Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology

Oliver A. Cornely,[1,2] Angelika Böhme,[3] Dieter Buchheidt,[4] Hermann Einsele,[5] Werner J. Heinz,[5] Meinolf Karthaus,[6] Stefan W. Krause,[7] William Krüger,[8] Georg Maschmeyer,[9] Olaf Penack,[10] Jörg Ritter,[11] Markus Ruhnke,[12] Michael Sandherr,[13] Michal Sieniawski,[14] Jörg-Janne Vehreschild,[1] Hans-Heinrich Wolf,[15] and Andrew J. Ullmann[16]

[1]Klinik I für Innere Medizin, Klinikum der Universität Köln, and [2]Zentrum für Klinische Studien (01KN0706), Köln; [3]Onkologikum Frankfurt am Museumsufer, Frankfurt; [4]III. Medizinische Klinik, Universitätsklinikum Mannheim gGmbH, Mannheim; [5]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg; [6]Klinik für Hämatologie und Onkologie, Klinikum Neuperlach, München; [7]Medizinische Klinik 5, Hämatologie und Internistische Onkologie, Universitätsklinikum Erlangen, Erlangen; [8]Medizinische Klinik C, Ernst-Moritz-Arndt-Universität, Greifswald; [9]Medizinische Klinik Hämatologie und Onkologie, Klinikum Ernst von Bergmann, Potsdam; [10]Charité, Campus Benjamin Franklin, Klinik für Hämatologie und Onkologie, Berlin; [11]Pädiatrische Hämatologie/Onkologie, Universitätsklinikum Münster, Münster; [12]Charité Universitätsmedizin, Campus Charité Mitte, Medizinische Klinik und Poliklinik II, Berlin; [13]Schwerpunktpraxis für Hämatologie und Onkologie, Weilheim, Germany; [14]Haematological Sciences (CALS), Leech Building, Medical School, Newcastle upon Tyne, United Kingdom; [15]Martin-Luther-Universität Halle-Wittenberg, Halle, and [16]Johannes Gutenberg-Universität, III. Medizinische Klinik, Mainz, Germany

ABSTRACT

There is no widely accepted standard for antifungal prophylaxis in patients with hematologic malignancies. The Infectious Diseases Working Party of the German Society for Haematology and Oncology assigned a committee of hematologists and infectious disease specialists to develop recommendations. Literature data bases were systematically searched for clinical trials on antifungal prophylaxis. The studies identified were shared within the committee. Data were extracted by two of the authors (OAC and MSi). The consensus process was conducted by email communication. Finally, a review committee discussed the proposed recommendations. After consensus was established the recommendations were finalized. A total of 86 trials were identified including 16,922 patients. Only a few trials yielded significant differences in efficacy. Fluconazole 400 mg/d improved the incidence rates of invasive fungal infections and attributable mortality in allogeneic stem cell recipients. Posaconazole 600 mg/d reduced the incidence of IFI and attributable mortality in allogeneic stem cell recipients with severe graft versus host disease, and in patients with acute myelogenous leukemia or myelodysplastic syndrome additionally reduced overall mortality. Aerosolized liposomal amphotericin B reduced the incidence rate of invasive pulmonary aspergillosis. Posaconazole 600 mg/d is recommended in patients with acute myelogenous leukemia/myelodysplastic syndrome or undergoing allogeneic stem cell recipients with graft versus host disease for the prevention of invasive fungal infections and attributable mortality (Level A I). Fluconazole 400 mg/d is recommended in allogeneic stem cell recipients until development of graft versus host disease only (Level A I). Aerosolized liposomal amphotericin B is recommended during prolonged neutropenia (Level B II).

Key words: invasive fungal infection, antifungal prophylaxis, itraconazole, fluconazole, posaconazole, amphotericin B, liposomal.

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Correspondence: Oliver A. Cornely, MD, Klinikum der Universität zu Köln, Klinik I für Innere Medizin Zentrum für Klinische Studien (BMBF 01KN0706) 50924 Köln, Germany. E-mail: oliver.cornely@ctuc.de
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Introduction

The rising incidence of invasive fungal infections, especially invasive aspergillosis, compromises therapeutic outcomes in hematologic cancer patients and in transplant recipients.[1-5] The utilization of newly introduced antifungal agents clearly improved the tolerability of patients combating severe underlying diseases.[6,7] Despite better outcome in primary treatment of invasive aspergillosis in comparison to conventional amphotericin B, response and survival require further improvement.[8,9] Additionally, early diagnosis of invasive fungal infections is critical.[10] But usually diagnosis is delayed and thus hampers further treatment outcome.[11] Therefore, the prevention of invasive fungal infections upfront has become the major goal in patient care in high-risk patient populations. Since the first edition of these recommendations regarding antifungal prophylaxis, close to 20 relevant publications have been added to the field, necessitating an updated review of their impact on clinical decision making.[12] On the other hand new meta-analyses on prophylaxis of invasive fungal infections have also been published, but do not differentiate between specific patient populations and risk factors.[13,14] To maintain comparability with the previous recommendation, the EBM criteria proposed by the Infectious Diseases Society of America (IDSA) are again employed throughout this document (Table 1).[15]

Several newly introduced antifungal agents have been utilized in prophylaxis for the first time. These and other new studies have been incorporated into this updated guideline of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Oncology. The aim of this review is to provide the treating physician an up-to-date tool for the daily bedside decisions on primary antifungal prophylaxis.

Objectives of antifungal prophylaxis

It is evident that the most relevant endpoint of antifungal prophylaxis is the reduction of mortality. However, death attributable to invasive fungal infection is difficult to prove and a reduction in overall mortality as a desirable endpoint of any clinical decision is difficult to achieve in the context of multiple competing illnesses in a severely immunocompromised host. Thus usually the reduction of the incidence rate of breakthrough invasive fungal infection is chosen as the primary endpoint of clinical trials. Improving rates of mucosal or other superficial infection and reducing colonization are no proper endpoints for antifungal prophylaxis with systemically active compounds.

Design and Methods

The guideline was prepared by a group of German clinicians. Systematic literature search comprised Medline, CancerLit, Embase, Cochrane Library and conference proceedings of Advances Against Aspergillosis, ASH, EBMT, ECCMID, ESMO, Focus on Fungal Infections, and ICAAC/IDSA, yielding a total of 86 clinical trials comprising 16,922 patients. Data extracted by OAC and MSi from each clinical study identified, were patient characteristics and outcomes, year published, number of patients, demographic characteristics, underlying malignancy, type of transplant, type of control group, prophylactic regimens including dosage, duration of neutropenia, isolation measures, mucositis grade, central venous catheters, duration of prophylactic treatment, adverse events, premature discontinuations, incidence and etiology of invasive and superficial fungal infections, level of certainty of diagnosis (proven, probable, possible), overall and invasive fungal infections attributable mortality. For easier comparison, this consensus paper contains comprehensive tables of the trials on antifungal prophylaxis published to date (*Online Supplementary Tables S1 to S7*). Trials published as abstracts only, and meta-analyses were not taken into account for the recommendations. Clean air systems are not addressed in this guideline.

Data extracted were tabulated and distributed to the committee together with a first manuscript drafted by OAC and AJU. The consensus process was performed as an email based discussion group moderated by OAC. In a second step the panelists´ draft was peer reviewed by the review committee of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. The resulting recommendations are based on scientific publications and information published at the conferences named above. In case of a lack of uniform consensus, the vote of the majority of group members was adopted. Both committees serve as the authors of the recommendation. Since the IDSA criteria are most commonly used in infectious diseases, the ID Working Party of the DGHO decided to adopt these. Thus, meta-analyses and studies not published as a full paper are reported when considered appropriate, but do not influence the levels of evidence given.

Results

Azoles

Fluconazole (*Online Supplementary Table S1*) is the antifungal with the highest number of well-designed prophylaxis trials. In comparative trials oral daily doses from 50 mg up to 400 mg were given.[16,17] The two most relevant trials were placebo controlled, double blinded and involved mainly allogeneic stem cell transplant recipients.[16-18] Fluconazole 400 mg/d was significantly superior to placebo in both the reduction of breakthrough invasive fungal infection and the decrease of IFI attributable mortality. In a longitudinal observation survival benefit extended beyond the period of fluconazole treatment (75 days) and was accompanied by a lower incidence of intestinal graft versus host disease.[19] Moreover, fluconazole has been reported to protect from cyclophosphamide toxicity.[20] A particular strength of both trials was the homogeneous, strictly defined and high-risk patient population. Other trials mostly examined heterogeneous patient groups with different underlying conditions and risk groups, and subsequently failed to demonstrate an advantage over the com-

Table 1. Infectious Diseases Society of America, United States Public Health Service Grading System for ranking recommendations.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

parator drug. A large placebo-controlled trial on fluconazole 400 mg/d resulted in a significant reduction of proven invasive candidiasis and mortality attributed to fungal infection, but the study population was too heterogeneous to lead to a clear cut recommendation for a specific patient group.[21] Moreover, two more trials comparing fluconazole 400 mg/d versus placebo in non-transplant settings found no significant effect on the incidence rate of proven invasive fungal infections and mortality.[22,23] Doses lower than 400 mg/d failed to show a marked benefit and have not been carried out in a placebo controlled fashion.[17,24-27] Since moulds and *Candida krusei*, harbor intrinsic resistance to fluconazole and only dose dependent activity against *Candida glabrata*, breakthrough infections with these fungi have occurred.[16,21,23,28,29] The clinical relevance of the development of resistance during fluconazole prophylaxis is still a matter of debate,[30,31] while a general shift towards higher rates of strains exhibiting primary resistance have been clearly shown in the intensive care setting.[32] The favorable safety profile and patient compliance rate of fluconazole resulted in discontinuation rates of less than 8%. There is good evidence (Level A I) that primary prophylaxis with fluconazole 400 mg/d reduces the incidence of invasive candidiasis and the mortality rate after allogeneic hematopoietic stem cell transplant. For patients with acute leukemia prophylaxis with fluconazole 400 mg/d cannot be recommended with similar strength (Level C I). Doses less than 400 mg/d have not been effective in well designed trials (Level E I).

Itraconazole (*Online Supplementary Table S2*) has a broader spectrum of activity than fluconazole including *non-albicans Candida* species and moulds. Itraconazole capsules lead to adequate plasma levels with delay, if at all, and thus are not recommended as a start-up for prophylaxis of invasive fungal infection.[27,33,34] A superior bioavailability is achieved with itraconazole oral suspension. A double-blind, double dummy, placebo controlled trial comparing the suspension at a dose of 2.5 mg/kg bid plus nystatin 500.000 IU qid to nystatin alone found a more effective reduction in the rate of fatal candidemia from 2% to zero. Invasive mould infections and death due to fungal infection were not prevented.[35] Lower daily doses of itraconazole oral suspension did not effectively reduce the incidence of invasive fungal infections or mortality.[36] Itraconazole oral solution 2.5 mg/kg bid compared to fluconazole 400 mg/d showed no difference in the incidence rate of fungal infection or mortality in patients with hematologic malignancies.[37] A randomized trial on allogeneic stem cell transplant recipients compared intravenous followed by oral itraconazole solution 400 mg/d versus fluconazole 400 mg/d given until day 100 post transplant (for treatment schedules see *Online Supplementary Table S2*). Itraconazole reduced proven invasive fungal infections more effectively, but failed to improve attributable mortality.[38] Another controlled trial compared intravenous itraconazole 200 mg/d or oral suspension 7.5 mg/kg/d with parenteral or oral fluconazole 400 mg/d. The trial included 304 allogeneic transplant recipients. In patients on itraconazole therapy, a statistically significant reduction of breakthrough mould infection was achieved. But a reduction in the rate of proven and probable invasive fungal infections, and overall or attributable mortality, was not observed. Prophylaxis was associated with a higher rate of toxicity and gastrointestinal intolerance leading to a 36% withdrawal rate.[39] Moreover the concomitant use of the chemotherapy regimen busulfan/cyclophosphamide and itraconazole resulted in a higher toxic death rate documented here for the first time.[40] Clinical trial protocols thereafter did not allow for concomitant azole prophylaxis during chemotherapy with busulfan, cyclophosphamide and – for theoretical concerns of cardiotoxicity – anthracyclines. In the non-transplant setting high withdrawal rates had been previously reported with itraconazole oral solution given at doses of 2.5 mg/kg bid and 400 mg/d. These withdrawals were primarily due to gastrointestinal adverse events.[26,35] While no single study demonstrated a lower rate of death attributed to invasive fungal infection, only one meta-analysis suggested that itraconazole oral suspension is effective to this regard.[41] Close patient supervision and motivation appears to be warranted because of the unpleasant taste of the oral solution. Moreover, the use of itraconazole demands frequent plasma level monitoring to evaluate whether plasma concentrations of greater than 500 ng/mL are reliably reached within a few days.[42] This concentration is achieved by the majority of patients after one week of prophylactic itraconazole oral solution 400 mg/d plus capsules 800 mg/d.[42] Other investigators evaluated intravenous loading dose concepts.[43,44] In summary, itraconazole has been shown to be effective in reducing breakthrough fungal infections in randomized trials, but did not reduce attributable or overall mortality rates. There is poor evidence for the use of itraconazole capsules alone (Level C I). For the reduction of mortality attributable to invasive fungal infections, there is poor evidence as well as for the use of

itraconazole 400 mg/d oral solution (Level C I), with or without an intravenous equivalent dose loading period. Itraconazole exposure should be avoided during the chemotherapy period, especially vincristin and cyclophosphamide.

Posaconazole (Online Supplementary Table S3) has been compared to fluconazole 400 mg/d or itraconazole 400 mg/d in a randomized, open-label clinical trial in patients undergoing induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. At a dose of 600 mg/d posaconazole resulted in a significant reduction in proven and probable invasive fungal infections, mainly by reducing the incidence rate of aspergillosis. Attributable and overall mortality were significantly reduced as well. Safety, including the overall rate of patients with serious adverse events, was comparable between the three drugs. The only difference was a higher rate of patients on posaconazole experiencing possibly or probably related serious adverse events than patients on fluconazole or itraconazole prophylaxis. However, these events did not translate into a higher rate of study drug discontinuation.[28] In addition, this study was open-labeled and evaluation of adverse events was not without possible investigator bias. In another trial, allogeneic hematopoietic stem cell recipients with severe graft versus host disease (GvHD) were randomly allocated to receive posaconazole 600 mg/d or fluconazole 400 mg/d in a double blinded fashion. Patients receiving posaconazole prophylaxis had reduced rates of proven and probable invasive fungal infections and attributable mortality. Posaconazole was found to be as safe and tolerated as fluconazole in this trial.[29] Prophylaxis with posaconazole 600 mg/d is recommended during induction chemotherapy induced neutropenia in patients with AML or MDS due to its effects on the rate reduction of invasive fungal infection and death (Level A I). Posaconazole 600 mg/d is recommended in hematopoietic stem cell recipients with GvHD because of the reduction in the rates of invasive fungal infection and attributable mortality (Level A I).

Voriconazole (Online Supplementary Table S3) prophylaxis has been evaluated in a small clinical trial.[45] Currently prospective clinical trials are either ongoing (clinicaltrials.gov Identifier NCT00289991;) or have recently been presented at conferences.[46] As of yet no data are available from peer-reviewed publications of sufficiently powered randomized trials in this indication. In case series prolonged voriconazole exposure has been associated with a reduction of invasive aspergillosis, but an increase in breakthrough zygomycosis.[47-49] To date voriconazole prophylaxis cannot be recommended (Level C II).

Ketoconazole (Online Supplementary Table S4) is used as a prophylactic option in very few centers. The majority of trials published have evaluated a daily dose of 400 mg. Virtually all of these trials are underpowered, so that a reliable conclusion is not achievable.[50-58]

Miconazole (Online Supplementary Table S4) did not effectively reduce the incidence rate of invasive fungal infections at a dose of 2 g/d in a small randomized placebo-controlled trial.[59] Another trial evaluated miconazole inhalation, but was too small to uncover any statistically significant difference to the comparator, fluconazole 400 mg/d.[60]

Clotrimazole (Online Supplementary Table S4) at a dose of 20 mg/d applied together with nystatin 2 Mill IU was inferior to fluconazole 200 mg/d in a single trial evaluating the prophylactic benefit of this drug.[61]

In summary, there is poor evidence for the prophylactic use of ketoconazole, miconazole or clotrimazole (Level E II).

Polyenes

Amphotericin B has broad spectrum antifungal activity. It is frequently used as oral suspension at doses of 1.5 to 3 g/d. Lozenges and suspension may lower the incidence of superficial fungal infections.[17,62] Prevention of invasive candidiasis was not demonstrated and reduction of aspergillosis acquired by inhalation can obviously not be expected from a non-absorbable oral drug.

Amphotericin B inhalation (Online Supplementary Table S6) in the deoxycholate formulation was considered active in reducing invasive pulmonary aspergillosis on the basis of non-comparative studies.[63,64] The only large multicenter trial did not confirm these results (Level E I).[65] In a non-comparative evaluation of inhalational amphotericin B lipid complex 50 mg/d and concomitant fluconazole 400 mg/d were found to be safe in allogeneic stem cell recipients.[66] A placebo-controlled trial on aerosolized liposomal amphotericin B resulted in a significant reduction of invasive pulmonary aspergillosis, but did not improve survival. All patients received fluconazole at an undisclosed dose and route.[67] Aerosolized liposomal amphotericin B appears to be effective, but does not prevent invasive fungal infections other than pulmonary (Level B II). Adverse events in these trials included coughing, bad taste and nausea.[65-67]

Polyenes have been applied intranasally, but there has never been any supporting randomized trial.

Amphotericin B deoxycholate infusion (Online Supplementary Table S5) has been evaluated in different dosages ranging from 0.1 mg/kg/d to 1.0 mg/kg/tiw. A low dose of 0.1 mg/kg/d had no benefit over placebo.[68] A prospective trial of amphotericin B 0.2 mg/kg/d versus fluconazole 400 mg p.o. in allogeneic and autologous stem cell transplant recipients showed comparable efficacy, but a higher toxicity of amphotericin B.[69] Amphotericin B 0.5 mg/kg three times weekly resulted in a 22% rate of serum creatinine increases above 2 mg/dL and an 11% withdrawal rate in a small trial conducted in the early 1990s.[70] A historically controlled study suggested efficacy of intravenous prophylaxis with amphotericin B 1 mg/kg/q48h in reducing proven and probable invasive fungal infections. Amphotericin B had to be discontinued due to adverse events in 4% of patients only,[71] and in another historically controlled trial 1 out of 10 patients withdrew from prophylaxis.[72] As of today amphotericin B in a dose higher than 0.2 mg/kg/d has not been evaluated in a sufficiently powered well-designed trial. Amphotericin B deoxycholate is a toxic drug, but preventive measures such as sodium chloride loading evolved over the years.[73] Other trials could not confirm that toxicity is preventable.[74,75] Due to its infusion related and other toxic potential, ampho-

tericin B deoxycholate needs an experienced team if it is ever to be considered to be used in patients. Its prophylactic use is strongly discouraged due to its toxicity profile (Level E I). The drug has now been replaced in almost all its former indications.[76]

Lipid-based amphotericin B formulations (Online Supplementary Table S5). Prophylactic use of liposomal amphotericin B remains attractive due to its lower toxicity. Its efficacy has been shown in a murine model.[77] Liposomal amphotericin B was evaluated in a small study population at 1 mg/kg/d versus placebo, but no significant effect could be detected.[78-80] A second placebo-controlled but underpowered trial also failed to disclose an advantage of liposomal amphotericin B 2 mg/kg/tiw.[81] Recently a randomized clinical trial (n= 132) compared liposomal amphotericin B 50 mg q48h with no prophylaxis in a population with hematologic malignancies. In this reasonably sized and dosed study on the prophylactic properties of the drug the investigators observed a significant reduction in the rates for proven and probable invasive fungal infections as well as IFI-attributable mortality rates.[82] The results contrast those of a previous placebo controlled trial evaluating a similar approach.[81] A pilot trial evaluated a novel loading dose concept of liposomal amphotericin B 10 mg/kg qw; while the regimen was feasible in acute leukemia, it was associated with adverse events leading to treatment discontinuation in 6 of 8 stem cell recipients.[83] Intravenous Amphotericin B Lipid Complex and Amphotericin B Colloidal Dispersion prophylaxis may be conceivable as well.[84] However, neither approach has been sufficiently evaluated and cannot be recommended at present.

In conclusion, prophylaxis with topical amphotericin B is not recommended (Level E I). For aerosolized amphotericin B deoxycholate there is evidence against a recommendation (Level E I). Aerosolized liposomal amphotericin B reduces the incidence of invasive pulmonary aspergillosis, but yields no protection for extrapulmonary infections (Level B II). Intravenous prophylaxis with amphotericin B deoxycholate is not recommended (Level E I). Liposomal amphotericin B prophylaxis at a dose of 50 mg q48h can be considered (Level C II).

Nystatin use has been criticised in a recent Cochrane review because its efficacy against invasive fungal infections has not been demonstrated.[85] A trial conducted in the 1980s suggested a reduction in the colonization rate, but in the end the results were inconclusive.[86]

In summary, there is no evidence to support the prophylactic efficacy of nystatin (Level E II).

Echinocandins

Caspofungin (Online Supplementary Table S7) prophylaxis at a dose of 50 mg/d has been compared with intravenous itraconazole 400 mg/d in a randomized open-label study. In 192 patients with acute myelogenous leukemia, similar efficacy and safety was found in both treatments.[87]

Micafungin (Online Supplementary Table S7) at a dose of 50 mg/d has been compared to fluconazole 400 mg/d in a large double-blind trial on 882 patients undergoing autologous or allogeneic hematopoietic stem cell transplantation. Invasive candidiasis was effectively prevented by both regimens, and the rate of aspergillosis was lower in the micafungin group but did not reach significance in those subgroups despite the fact of successful prophylaxis in the primary composite endpoint. Unfortunately, possible invasive fungal infections were part of the primary endpoint of the trial, impairing comparability with other clinical trials.[88] No significant reduction of the overall and attributable fungal mortality was detected. The study population comprised autologous and allogeneic stem cell recipients with various underlying malignant diseases and were studied only during the neutropenic phase.[89] The results may be difficult to put into the context of other trials, since for the 46% autologous transplant patients, who are not at risk for invasive fungal infection, both treatment arms have to be considered experimental.[88]

In summary, there is limited evidence supporting the prophylactic use of micafungin (Level C I) during the neutropenic phase of hematopoietic stem cell transplantation and caspofungin use during neutropenia (Level C I).

Conclusions

The following recommendations are summarized in Tables 2A-C. Improvement of mortality attributable to invasive fungal infection and a reduced rate of candida infections have been shown for fluconazole 400 mg/day in allogeneic transplant recipients from conditioning until day 75. Since posaconazole reduced the incidence of proven and probable invasive fungal infections and attributable mortality in allogeneic hematopoietic stem cell recipients with severe GvHD (Level A I) the recommendation of fluconazole 400 mg/day is now limited for the time from conditioning until development of severe GvHD (Level A I). Prophylactic use of posaconazole 600 mg/d demonstrated a reduction of the incidence rates of proven and probable invasive fungal infections and more importantly a reduction of attributable and overall mortality in patients with AML/MDS remission induction chemotherapy (Level A I). At present, data advocating itraconazole prophylaxis are less conclusive (Level C I). Data quality on voriconazole prophylaxis is currently inadequate, but emerging zygomycosis has been reported with its prolonged use (Level C II). Studies of the echinocandins, caspofungin and micafungin harbor limited support in prophylactic use during neutropenia (Level C I). Intravenous liposomal amphotericin B 50 mg q48h can be applied in neutropenic leukemia patients (Level C II). Aerosolized liposomal amphotericin B significantly reduced the incidence rate of invasive pulmonary aspergillosis, but was given with concomitant fluconazole (Level B II). The use of amphotericin B deoxycholate in antifungal prophylaxis is discouraged (Level E I). Despite several trials in less aggressive chemotherapy, evidence for the use of antifungal prophylaxis in these situations is poor (Level E I). Further the authors recommend not utilizing antifungal

Table 2A. Recommended antifungal prophylaxis in patients with neutropenia (<500 cells/μL for more than 7 days).

Drug	Dosage	Level of evidence
Posaconazole oral suspension	200 mg tid po	A I[1]
Amphotericin B, liposomal	12.5 mg biw inhalation	B II[2]
Amphotericin B, liposomal	50 mg q 48h iv	C II
Itraconazole oral solution	2.5-7.5 mg/kg/d	C I
Fluconazole	400 mg qd po	C I
Itraconazole capsules, any formulation	Any dose	C I
Caspofungin	50 mg qd iv	C I
Amphotericin B, deoxycholate	Any dose iv	E I
Amphotericin B, deoxycholate	20 mg qd inhalation	E I

[1]*Recommended in AML/MDS remission induction chemotherapy only.*
[2]*All patients received fluconazole, dose and route were not reported.*

Table 2B. Recommended antifungal prophylaxis in allogeneic hematopoietic stem cell recipients.

Drug	Dosage	Level of evidence
Fluconazole	400 mg qd po	A I*
Posaconazole oral suspension	200 mg tid po	A I§
Itraconazole oral solution	400 mg qd po	C I
Micafungin	50 mg qd iv	C I‡

**Prior to GvHD only; §after onset of severe GvHD; ‡during neutropenia only.*

Table 2C. Other recommendations on antifungal prophylaxis.

Risk group	Drug	Dosage	Level of evidence
Any	Itraconazole	Any dose of capsules	C I
	Voriconazole	Any	C II
	Fluconazole	Less than 400 mg/d	E I
	Ketoconazole, miconazole, clotrimazole, nystatin	Any	E II

agents such as ketoconazole, miconazole and clotrimazole (Level E II).

Invasive fungal infections are an ongoing diagnostic and prognostic challenge for clinicians in the everyday care of immunocompromised patients. The principal efficacy of antifungal prophylaxis has been proven in certain high-risk patient populations but not for others. Intensive efforts need to be undertaken to decrease the incidence and attributable mortality of invasive fungal infections by targeted prophylaxis or improved diagnostic procedures.

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