Aus dem Zentrum für Innere Medizin der Universität zu Köln
Klinik I für Innere Medizin

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# Optimization of Antifungal Prophylaxis in Haematological High-Risk Patients

# Optimierung der antimykotischen Prophylaxe bei hämatologischen Hochrisikopatienten

Habilitationsschrift zur Erlangung der venia legendi
für das Fach Innere Medizin
an der Hohen Medizinischen Fakultät
der Universität zu Köln

vorgelegt von

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Dedicated to

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## Abbreviations

| | |
|---|---|
| AML | Acute myelogenous leukemia |
| CSA | Cyclosporine |
| CYP | Cytochrome P |
| FDA | Food and Drug Administration |
| HEPA | High-efficiency particulate air |
| IFD | Invasive fungal disease |
| MDS | Myelodysplastic syndrome |
| MIC | Micafungin |
| NNT | Numbers needed to treat |
| NONMEM | Non-linear mixed effect modeling |
| POS | Posaconazole |
| SCT | Stem cell transplantation |
| TAC | Tacrolimus |
| TDM | Therapeutic drug monitoring |
| UHC | University Hospital Cologne |
| VCZ | Voriconazole |

## German Summary – Deutsche Zusammenfassung

Patienten, die an einer hämatologischen Grunderkrankung leiden, sind einem hohen Risiko invasiver Mykosen ausgesetzt, insbesondere bei Vorliegen einer langen und tiefen Neutropenie oder im Rahmen einer allogenen Stammzelltransplantation. Unter diesen Umständen hat sich die Verabreichung einer antimykotischen Prophylaxe zu einer populären Strategie entwickelt, wobei hier hauptsächlich Präparate aus der Gruppe der Azole sowie das Echinocandin Micafungin genutzt werden. Die vorliegende kumulative Habilitationsschrift beschreibt ein breites Spektrum an Faktoren, die die klinische Effektivität und Verträglichkeit der antimykotischen Prophylaxe beeinflussen können, wobei der Fokus auf epidemiologische, pharmakokinetische und pharmakodynamische Aspekte gelegt wurde. Eine Reihe an Empfehlungen mit Bezug auf die Behandlung von Patienten mit hämatologischen Erkrankungen können aus den dargestellten Ergebnissen abgeleitet werden.

Erstens empfiehlt sich vor Etablierung einer antimykotischen Prophylaxe eine Erhebung der lokalen Inzidenz invasiver Mykosen in der betroffenen Risikopopulation. Nur in einer Population mit hoher Inzidenz kann ein effizienter Schutz vor invasiven Mykosen gewährleistet werden, ohne dabei eine große Anzahl an Patienten unnötigen Therapien und evtl. Nebenwirkungen auszusetzen. Zweitens zeigen verschiedene epidemiologische Erhebungen eine Zunahme vormals seltener Mykosen, insbesondere von Species aus der Klasse der Mucorales, *Candida* non-*albicans* spp. und Azol-resistenten *Aspergillus* spp. Sollten diese epidemiologischen Veränderungen anhalten, könnte die Effizienz aktueller antimykotischer Strategien in Zukunft gefährdet sein, da in diesem Zusammenhang eine Verschiebung der Resistenzspektren zu erwarten ist. Drittens konnte anhand von Surveillance-Studien gezeigt werden, dass bei Vorliegen bestimmter meteorologischer Konstellationen sowie im Rahmen von Ausbrüchen respiratorischer viraler Erkrankungen ein gehäuftes Auftreten von invasiven Mykosen bei hämatologischen Patienten zu erwarten ist. In diesen Situationen sollten behandelnde Ärzte die Möglichkeit von Durchbruchinfektionen unter antimykotischer Prophylaxe in Ihre diagnostischen Erwägungen mit einbeziehen. Schließlich konnte der Einfluss verschiedener Faktoren auf die Antimykotikaexposition des einzelnen Patienten gezeigt werden. Belastbare Grenzwerte für die klinische Interpretation von Antimykotikaspiegeln konnten bisher nur für Itraconazol und Voriconazol etabliert werden, jedoch nicht für Posaconazol und die Echinocandine.

Aus heutiger Perspektive sollten verschiedene Ansätze zur weiteren Optimierung der antimykotischen Prophylaxe bei hämatologischen Hochrisikopatienten verfolgt werden. Zum einen empfiehlt sich der weitere Ausbau nationaler und internationaler Surveillance Netzwerke, um eine zeitnahe Reaktion auf signifikante epidemiologische Entwicklungen zu ermöglichen. Zum anderen könnten immunologische Studien den genauen Zusammenhang zwischen pulmonalen Virus- und Pilzinfektionen des immunsupprimierten Patienten genauer zu untersuchen. Schließlich ist es notwendig, vorgeschlagene Grenzwerte für eine optimale Antimykotikaexposition anhand kontrollierter randomisierter Studien zu validieren.

# 1. Introduction

Patients with hematological malignancies, particularly those experiencing prolonged periods of neutropenia or immunosuppression, are at a high risk of contracting invasive fungal diseases (IFD). *Aspergillus* spp. and *Candida* spp. are considered the most prevalent fungal pathogens in this setting, accounting for over 95 % of all IFDs.[1-3] While invasive aspergillosis commonly manifests itself as an invasive pulmonary infection, invasive candidiasis is usually diagnosed as a bloodstream infection. Less frequently isolated pathogens include the Mucorales, *Fusarium* spp. and a number of rare yeasts, e.g. *Geotrichum* and *Trichosporon* spp. [1-3] In spite of the continuing expansion of the antifungal armamentarium over the last decade, the 12-week mortality rate associated with invasive aspergillosis and candidiasis of the immunocompromised patient remains high at 18-36% and 15-49%, respectively.[1,3] At the same time, the negative effect of delayed antifungal treatment initiation on patient outcome has been demonstrated in a number of studies.[4-6] In the clinical setting, such delays are frequently encountered, as prolonged thrombocytopenia often forbids an interventional diagnostic workup that would be necessary to overcome the lack of reliable non-invasive diagnostic tools for rapid identification of fungal pathogens. Under these circumstances, the concept of antifungal prophylaxis has grown in popularity, instigating a number of major clinical trials on the issue.

The first trial to demonstrate a survival benefit for patients receiving antifungal prophylaxis was conducted in the setting of allogeneic stem cell transplantation (SCT).[7] Based on its results, SCT centers worldwide established fluconazole prophylaxis as their standard of care. Since fluconazole has the disadvantage of lacking activity against molds, further trials in this setting used antifungals with a broader spectrum, i.e. itraconazole, voriconazole, or micafungin.[7-9] While these studies demonstrated a trend towards less breakthrough mold infections and less need for empiric or targeted antifungal treatment compared to fluconazole, they did not result in improved overall survival. However, a trial in patients receiving immunosuppressants for severe graft-versus-host disease demonstrated significantly improved attributable survival rates for posaconazole as opposed to fluconazole or itraconazole.[10]

The other group of hematological high risk patients that has been shown to profit from antifungal prophylaxis are those undergoing remission induction chemotherapy for acute

myelogenous leukemia (AML) or myelodysplastic syndrome (MDS). For patients receiving posaconazole prophylaxis, a significantly reduced incidence of IFD, as well as improved overall survival could be shown, when compared to patients receiving antifungal prophylaxis with fluconazole or itraconazole.[11]

Finally, patients undergoing induction chemotherapy for acute lymphatic leukemia are exposed to prolonged periods of neutropenia, as well. However, due to their interaction with vinca-alkaloids, prophylaxis with azole antifungals is contraindicated in this setting. An interventional study assessing the prophylactic efficacy of intermittent liposomal amphotericin B is currently recruiting.[12]

The above mentioned trials have provided clinicians with sound evidence to support specific prophylactic regimens in different therapeutic settings (Figure 1), however, outside the controlled environment and highly selected patient collectives of interventional trials, a variety of factors, including epidemiology, finances, tolerance as well as pharmacokinetics and pharmacodynamics, have been shown to impact on the successful implementation and efficacy of antifungal prophylaxis. By consideration of these aspects, antifungal prophylaxis strategies can be improved beyond the answers derived from randomized trials.

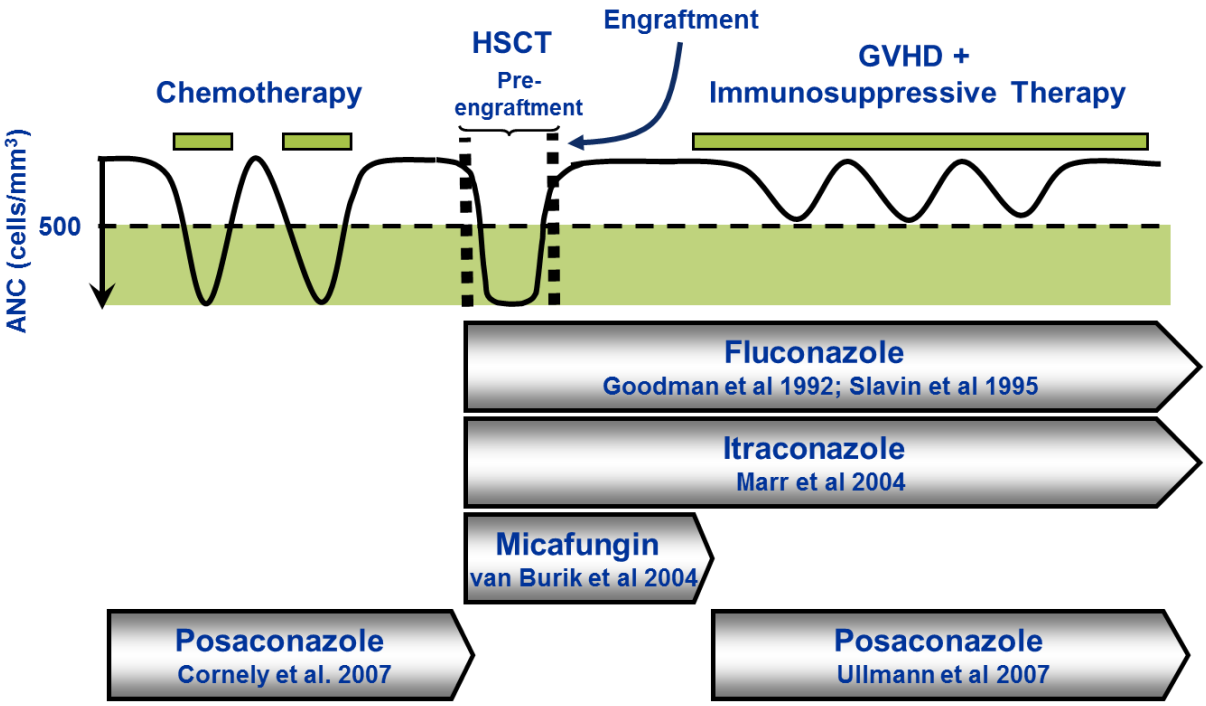


Figure 1: Established antifungal prophylaxis strategies (with permission from Prof. Oliver A. Cornely)

The present cumulative habilitation treatise will focus on a detailed presentation and discussion of epidemiological, pharmacodynamic and pharmacokinetic factors influencing the clinical efficacy of antifungal prophylaxis in hematological high risk patients. In order to demonstrate the author's own contributions to this area of research, her published original works will be set in the context of the current basis of evidence.

# 2. Epidemiological Factors

## 2.1. Incidence of Invasive Fungal Diseases

Before implementation of any antifungal prophylaxis regimen, data on the local incidence of IFDs should be collected, analyzed and scrutinized with respect to the expected impact of antifungal prophylaxis on morbidity and mortality. The concept of "number needed to treat" (NNT) can be very helpful in this process. In this case, the local NNT reflecting the number of patients requiring prophylaxis, in order to prevent one IFD or patient death, would be of interest. While a low NNT suggests efficacious protection without excessive exposure to antifungals of patients who will never develop IFD, the inverse is true for high NNT. However, there is no official cutoff for acceptable NNT, particularly as such a statement would implicitly involve a statement on the subjective value of protecting one patient from an infection.[13] The advantages and limitations of NNT calculations will be demonstrated at the example of posaconazole prophylaxis for patients undergoing remission induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS). This prophylactic regimen was shown to significantly reduce the incidence of IFD and improve overall survival in the above described population. The incidence of IFD was 2% in the posaconazole group and 8% in the comparator group receiving itraconazole or fluconazole.[11] Based on these findings, a NNT of 16 was calculated for the prevention of one IFD.[14]

In response to this publication, posaconazole prophylaxis for AML/MDS patients was introduced at the 1st Department of Internal Medicine of the University Hospital Cologne (UHC), Germany. However, to avoid unnecessary administration of antifungal prophylaxis in a low incidence setting, a prospective cohort study was conducted. Patients undergoing remission/induction chemotherapy for AML before and after the introduction of posaconazole prophylaxis were compared with respect to IFD. The incidence of IFD was 30.8% in patients receiving topical polyene prophylaxis, only and 17.4% in patients receiving posaconazole. The corresponding NNT to prevent one IFD was 7. Since this was considered low in comparison with the corresponding interventional trial, posaconazole prophylaxis was definitely incorporated into the UHC standard of care.[15]

Published in:

*Vehreschild JJ, **Rüping MJ**, Wisplinghoff H, Farowski F, Steinbach A, Sims R, Stollorz A, Kreuzer KA, Hallek M, Bangard C, Cornely OA (2010) Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort. J Antimicrob Chemother 65(7):1466-71*

## 2.2. Environmental Factors

As discussed in the previous chapter, knowledge of the local incidence of IFDs is crucial in the process of implementing a new antifungal prophylaxis regimen. However, incidence rates cannot be expected to remain stable over time, as they depend on numerous environmental factors. As most infections in the hematological patient are caused by molds, disease transmission usually occurs through inhalation of fungal spores, ubiquitously found in breathing air. In the absence of functioning alveolar macrophages and neutrophils, these spores may germinate and penetrate the alveolar lining, eventually resulting in IFD. Depending on the density of spores in the inhaled air, the likelihood of contracting an IFD varies.[16]

High environmental conidia loads have been reported in association with construction works as well as certain meteorological constellations of temperature, relative humidity of the air, dew point, wind velocity and barometric pressure.[17-19] At the same time, high-efficiency particulate air (HEPA) filtration has been shown to reduce the incidence of IFDs.[20, 21]

To assess the impact of meteorological factors on environmental spore counts at different sites inside and outside the UHC main building, a surveillance study based on continuous air sampling was conducted between December 2007 and November 2008. While no correlation between environmental conidia load and any single meteorological factor could be identified, conidia levels were shown to be highest in fall and lowest during the summer (Figure 2).[22]

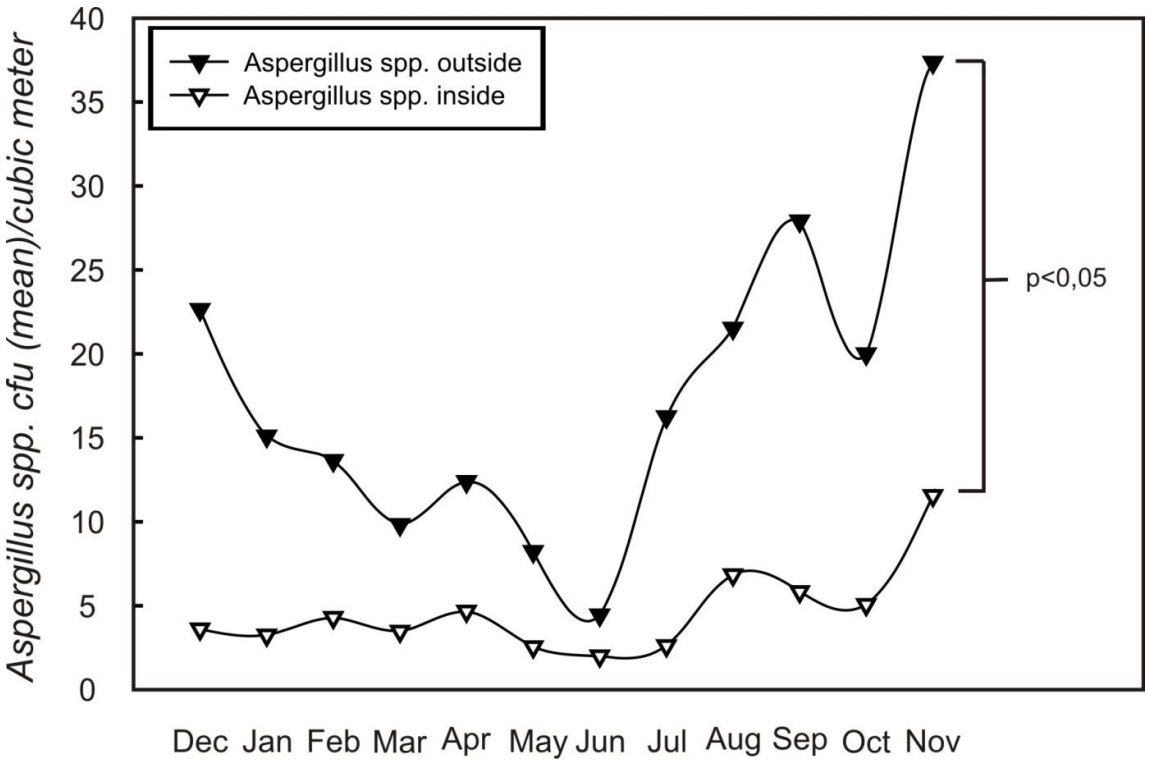


Figure 2: Seasonal variation of *Aspergillus* spp. mean concentration in samples collected inside and outside the main building[22]

Published in:

***Rüping MJ**, Gerlach S, Fischer G, Lass-Flörl C, Hellmich M, Vehreschild JJ, Cornely OA (2011) Environmental and clinical epidemiology of Aspergillus terreus: data from a prospective surveillance study. J Hosp Infect 78(3):226-30*

## 2.3. Pathogen Interaction

Viral co-infections are emerging as a potential risk factor for IFDs during the cold season. Until 2009, only limited data on a possible association with previous parainfluenza and respiratory syncytial virus infection had been published.[23, 24] However, a workup of data collected during the 2009 H1N1 influenza pandemic revealed an unexpected rise in the incidence of IFDs in patients who had previously contracted H1N1 influenza.[25-27] At the UHC, three out of five patients receiving remission-induction chemotherapy for AML presented with breakthrough aspergillosis under posaconazole prophylaxis. In comparison, an analysis of the three years preceding the influenza pandemic revealed an incidence rate of only 2/77

patients.[28] While the underlying pathomechanism remains elusive, loss of barrier function, reduced ciliary clearance of respiratory tract epithelium and modulation of the cell-mediated immune response might contribute to the development of IFDs.[29]

Published in:

*Vehreschild JJ, Bröckelmann PJ, Bangard C, Verheyen J,* ***Vehreschild MJ****, Michels G, Wisplinghoff H, Cornely OA (2011) Pandemic 2009 influenza A(H1N1) virus infection coinciding with invasive pulmonary aspergillosis in neutropenic patients. Epidemiol Infect 8:1-5.*

## 2.4. Emerging Fungal Pathogens

Since *Aspergillus* spp. and *Candida* spp. are considered the most frequent cause of IFDs in patients with hematological malignancies, the spectrum of activity of most available antifungals is tailored to these pathogens. However, during the last decades, a shift towards so-called emerging IFDs has been observed.[1-3] These observations are of crucial importance when evaluating the expected efficacy of a selected antifungal prophylaxis regimen, as epidemiological shifts are often associated with shifts in antifungal susceptibility. Concerning mold infections, particularly species from the order Mucorales (formerly often classified under the more general term “Zygomycetes”) are being diagnosed at an increased rate in immunocompromised patients.[30-32] These infections are associated with a considerable mortality that may surpass 50% in immunocompromised populations.[1, 33, 34] Among the azole antifungals, fluconazole and voriconazole display no activity against the Mucorales, while posaconazole and itraconazole both display activity against some species.[35-37]

At the UHC, Fungiscope - A Global Database for Emerging Fungal Infections was developed and used to collect data on IFDs with Mucorales. In a series of 41 cases of Mucorales infections, ten patients (24.4%) experienced a breakthrough infection during continuous antifungal prophylaxis, four of whom were using posaconazole or itraconazole. Details are given in Table 1.[34]

Table 1: Breakthrough IFD by Mucorales

| Antifungal prophylaxis | n | % | Average duration [d] | Median duration [d] |
|---|---|---|---|---|
| Overall | 10 | 24.4 | 46.6 | 31 |
| *Voriconazole* | 4 | 9.8 | 48 | 23 |
| *Posaconazole* | 3 | 7.3 | 33 | 35 |
| *Fluconazole* | 2 | 4.8 | 73 | 73 |
| *Itraconazole* | 1 | 2.4 | 31 | 31 |

Further breakthrough infections under these potentially protective prophylaxis regimens have been reported in the literature.[33, 38-42] While inadequate serum levels of the prophylactic agents used cannot be excluded in all cases, breakthrough IFDs with Mucorales should be expected to increase in number, if the epidemiological trend towards a more frequent diagnosis of emerging IFDs continues.

Another recently observed epidemiological shift concerns the emergence of resistant *Candida* and *Aspergillus* spp. Until today, *C. albicans* remains the leading cause of invasive candidiasis, however, the rate of infections with non-*albicans Candida* spp., such as *C. glabrata, C. parapsilosis*, *C. tropicalis* and *C. krusei,* is increasing worldwide.[43-45] It has been argued that selection of non-*albicans Candida* spp. may be a consequence of selection pressure under the increasing use of fluconazole prophylaxis.[46, 47] Many of the non-*albicans Candida* spp. display reduced susceptibility to fluconazole, e.g., *C. glabrata* displays a dose-dependent and *C. krusei* an intrinsic resistance to fluconazole. [48-51] In response to these developments, antifungal prophylaxis with echinocandins or broad spectrum azoles instead of fluconazole is likely to become increasingly popular.

Finally, the emergence of triazole-resistant *Aspergillus* spp. has quickly evolved into a matter of major concern. In 2008, a surveillance study from the Netherlands reported on the identification of 32 *Aspergillus fumigatus* isolates with resistance to itraconazole and reduced susceptibility to posaconazole, voriconazole and ravuconazole. All isolates stemmed from clinical specimens, and in 94%, the substitution of leucine 98 for histidine in the cyp51A gene, together with two copies of a 34-bp sequence in tandem in the gene promoter (TR/L98H), was identified as the underlying resistance mechanism.[52] Further studies revealed the presence of isolates with the same resistance mechanism in the environment.[53]

These isolates also displayed a cross-resistance to the fungicides metconazole and tebuconazole, frequently used in agricultural settings.[53] Soon after the publication of these findings, the potential clinical relevance of this development became apparent, as clinical cases of IFD caused by triazole-resistant isolates carrying the TR/L98H mutation were reported from different European countries.[54-57] At the UHC, the first infection of a hematological patient with an isolate carrying the TR/L98H mutation in Germany was diagnosed in the context of an ongoing surveillance study.[58] Further surveillance studies conducted in China and India indicate a relevant prevalence of resistant isolates in countries outside Europe.[59, 60] *In vitro* experiments and molecular analyses of environmental isolates support the hypothesis, that fungicide-driven selection of triazole-resistant isolates in the environment has caused cross-resistance to medical triazoles.[53, 60, 61]

The impact of these findings on future antifungal prophylaxis strategies remains elusive. Since triazoles are the most frequently administered antifungal agents with mold activity, a further rise in the incidence of IFD with isolates carrying the TR/L98H mutation might challenge current standards of care. However, at this point in time, the dynamics of resistance development cannot be foreseen, and further surveillance studies are warranted.

Published in:

***Rüping MJ**, Heinz WJ, Kindo AJ, Rickerts V, Lass-Flörl C, Beisel C, Herbrecht R, Roth Y, Silling G, Ullmann AJ, Borchert K, Egerer G, Maertens J, Maschmeyer G, Simon A, Wattad M, Fischer G, Vehreschild JJ, Cornely OA (2010) Forty-one recent cases of invasive zygomycosis from a global clinical registry. J Antimicrob Chemother 65(2):296-302*

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## 3. Pharmacokinetic Factors

Pharmacokinetic studies assess the absorption and distribution, modification and excretion of drugs and their metabolites. All of these aspects play a major role in the optimization of any prophylactic or therapeutic agent, including antifungals. In this chapter, the most relevant aspects will be discussed in detail.

As most azoles act as a substrate and/or an inhibitor of cytochrome P (CYP) isoenzymes, they are associated with a significant potential for drug-drug interactions. As an example, clinically relevant drug-drug interactions of voriconazole with other drugs frequently used in the hematology setting are shown in Table 2.[62]

Table 2: Voriconazole drug-drug interactions in the hematology setting (adapted from[62])

| Drug | Interaction | Recommendations |
|---|---|---|
| Sirolimus | ↑ sirolimus concentration (CYP3A4 inhibition by VCZ) | Co-administration contraindicated |
| CSA/ TAC | ↑ CSA/TAC concentrations (CYP3A4 inhibition by VCZ) | Carefully monitor CSA/TAC levels; pre-emptive dosage adjustment may be necessary |
| Benzodiazepines (midazolam, triazolam, alprazolam) | ↑ benzodiazepine concentration (CYP3A4 inhibition by VCZ) | Frequent monitoring for benzodiazepine adverse events and toxicity recommended |
| Long acting opioids (methadone, fentanyl, alfentanil, oxycodone) | ↑ opioid concentration (CYP3A4 inhibition by VCZ) | Extended and frequent monitoring for opioid associated adverse events recommended; opioid usage reduction may be necessary |
| Statins | ↑ statin concentration (CYP3A4 inhibition by VCZ) | Frequent monitoring for statin adverse events (e.g. rhabdomyolysis) recommended; statin dosage reduction may be necessary |
| Vinca alkaloids | ↑ vinca alkaloids concentration (CYP3A4 Inhibition by VCZ) | Frequently monitor for VCZ adverse events and toxicity (neurotoxicity); adjustment of vinca alkaloid dosage may be necessary |
| Omeprazole (two-way interaction) | ↑ omeprazole concentration (CYP2C19 inhibition by VCZ) ↑ VCZ concentration (CYP2C19 and 3A4 inhibition by omeprazole) | Monitor for signs of VCZ toxicity (neurotoxicity, hepatotoxicity); omeprazole dosage reduction may be necessary |

VCZ: voriconazole; CSA: cyclosporine; TAC: tacrolimus

Less drug-drug interactions have been observed for posaconazole, as its metabolism is not mediated through CYP oxidation, but UDP glucuronidation and p-glycoprotein efflux mechanisms.[63] Therefore, its exposure is not affected by co-administration of CYP inducers

or inhibitors. On the other hand, a strong inhibition of the CYP3A4 pathway by posaconazole has been observed. This may lead to increased concentrations of any CYP3A4 substrate, e.g. cyclosporine, tacrolimus and sirolimus, benzodiazepines, certain statins, as well as the ergot alkaloids.[64-66]

Genetic polymorphisms in CYP metabolization pathways may result in unpredictable drug dose-exposure relationships, e.g. the CYP2C19 isoenzyme displays genetic polymorphism and plays a significant role in the metabolism of voriconazole. While most patients are homozygous extensive metabolizers, up to 20% of non-Indian Asians and 5% of Caucasians or African-Americans are heterozygous poor metabolizers.[67, 68] The latter population is consequently exposed to significantly higher voriconazole serum concentrations that may induce unwanted side effects.[69] No allelic variation as a result of CYP polymorphism has been observed for posaconazole.

Patients undergoing chemotherapy for a hematological or allogeneic SCT malignancy are likely to experience side effects such as nausea, vomiting, mucositis and diarrhea that might impair the intestinal absorption of oral antifungals.[70, 71] In severe cases, the patient may not be able to ingest any oral medication at all. Under these circumstances, serum levels of oral antifungal prophylaxis agents may drop, thus jeopardizing their protective effect.[10, 72] On the other hand, certain alimentary standards may improve antifungal serum levels. For example, mean posaconazole serum levels can be 2-3 fold increased if administration is accompanied by food intake. Concurrent ingestion of a high-fat meal may even increase bioavailability by 4-fold.[73]

At the UHC, factors influencing pharmacokinetics of prophylactic posaconazole in patients undergoing allogeneic SCT or induction chemotherapy for AML were examined by two separate population pharmacokinetic models using non-linear mixed effect modeling (NONMEM). The term NONMEM analysis describes a multi-step approach that starts with the building of a basic population pharmacokinetic model. To select the most appropriate model, observed serum posaconazole concentrations and respective predicted values are inspected visually. For the best model, a more random distribution across the line of unity in comparison to alternative models should be present. An example of this process is given in Figure 3.[74] For validation of the thus selected model, potentially relevant covariates are

assessed by univariate analysis, multiple regression analysis with forward selection and finally multiple regression analysis with backward elimination (Figure 2).[74, 75]

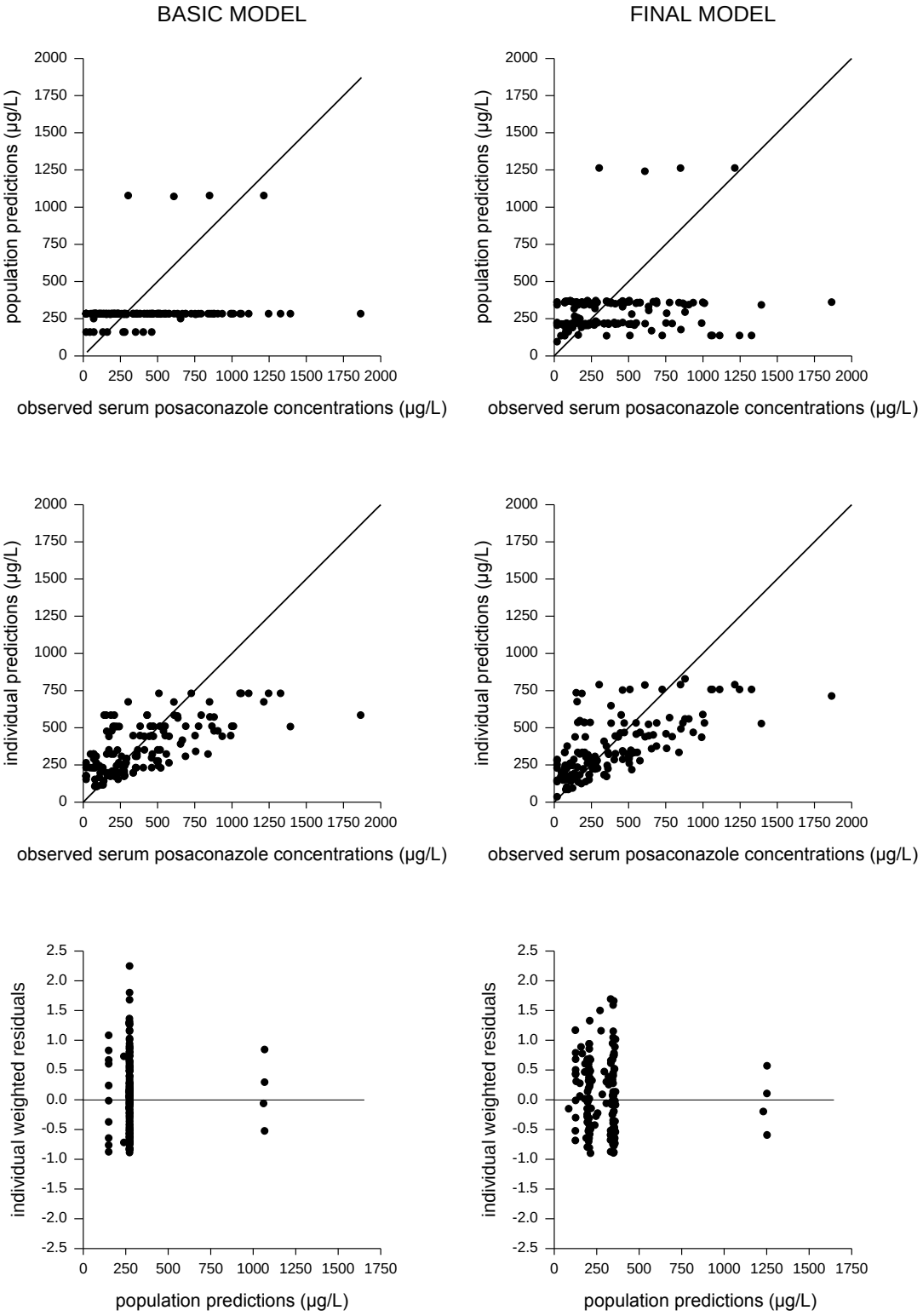


Figure 3: Overview of goodness-of-fits plots, and their improvement in two constructed models.[74]

*Model 1 (left column) is the basic model; Model 2 (right column) represents the final model with age and diarrhoea as covariates. The solid lines in the upper panels represent unity.*

For patients undergoing induction chemotherapy for AML, significant effects on posaconazole exposure were shown for patient weight (33.4 L larger apparent volume of distribution per kilogram), presence of diarrhea (1.5--fold increase in apparent clearance), and concomitant administration of chemotherapy (0.6-fold lower apparent volume of distribution) or pantoprazole (1.6--fold increase in apparent clearance).[75] In the allogeneic SCT population, significant effects were shown for age (decrease in the volume of distribution of 123 L per year of age) and the presence of diarrhea (59% loss of bioavailability).[74] Based on these results, particularly adjustments of the starting dose according to the presence of diarrhea seem warranted to improve posaconazole serum levels.

In order to validate this hypothesis, an interventional trial, assessing different dosing strategies that may result in increased posaconazole bioavailability in patients with compromised gastrointestinal function and at high risk for IFD was conducted. Overall, 49/75 patients were eligible for pharmacokinetic analyses. Documented posaconazole mean plasma concentrations were 230, 346, and 637 ng/ mL on days 2, 3, and 8, respectively. Posaconazole doses of 200 mg three times daily, 400 mg twice daily, and 400 mg three times daily were associated with plasma levels of 660, 930, and 671 ng/ mL, respectively on day 15. Twelve patients presented with a day 8 plasma concentration of <250 ng/ mL, and their exposure to posaconazole was not significantly increased through application of one of the two higher dosing strategies. In addition, these “poor absorbers” did not present with higher posaconazole serum levels after an increase of the dose on day 9. It was concluded that poor posaconazole absorption can be enhanced by a high-fat meal, co-administration of a nutritional supplement, or acidification. However, the beneficial effects of a dose modification seem at best limited.[76]

As presented above, the problem of reduced posaconazole absorption in patients with gastrointestinal disturbances has not been solved to a satisfactory extent. This used to be an issue of particular concern to physicians involved in the care of allogeneic SCT patients at the UHC. In 2006, administration of oral posaconazole prophylaxis from the start of the conditioning chemotherapy regimen until day 100 after SCT was introduced as a standard of care. However, as a considerable percentage of patients develop severe mucositis, nausea and/or diarrhea shortly after SCT, administration of posaconazole could rarely be performed

in a continuous fashion. As soon as encouraging data on micafungin prophylaxis during and after SCT was published,[77-79] bridging with intravenous micafungin in the above described situations was included into the standard of care. To assess the clinical efficacy of this new approach, a prospective cohort study was conducted.

Results showed that patients for whom bridging with micafungin was available were less likely to present with an unspecific pneumonic infiltrate (36.3% and 23%; P=0.025) or an infiltrate typical of IFD (15.9% and 5.2%; P=0.006). Furthermore, they experienced significantly less febrile days (6.15 ± 7.18 and 4.43 ± 4.48; P= 0.018). Finally, a significant improvement in fungal-free survival at day 100 could be demonstrated (p=0.031, Figure 4), while there were no significant differences in overall survival at day 100 and 36.

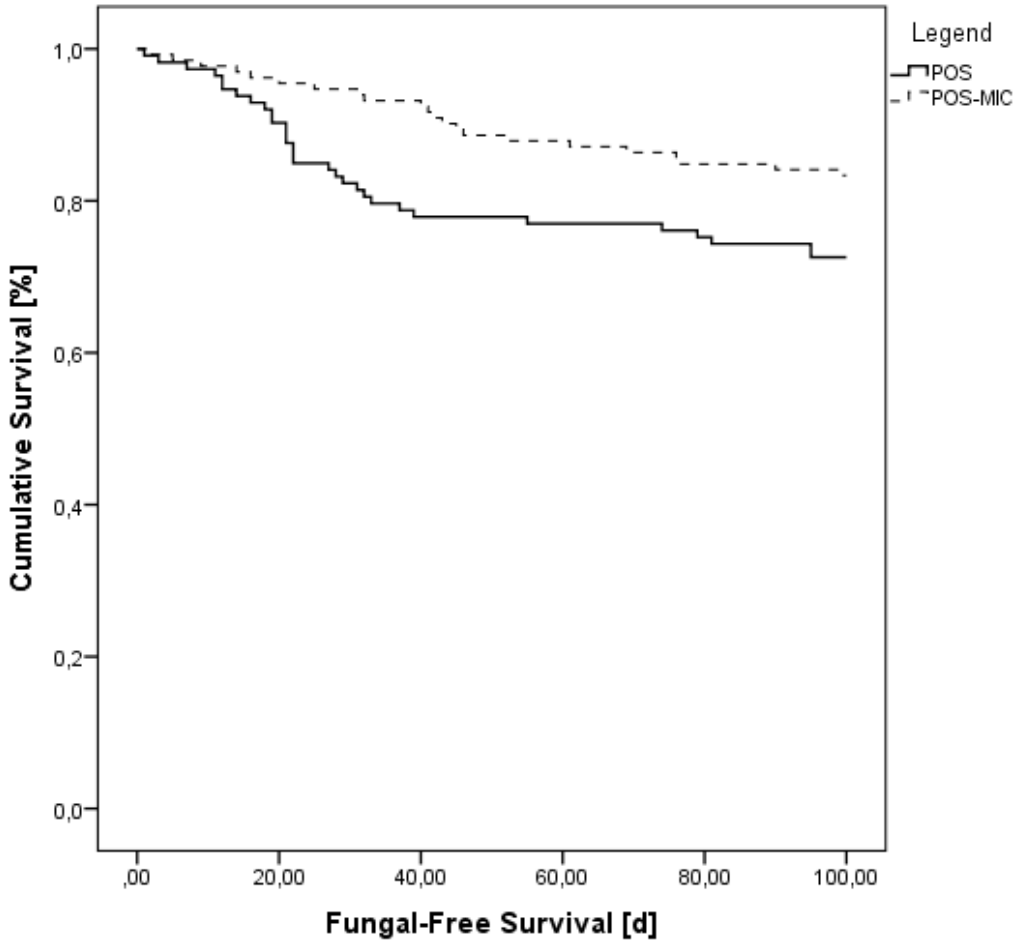


Figure 4: Fungal-free Survival (Kaplan-Meier-plot)

*Follow-up was complete for all patients in the trial (no cases censored). Table shows patients at risk during different time periods (p=0.031); POS=posaconazole; POS-MIC=posaconazole with micafungin bridging*

These results suggest that allogeneic SCT recipients receiving posaconazole prophylaxis profit from bridging with intravenous micafungin during periods of oral intolerance or disturbed intestinal absorption.[80]

Not only in patients with compromised gastrointestinal function, but also in those at risk of fungal meningo-encephalitis, increasing exposure to antifungals is a major concern. However, in the latter population, penetration of the administered antifungal into the central spinal fluid (CSF) as opposed to the serum is most likely required to ensure protection against IFD. Even though fungal meningo-encephalitis is associated with a dire prognosis[81], data on the penetration of different antifungal substances into the CSF is limited. Among those agents used for antifungal prophylaxis, satisfactory central nervous system penetration has been shown for fluconazole and voriconazole, but not for itraconazole and the echinocandins.[82-84] Concerning posaconazole penetration into the central nervous system (CNS), confliciting data has been published. To elucidate this issue, data from three patients with available posaconazole concentrations from serum or plasma and CSF or cerebral abscess fluid, respectively, were analyzed at the UHC. The results suggested that posaconazole penetration into the CNS and CSF is limited, unless a disturbance of the blood-brain barrier is induced by an inflammatory process.[85] These findings are consistent with results from a clinical trial in which a satisfactory activity of posaconazole in the treatment of fungal CNS infections was observed.[86] Furthermore, allogeneic SCT recipients under posaconazole prophylaxis and without any signs of CNS infection or inflammation, displayed low CSF posaconazole levels.[87]

Published in:

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## 4. Pharmacodynamic Factors

While the impact of various pharmacokinetic factors on antifungal exposure has been explored in the previous chapter, little has been said about dose-effect relationships. In theory, it could be assumed that the measurement of drug concentrations, followed by an individualized dose adaptation, enhances efficacy and safety of antifungal prophylaxis. However, in clinical practice, the relevance of therapeutic drug monitoring (TDM) is determined by three aspects: technical feasibility, high inter-patient variability of antifungal exposure in response to standard dosing and establishment of a dose-effect relationship. Technical feasibility can be acknowledged, as TDM has been established for all clinically relevant triazoles (itraconazole, voriconazole and posaconazole) and the echinocandins.[88, 89] As shown in the previous section on pharmacokinetic factors, unpredictable exposure after administration of a standard dose has also been observed, but is probably limited to the triazoles.[68, 69, 64-66, 69] Concerning itraconazole, the existence and nature of a dose-effect relationship has been demonstrated,[90] however, concerning voriconazole and posaconazole, there is little agreement on the nature of their respective dose-effect relationship and the corresponding cutoffs to be used in clinical practice.[62]

There exist numerous publications on a possible dose effect relationship for voriconazole. The most relevant works are summarized in Table 3. Despite of this large data collection, interpretation of the available results is hampered by a number of factors. Most data is derived from small, monocentric, retrospective studies. Their study design and reporting is often heterogeneous, complicating direct comparison of results from different studies. Under these circumstances, the current basis of evidence suggests a rather broad range for acceptable voriconazole trough concentrations, i.e. 0.35‑2.2 mg/ L. A correlation of voriconazole exposure and toxicity proves even more problematic. Many studies did not assess safety endpoints, and even if data on neurotoxicity and hepatotoxicity was reported, results often turned out to be conflicting. In spite of these difficulties, it seems justified to conclude that voriconazole trough concentrations exceeding 5 mg/ L are associated with an increased likelihood of neuro- or hepatotoxicity. A randomized controlled trial is certainly warranted to further assess these hypotheses.

Table 3: Major studies assessing voriconazole dose-efficacy and/or dose-toxicity relationships (adapted from[62])

| **Study Design** | **Patient population** | **Efficacy** | **Toxicity** |
|---|---|---|---|
| Prospective observational[91] | 52 patients; 60% with hematological malignancy; VRZ was used as primary or secondary therapy | Therapy failure more frequently with trough ≤ 1 mg/ L relative to > 1 mg/ L (46% versus 12%)<br><br>Non-responders with levels < 1 mg/ L responded upon dosage escalation | 31% of patients with trough levels > 5.5 mg/ L experienced neurotoxicity vs. none with levels ≤ 5.5 mg/ L<br><br>Cholestatic hepatopathy was twice as common in patients with trough levels > 5.5 mg/ L (not statistically significant) |
| Open-label non-comparative[92] | 116 patients; 78% with leukemia/SCT; VRZ as primary or salvage therapy | Almost a third of patients failed treatment<br><br>Treatment success in 70% of patients with random level > 0.5 mg/ L versus 20% in patients with random levels < 0.25 mg/ L | 27% of patients with level > 6 mg/ L developed elevated LFTs or liver failure |
| Retrospective observational[93] | 71 allogeneic SCT recipients with hematological malignancy; VRZ used for antifungal prophylaxis | 6/43patients with trough level < 2 mg/ L had breakthrough fungal infection vs. no patients with trough level > 2 mg/ L (P = 0.061) | Not reported |
| Retrospective analysis of safety and data from 10 phase II/III clinical trials[94] | 1053 heterogeneous immunocompromised patients; 50% neutropenic; VRZ used both as empirical and targeted antifungal therapy | Not reported | Positive association between mean VRZ levels and visual adverse events (p = 0.011) and a weaker but still significant association with increased LFTs |
| Prospective cohort study[95] | 72 patients with cancer | Not reported | 6 patients developed audio and visual hallucinations. VRZ trough levels in 5/6 were > 5 mg/ L |

LFT: Liver function tests; SCT: stem cell transplantation; VCZ: voriconazole

The evidence to support posaconazole TDM is even more limited. Based on the US Food and Drug Administration (FDA) clinical pharmacology review of two randomized, active-controlled clinical studies, an exposure-response relationship for posaconazole antifungal prophylaxis was proposed in 2010. This proposition was based on an inverse association between average posaconazole plasma concentrations and clinical failure rate. A cutoff of 700 ng/ mL was suggested to ensure protection from IFDs.[96] The assumption of such an inverse association represents a reasonable hypothesis which had already been confirmed by data from a previous analysis.[97] However, due to significant methodological shortcomings and the lack of a validation study, the proposed cutoff of 700 ng/ mL has not obtained general acceptance.[98] Furthermore, some authors have proposed a potential role for alternative compartments, e.g. alveolar or blood cells, as opposed to plasma, in the establishment of a dose-efficacy relationship.[99] At the UHC, a co-operation between the hematology/oncology department and the pharmacology department has been formed to further elucidate this issue. Liquid chromatography-tandem mass spectrometry has been used to establish a method for the determination of intracellular concentrations of posaconazole, micafungin and anidulafungin in different compartments of peripheral blood.[100-102] However, clinical studies assessing the potential relationship of these measurements with the prophylactic efficacy of posaconazole or micafungin have not been conducted, yet.

In conclusion, regular TDM for prophylactic posaconazole cannot be recommended, as reliable cutoffs have not been established. In individual cases, its application is justified to monitor compliance or if a severe reduction of plasma levels is suspected. In these cases, knowledge on plasma levels may help to decide, whether a switch to a systemic antifungal should be performed. Future clinical studies are warranted to evaluate the role of alternative departments and establish reliable cutoffs.

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## 5. Conclusion and Perspective

Patients with hematological malignancies, particularly those experiencing prolonged periods of neutropenia or immunosuppression, are at a high risk of contracting IFDs. Antifungal prophylaxis has become a popular strategy in this setting, relying mainly on the group of azole antifungals, as well as micafungin from the echinocandin group. In the present cumulative treatise, a broad range of factors impacting on the clinical efficacy of antifungal prophylaxis has been explored, with a focus on epidemiological, pharmacokinetic and pharmacodynamic issues. Firstly, in a defined patient population, a high incidence of IFD should be given to guarantee efficacious protection without excessive exposure to antifungals.[103] Secondly, epidemiological changes are likely to be associated with shifts in antifungal susceptibility. Especially the emergence of species from the order Mucorales, *Candida* non-*albicans* spp. and azole-resistant *Aspergillus* spp. might jeopardize the future efficacy of current antifungal prophylaxis strategies.[34, 58] Thirdly, surveillance studies have shown an increased incidence of IFDs in association with certain meteorological constellations and during outbreaks of respiratory infections of viral origin.[22, 28] In these settings, physicians should be particularly sensitive to the possibility of breakthrough IFDs. Finally, a broad variety of factors have been shown to impact on antifungal exposure,[74, 75] however, reliable cutoffs for the application of TDM have only been established for itraconazole and voriconazole, but not for posaconazole and the echinocandin class.

From the current perspective, future studies with the aim of improving the efficacy of antifungal prophylaxis in hematological high risk patients may focus on various issues. The establishment and extension of national and international surveillance networks is warranted to monitor and react to further epidemiological shifts. Immunological studies might focus on the identification of viral infections in the hematology setting and their interaction with the immune system of the neutropenic patient. Concerning TDM, randomized controlled trials are warranted to evaluate the role of alternative compartments and establish reliable and efficient cutoffs.

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