment rate of success was 0.5 mg/L, perhaps suggesting that lower exposures were needed for treatment of this organism and this infection site.

Another unique area of itraconazole monitoring has been in the study of antifungal drug prophylaxis for patients at high risk of invasive fungal infection such as those patients with hematologic malignancy and bone marrow transplantation. In general, these studies have also demonstrated a relationship between itraconazole serum concentration and effect as measured by prevention of fungal infections. Although the relationship is similar to that observed in treatment studies, the concentration associated with effective disease prevention is two- to fourfold lower than that shown necessary for fungal disease treatment. For example, two independent studies of itraconazole prophylaxis in neutropenic patients included assay of trough concentrations by HPLC. Results from both investigations observed the development of invasive fungal infection in 50% of the cohort with itraconazole concentrations below 0.25 mg/L. In contrast, only 30% of patients with concentrations exceeding this value presented with infections. In another study, the investigators demonstrated a relationship between itraconazole trough concentrations and patient mortality resulting from breakthrough invasive fungal infections. In this case, the concentration associated with poor outcome was less than 0.5 mg/L.

In summary, there are numerous justifications for therapeutic drug monitoring of itraconazole. The compound has irregular absorption that is even more pronounced in patients with pathologic conditions that may affect the gastrointestinal system, including neutropenic patients, those with AIDS, and organ transplant recipients. The drug has a variable dose–concentration relationship and alterations in kinetics during long-term treatment. Itraconazole, like all of the triazoles, exhibits multiple important drug interactions, most notably with cytochrome P450-inducing drugs. Taken together, existing evidence strongly supports therapeutic drug monitoring to optimize clinical efficacy when this drug is used in prophylaxis and therapy of invasive fungal infections.

### Voriconazole

Voriconazole is a more recently developed triazole antifungal with broad-spectrum antifungal activity, including enhanced potency against aspergillus species. The compound is available in both intravenous and oral formulations. The oral formulation has demonstrated near complete bioavailability. Although pharmacokinetic and pharmacodynamic study of this compound is less complete, studies thus far demonstrate some of the cardinal indications for therapeutic drug monitoring. Healthy volunteer pharmacokinetic investigation demonstrated wide intersubject variability in serum concentrations. This variability was observed with both intravenous and oral formulations. Thus, unlike itraconazole, the variability was not attributable entirely to variable absorption, at least in this healthy cohort. Subsequent studies demonstrated that most of the pharmacokinetic variability is the result of differences in the ability to metabolize voriconazole through the CYP2C19 P450 enzyme. Polymorphisms in the gene encoding this enzyme are common and result in variable rates of voriconazole metabolism. Those patients who are homozygous extensive metabolizers at CYP2C19 have less than half the average serum concentration of voriconazole compared with patients who are homozygous poor metabolizers at CYP2C19. Although these polymorphisms can occur in any individual, they are more common in certain ethnic groups. For example, roughly 5% of the white population of the United States is homozygous poor metabolizers of CYP2C19, whereas 75% are homozygous extensive metabolizers. In contrast, patients of Asian descent have a 20% frequency of homozygous poor metabolizer status and only 35% are homozygous extensive metabolizers. More recently, population pharmacokinetic investigation has suggested that the interpatient variability is probably greater in certain patient cohorts. For example, in a recent study of bone marrow transplant recipients receiving voriconazole for antifungal prophylaxis, 87 patients had voriconazole trough concentrations assayed over 5 days of therapy. In this population, 15% had undetectable levels and 27% had concentrations below 0.5 μg/mL, whereas only 62% had measurements over 2 μg/mL (the median concentration in healthy subject studies). Another study in a bone marrow transplant patient population also demonstrated pharmacokinetic variability with trough concentrations ranging from 0.2 to 6.8 mg/L. Recent investigation of voriconazole monitoring has also been undertaken in the solid organ transplant population. In a cohort of 48 lung transplant recipients, peak and trough concentrations were measured. The investigators defined a therapeutic goal as trough concentrations of 1.5 ± 0.5 mg/L and peak values as 4 ± 1 mg/L. These concentration goals were met in only 20% of patients after 1 week. These observations were similar for patients receiving both oral and intravenous voriconazole.
therapy. In this patient group, doses of 800 mg per day were needed to achieve detectable concentrations. In a much smaller study of critically ill patients in an intensive care unit setting, eight were given 200 mg voriconazole by nasogastric tube twice daily. The mean trough concentration was 4.6 \( \mu \text{g/mL} \), whereas two of eight had a trough less than 2 mg/L and one of eight had an undetectable level. These patient data suggest that variables other than CYP2C19 metabolizer status may impact on voriconazole drug exposure.

A number of patient studies examining the relationship between voriconazole exposure and outcome were pursued during clinical development (FDA.gov). Two interesting associations between voriconazole pharmacokinetics and toxicity were observed. The most common adverse effect associated with administration of this compound is an unusual and self-limited visual phenomenon, termed photopsia, which is reported by up to 30% of patients. The median voriconazole plasma concentration in patients reporting this side effect was 3.52 \( \mu \text{g/mL} \); median concentration in those without this visual adverse effect was 2.72 \( \mu \text{g/mL} \). Because of the self-limited nature of this phenomenon, this relationship should not warrant therapeutic drug monitoring. Another potentially more significant but much less common toxicity associated with administration of all triazole drugs, including voriconazole, is hepatotoxicity. Pharmacodynamic evaluation of voriconazole and liver function abnormalities has been examined and a relationship identified. Studies demonstrated that the risk of developing elevated liver function test values increased by 7% to 17% for every 1-\( \mu \text{g/mL} \) increase in the random voriconazole concentration. However, the relative risk of this toxic effect is low. Given the self-limited nature of the visual side effect and the infrequency of the associated liver function abnormality, it is difficult to recommend monitoring on the basis of toxicity. Simply put, just because we have knowledge of a concentration–effect relationship does not mean that we can generate a better outcome for patients.

Another area of pharmacodynamic investigation for voriconazole has been the evaluation of the relationship between exposure and treatment efficacy. Preclinical animal model studies have defined the voriconazole exposure associated with treatment efficacy. Using an invasive candidiasis model, studies demonstrated that a voriconazole exposure expressed as the unbound area under the concentration curve (AUC) in relation to the MIC needed to produce 50% of the maximal microbiologic effect or a 2-log reduction in organism burden compared with control subjects was a value near 25. The value identified for this triazole is nearly identical to that shown to be of importance for other drugs in this class, including fluconazole and posaconazole. Examination of the clinical candidemia trial data suggests a similar relationship is relevant for patient outcome. Although therapeutic drug monitoring was not performed in this trial, organism MIC data are available. Using estimates of patient AUC from clinical trials, one can examine the relationship between the voriconazole-free drug AUC/MIC and patient outcome. In the patient cohort with estimated AUC/MIC values below 25, clinical success ranged from 52% to 60%. However, in the group with exposures of 32 or greater, success was reported in nearly 80% of patients. Three studies have examined the impact of voriconazole exposure in the treatment of another invasive fungal infection, aspergillosis. The largest data set examined random voriconazole concentrations in 142 patients from an open-label treatment trial. Similar to other voriconazole pharmacokinetic studies, a wide range of concentrations were observed (range, 0.1–9.7 \( \mu \text{g/mL} \)). The patient cohort with very low concentrations (less than 0.25 \( \mu \text{g/mL} \)) experienced treatment failure 80% of the time, whereas those with values equal to or above 0.5 \( \mu \text{g/mL} \) were treated successfully in nearly 70% of cases. In a retrospective study of 188 patients who received voriconazole, 28 had concentrations measured because of perceived disease progression (n = 17) or hepatotoxicity (n = 11). Twenty-four of the 28 patients had probable or proven invasive aspergillosis. Ten patients with concentrations greater than 2.0 \( \mu \text{g/mL} \) survived. Forty-four percent of patients with a concentration less than 2.0 \( \mu \text{g/mL} \) survived (\( P < 0.02 \)). The voriconazole dose was increased in 11 patients with concentrations less than 2.0 \( \mu \text{g/mL} \) of whom eight of 11 survived. In another study of voriconazole monitoring, 37 patients with invasive fungal infections were examined. Patients with voriconazole drug concentrations less than 1 \( \mu \text{g/mL} \) exhibited a response rate of just over 50%. Conversely, patients with concentrations over 1 \( \mu \text{g/mL} \) had response rates of 90%. Taken together, these three studies suggest a strong relationship between voriconazole exposure and treatment efficacy in aspergillosis. Whether the optimal concentration of voriconazole is a trough concentration of 0.5, 1.0, or 2.0 \( \mu \text{g/mL} \) remains to be defined definitively in future studies.

**Posaconazole**

Posaconazole is the most recently approved triazole antifungal. The drug exhibits an enhanced spectrum against filamentous fungi, including the emerging Zygomycetes fungal group. Posaconazole is available as an oral formulation and has an extremely prolonged elimination half-life (>24 hours). Despite the prolonged half-life, the compound is optimally administered multiple times daily (two to four times) as a result of saturable absorption. Similar to the triazoles, voriconazole and itraconazole, pharmacokinetic investigation has identified marked interpatient variability in both healthy volunteers and in patient populations. Not surprisingly, the variability has been more pronounced in ill patient cohorts. This may be in part as a result of alteration in the gastrointestinal mucosa as well as the reduced food intake in these patient cohorts because the absorption of posaconazole is significantly enhanced with food. For example, in one study of 98 patients with refractory febrile neutropenia or known invasive fungal infection, concentrations of posaconazole were 52% lower in allogeneic bone marrow transplant recipients than in patients without transplants. In this study, the coefficient of variation was large (71–82%). Similar pharmacokinetic unpredictability was observed in a study of a population of neutropenic stem cell transplant recipients (variability of 38–68%).

The relationship between exposure and efficacy has been examined in both preclinical animal infection models and one clinical trial. Similar to the other triazoles, the pharmacodynamic exposure associated with efficacy in a murine candidiasis model identified the unbound 24 AUC/MIC target of 20 to 25. Animal model pharmacodynamic target
Polyenes and Echinocandins

Clear pharmacodynamic relationships for drugs from these classes have been elucidated. However, pharmacokinetic studies with drugs from these antifungal drug classes do not meet the criteria for therapeutic drug monitoring. The limited population pharmacokinetic data available demonstrates relatively predictable dose–exposure relationships for these antifungals.

SUMMARY

There is significant interpatient variability for several available antifungal drugs and exposure–effect relationships have been demonstrated for each of these compounds. Several clinical trials suggest that therapeutic drug monitoring of this group of antifungals can be useful to both reduce drug toxicity and optimize efficacy. Validated drug assays have been developed for each of these compounds. However, at present, the assays are available at only a few select reference laboratories. Optimal use of these measurements may be enhanced with in-house availability, reducing the turnaround time for results.

Despite the arguably incomplete data to guide antifungal therapeutic drug monitoring, it seems reasonable to offer the following guidance for those wanting to incorporate this tool into patient management (Table 2). For 5-FC, peak concentration monitoring should be considered in all patients early in the course of therapy (3–5 days) to reduce the incidence of toxicity. Measurements should also be performed when there are clinical manifestations of toxicity or any change in renal function. The target 5-FC concentration range should be 10 to 50 μg/mL. For itraconazole, trough concentrations should be assayed in all patients early in the course of prophylaxis or therapy (5–7 days) with evidence of clinical failure or after the initiation of any drug demonstrated to alter itraconazole metabolism. Trough concentration goals for prophylaxis using an HPLC assay should be 0.5 mg/L or greater and 1 to 2 mg/L in the case of treatment of fungal infection. Voriconazole trough concentrations should be monitored early in therapy (2–3 days) for all patients to determine if measurable concentrations are present. Assay should also be considered with poor clinical efficacy, addition of an interacting medication, or change in voriconazole dose (including change from intravenous to oral therapy). A definitive voriconazole trough concentration goal has not yet been identified but is likely to be in the range 0.5 to 2.0 mg/L. For posaconazole, trough concentration monitoring should be considered in all patients early in therapy (3–5 days). Similar to the other triazoles, assay should also be considered if there is poor clinical decline, addition of an interacting medication, or change in dosing regimen. The trough posaconazole goal should be 1.5 mg/L for patients being treated for invasive fungal infection. The goal for prophylaxis is not clear but may be lower as described for the related antifungal, itraconazole.

### TABLE 1. Justification for Therapeutic Drug Monitoring of Antifungals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Assay</th>
<th>Concentration Outcome</th>
<th>Pharmacokinetic Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Toxicity</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>HPLC/Bio</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>HPLC/Bio</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>HPLC/Bio</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>HPLC/Bio</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5-FC</td>
<td>HPLC/Bio/Enz</td>
<td>Yes</td>
<td>Yes (animal)</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>HPLC/Bio</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Amb</td>
<td>HPLC/Bio</td>
<td>No</td>
<td>Yes (animal)</td>
</tr>
</tbody>
</table>

5-FC, flucytosine; HPLC, high-performance liquid chromatography; Bio, Enz, abs, met, RF.

### TABLE 2. Recommendations for Therapeutic Drug Monitoring of Antifungals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Timing</th>
<th>Goal</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FC</td>
<td>Peak 3–5 days</td>
<td>10–50 μg/mL</td>
<td>Initial therapy, renal insufficiency, evidence of toxicity</td>
</tr>
<tr>
<td>Itraconazole (HPLC)</td>
<td>Random 5–7 days</td>
<td>Therapy &gt;1 μg/mL Prophylaxis &gt;0.5 μg/mL</td>
<td>Initial therapy, clinical decline, interacting medication</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Trough 2–3 days</td>
<td>&gt;0.5–2 μg/mL</td>
<td>Initial therapy, clinical decline, change in dose, interacting medication</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Random 3–5 days</td>
<td>&gt;1.5 μg/mL</td>
<td>Initial therapy, clinical decline, interacting medication</td>
</tr>
</tbody>
</table>

5-FU, flucytosine; HPLC, high-performance liquid chromatography.
studies are desperately needed to identify the optimal timing of monitoring, to refine the concentration goals, and to better delineate targeted monitoring for specific patient populations and clinical scenarios.

REFERENCES