Evidence-based assessment of primary antifungal prophylaxis in patients with hematologic malignancies

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Invasive fungal infection is an increasing source of morbidity and mortality in patients with hematologic malignancies, particularly those with prolonged and severe neutropenia (absolute white blood cell count < 100/μL). Early diagnosis of invasive fungal infection is difficult, suggesting that antifungal prophylaxis could be the best approach for neutropenic patients undergoing intensive myelosuppressive chemotherapy. Consequently, antifungal prophylaxis has been extensively studied for more than 20 years. Nonabsorbable polyenes reduce superficial mycoses but are not effective in preventing or treating invasive fungal infections. Intravenous amphotericin B and the newer azoles were used in numerous clinical trials, but the value of antifungal prophylaxis in defined risk groups with cancer is still open to discussion. Recipients of allogeneic stem cell transplants and patients with a relapsed leukemia are high-risk patient populations. In addition, certain risk factors are well defined, for example, neutropenia more than 10 days, corticosteroid therapy, sustained immunosuppression, and graft-versus-host disease. In contrast to study efforts, evidence-based recommendations on the clinical use of antifungal prophylaxis according to risk groups are rare. The objective of this review of 50 studies accumulating more than 9000 patients is to assess evidence-based criteria with regard to the efficacy of antifungal prophylaxis in neutropenic cancer patients. (Blood. 2003; 101:3365-3372)

Introduction

Evidence-based medicine is of growing importance in the treatment of cancer patients. Meta-analyses focusing on fungal infections have been performed but do not distinguish between different cancer types, patient populations, and risk groups.[1,2] Patients with cancer differ in their susceptibility to fungal infections on the basis of well-defined risk factors.[3] The aim of this review is to assist in evidence-based clinical decisions on the use of antifungal prophylaxis. In this article, criteria proposed by the Infectious Diseases Society of America are used (Table 1).[4]

In recent decades a steady rise in the incidence of systemic and superficial fungal infection compromises therapeutic outcomes particularly in patients with cancer and recipients of solid organs.[5-9] This rising incidence of fungal infection is associated with the use of intensified chemotherapy and the introduction of allogeneic as well as autologous stem cell and bone marrow and solid organ transplantation.[10,11]

Despite the improvement of diagnostic procedures, particularly noncultural methods, the difficulty remains to diagnose and confirm invasive fungal infections early. The complexity and high cost of therapy and most of all the high case fatality rate of systemic fungal infections are reasons for the ongoing prophylactic approaches.[12]

A number of comparative studies on the prophylactic use of various antifungal agents in hematology and oncology have been published in recent years. The efficacy and toxicity of the agents used for prophylaxis are presented as follows. For easier comparison, this review contains comprehensive tables of the major studies on antifungal prophylaxis published during the last 15 years (Tables 2-5). We conclude with a presentation of new agents awaiting market approval within the near future.

Is there a clinical need for antifungal prophylaxis?

It is necessary to clearly define the objectives before conducting antifungal prophylaxis. Superficial *Candida* species infections can be discovered early by physical examination and mostly respond well both to local and systemic antifungal agents. Nonetheless, it has been shown that prophylaxis of superficial candidiasis is justified because colonization of 2 independent anatomic regions is a documented risk factor for invasive candidiasis in patients with underlying hematologic disease.[13,14] The incidence of infections by *Aspergillus* species is, in part, highly dependent on the airborne spore level, a factor that varies significantly according to region and season.[15] The scope of this paper allows little more than a passing reference to prevention of exposure using special clean air systems such as laminar air flow (LAF) or high-efficiency particulate air (HEPA) filtration. The incidence of invasive fungal infection increases with the severity and duration of neutropenia. Invasive fungal infection is very rare in patients undergoing chemotherapy with a low myelotoxic risk, as in the treatment of solid tumors. Prophylaxis is not recommended in such cases because there are no evidence-based data for a prophylaxis and the benefit is likely to be slight (level CI). Moreover, an increased risk of bacteremia in patients receiving antifungal prophylaxis has recently been described in a multivariate analysis of a cohort of

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Submitted May 14, 2002; accepted August 16, 2002. Prepublished online as *Blood* First Edition Paper, August 29, 2002; DOI 10.1182/blood-2002-05-1356.

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Table 1. Infectious Diseases Society of America and United States Public Health Service grading system for ranking recommendations[4]

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

more than 3000 patients.[16] Therefore, a clear benefit documented in clinical studies should be a prerequisite for the use of antifungal prophylactic drugs.

Despite recent progress in diagnostic procedures, invasive fungal infection is detected in about 30% of neutropenic patients only by panfungal polymerase chain reaction (PCR),[17] but aspergillosis as well as candidiasis still are rarely confirmed by cultural methods or histology.[18] Typical indicators of invasive fungal infection are fever that fails to respond to antibacterial agents, persists after the end of neutropenia and, in chronic disseminated candidiasis, an increase in serum alkaline phosphatase activity for no other apparent reason.[19] Documented invasive fungal infections have a high case-fatality rate of up to more than 60%.[20] Additionally, intensive antifungal therapy for proven fungal infection may take months and may delay further antineoplastic treatment by a corresponding period.

In contrast to patients with solid tumors the incidence of invasive fungal infection is substantially higher in association with hematologic malignancies. The wide range in reported incidences (5%-24%) is partly due to a lack of uniform definitions.[10] Consensus definitions of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycosis Study Group (MSG) of the National Institutes of Health (NIH) were published in 2002.[21]

Evaluation of antifungal agents for prophylaxis

Fluconazole

Fluconazole is the most extensively studied triazole. Daily doses ranging from 50 to 400 mg orally have been used in comparative studies.[22,23] Currently, there is clear evidence (level AI) that fluconazole prophylaxis is of proven benefit in the primary prophylaxis at a daily dose of 400 mg in recipients of allogeneic bone marrow or hematopoietic stem cell transplants.

Two placebo-controlled studies involving allogeneic transplant recipients demonstrate the prophylactic efficacy of fluconazole 400 mg/d in terms of preventing a documented invasive fungal infection and the attributable mortality.[22,24] A longitudinal study of one of these allogeneic bone marrow transplant cohorts showed that the survival benefit extends beyond the 75 days of fluconazole exposure and is coupled with a lower incidence of intestinal graft-versus-host disease (GVHD).[25]

Rotstein and coworkers[26] describe a significant reduction of confirmed invasive fungal infection versus placebo in a patient population with various underlying malignancies, whereas 2 other study groups found no significant advantage of 400 mg/d over placebo in 255 patients with acute leukemia and 151 patients with underlying hematologic disease.[27,28] Lower doses in the 50- to 200-mg range have not demonstrated any significant efficacy in the prophylaxis of invasive fungal disease (level CI),[20,23,29-31] but low-dose placebo-controlled studies have not been carried out.

A drawback of fluconazole prophylaxis is that the agent is ineffective against molds and *Candida krusei*, and its activity against *Candida glabrata* is dose-dependent. Several large studies indicate breakthrough infections.[22,26,28] Researchers disagree on whether fluconazole prophylaxis is associated with the development of clinically relevant resistance.[14,32]

In the studies cited above, prophylaxis was discontinued because of subjective intolerance or toxic sequelae in only 0% to 8% of cases. Fluconazole has a favorable safety profile and patient compliance is good.

Itraconazole

Itraconazole is an agent suitable for oral (capsules and suspension) and intravenous administration. Its spectrum of action includes non–*albicans Candida* species and molds.

Oral itraconazole suspension was studied in a double-blind placebo-controlled trial. The dosage was 2.5 mg/kg twice a day. All patients additionally received nystatin 500 000 IU 4 times a day. The itraconazole arm was superior to the placebo arm in terms of reducing the rate of fatal candidemia (1.96% versus 0%). Effective prophylaxis against molds was not documented.[33] An open-label analysis of high-risk patients suggested that itraconazole oral suspension 100 mg twice daily was superior to polyenes.[34] Winston et al[35] randomized allogeneic bone marrow transplant recipients to receive either 400 mg itraconazole or 400 mg fluconazole. Preliminary results suggest itraconazole prophylaxis confers an advantage in terms of incidence of documented invasive fungal infections. Recently, a meta-analysis concluded that itraconazole prophylaxis

Table 2. Recommended prophylactic regimens and their levels of evidence

Drug used on patient population	Dosage	Level of evidence
Conventional chemotherapy		
Fluconazole	50–400 mg qd PO	CI
Itraconazole oral suspension	5 mg/kg qd	BI
Amphotericin B desoxycholate	1.0 mg/kg/48h IV	CII
Amphotericin B desoxycholate	20 mg inhalation	CI
Allogeneic transplantation		
Fluconazole	400 mg qd PO	AI
Fluconazole	50–200 mg qd PO	CI
Liposomal amphotericin B	1.0 mg/kg qd IV	CI

PO indicates orally; IV, intravenously; and qd, once daily.

Table 3. Randomized, controlled, blinded clinical trials of primary antifungal prophylaxis

Prophylactic regimen and daily dose/study arm	No.	Underlying disease	Allo/auto SCT, %	Invasive fungal infections/ per study arm, %			Mortality, %	
				Proven	Probable	Possible	Overall	Attributable
Chandrasekar et al[72,73]								
FLU 400 mg	23	91% AL, 9% other hematol	NA	8.6	0	0	17.4	8.6
Placebo	23			4.3	0	0	13	4.3
Goodman et al[22]								
FLU 400 mg	179	NA	48/52	3	NA	NA	30.7	0.6
Placebo	177			16	NA	NA	26	5.6
Slavin et al[24] and Marr et al[25]								
FLU 400 mg	152	20% AML, 10% ALL, 55% NHL + HD, 15% other	88/12	7	38*		28	13
Placebo	148			18	55		55	21
Winston et al[28]								
FLU 400 mg	123	80% AML, 20% ALL	NA	4	NA	NA	0.8	0
Placebo	132			8	NA	NA	3	0
Rotstein et al[26] and Laverdière et al[14]								
FLU 400 mg	141	50% AML, 10% ALL, 31% other hematol, 9% solid	0/44	2.8	3.5	36	11	0.7
Placebo	133	tumor		16.5	7.5	26	11	4.5
Schaffner and Schaffner[27]								
FLU 400 mg	75	72% AML, 28% NHL relapse	0/10	8	2.7	6.6	5.3	2.6
Placebo	76			9.2	1.3	7.9	6.6	2.6
Young et al[29]								
FLU 200 mg	86	68% AML, 25% ALL, 7% other	NA	4.7	NA	16	7	2
NYS 6×10^6 IU	78			7.7	NA	24	14	4
Huijgens et al[20]†								
FLU 100 mg	101	39% AL, 61% other hematol	NA	4	7	1	7	3
ITR caps 200 mg	101			4	4	2	11	6
Harousseau et al[74]								
ITR oral sol 5 mg/kg	281	57% AML, 13% ALL, 29% other hematol	NA	2.8	30		6	0.4
AmB caps 2 g PO	276			4.7	29		8	1.8
Menichetti et al[33]								
ITR oral sol 5 mg/kg + NYS 2×10^6 IU	201	76% AL, 24% other hematol	NA	2.5	21		7.5	0.5
Placebo + NYS 2×10^6 IU	204			4.4	29		8.8	2.5
Vreugdenhil et al[75]								
ITR caps 400 mg + AmB oral sol 4 g	46	64% AML, 24% ALL, 12% other hematol	NA	10.9	4.3	6.5	21.7	15.2
Placebo + AmB oral sol 4 g	46			19.6	2.2	10.9	30.4	15.2
Nucci et al[37]								
ITR caps 200 mg	104	60% AML, 20% ALL, 18% other hematol, 2% solid	NA	4.8	NA	NA	7.7	1.9
Placebo	106	tumor		8.5	NA	NA	6.6	0.9
Kelsey et al[64]								
L-AmB 2 mg/kg 3x/wk	74	27% AML, 12% ALL, 34% CML, 22% NHL/HD,	53/31	0	28.3		15	2.7
Placebo	87	5% other		2.3	35.6		14	2.3
Tollemar et al[61,62]								
L-AmB 1 mg/kg IV	36	25% AML, 22% ALL, 42% other hematol, 5% solid	83/NA	3	14		44	3
Placebo	40	tumor		8	18		36	8
Riley et al[76]								
AmB 0.1 mg/kg IV + LAF 82%	17	86% hematol, 14% solid tumor	69/NA	0	NA	29	0	0
Placebo + LAF 44%	18			28	NA	44	22	11
Perfect et al[53]								
AmB 0.1 mg/kg + HEPA	91	4% hematol, 96% solid tumor	0/100	1.1	NA	NA	3.3	0
Placebo + HEPA	91			9.9	NA	NA	12.1	2.2

Allo indicates allogeneic; auto, autologous; SCT, stem cell transplantation; FLU, fluconazole; AL, acute leukemia; hematol, other hematologic disease; NA, data not available; AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; NYS, nystatin; ITR, itraconazole; sol, solution; AmB, amphotericin B; L-AmB, liposomal amphotericin B; CML, chronic myelogenous leukemia; LAF laminar air flow; and HEPA, high-efficiency particulate air filter.

*Data between "Probable" column and "Possible" column indicate cases deemed "probable or possible" in studies in which no distinction was made between the two categories of likelihood.

†Huijgens et al[20] used a randomized double-blind design; all other authors used a randomized double-blind placebo design.

effectively reduces the incidence of invasive fungal infection and indicates that the oral suspension lowers the fungal infection–associated mortality[36] (level BI).

Itraconazole capsules are of limited value for prophylaxis,[20] because adequate plasma levels are achieved only after several days or up to weeks of treatment.[37,38] The bioavailability of oral itraconazole suspension is superior to capsules. It seems to be essential to recommend a close patient supervision because of the reportedly unpleasant taste of the oral suspension. Dropout rates because of adverse effects were high (18% and 22%) in 2 published studies in recipients of itraconazole oral solution in a dose of 2.5 mg/kg twice daily and 400 mg once daily.[31,33]

Table 4. Randomized, controlled, open clinical trials of primary antifungal prophylaxis

Prophylactic regimen and daily dose/study arm	No.	Underlying disease	Allo/auto SCT, %	Invasive fungal infections/ study arm, %			Mortality, %	
				Proven	Probable	Possible	Overall	Attributable
MacMillan et al[77]								
FLU 400 mg PO	124	36% AL, 25% CML, 17% NHL/HD	56/44	7.3	NA	NA	NA	NA
FLU 200 mg PO	129			2.3	NA	NA	NA	NA
Egger et al[78]								
FLU 400 mg PO/IV	43	46% AL, 18% CML, 16% NHL/HD	NA	NA	NA	NA	NA	2.3
NYS 72 $\times 10^6$ IU PO + MCZ inhalation, dose NA	46			NA	NA	NA	NA	0
Bodey et al[55]								
FLU 400 mg	41	94% AML, 6% ALL	NA	4.8	7.3	4.8	14.6	0
AmB 0.5 mg/kg 3x/wk IV	36			8.3	19.4	2.7	25	2.7
Wolff et al[54]								
FLU 400 mg	196	NA	29/71	4.1	NA	NA	12.2	2.6
AmB 0.2 mg/kg/d IV	159			7.5	NA	NA	11.9	1.3
Winston et al[35]								
FLU 400 mg IV od PO	67	NA	100/0	25	NA	NA	NA	18
d 1–2: ITR 400 mg IV; d 3, ITR 200 IV or ITR 400 sol	71			9	NA	NA	NA	9
Kern et al[79]								
FLU 400 mg + AmB 240 mg PO	36	100% AML relapse	NA	5.6	0	53	22	0
AmB 240 mg PO	32			6.3	0	34	19	0
Ninane[80]								
FLU 3 mg/kg	245	53% AL, 12% NHL/HD, 30% other	NA	0.8	NA	NA	1.2	NA
NYS 0.2 $\times 10^6$ IU/kg +/− AmB 100 mg/kg	257			1.9	NA	NA	2.3	NA
Ellis et al[81,82]								
FLU 200 mg	42	47% AML, 30% ALL, 8% NHL/HD, 16% other	26/NA	4.8	2.3	NA	NA	4.8
CLO 20 mg + NYS 2 $\times 10^6$ IU	48			21	2.1	NA	NA	18.8
Menichetti et al[30]								
FLU 150 mg	420	81% AML, 19% ALL	NA	2.6	NA	16	10.5	1.2
AmB oral sol 2 g	400			2.5	NA	21	10	0.8
Philpott-Howard et al[23] and Rozenberg-Arska et al[47]								
FLU 50 mg	256	76% AL, 22% other hematol, 2% solid tumor	21/NA	2.4	NA	NA	NA	NA
AmB oral sol 2 g or NYS 4 $\times 10^6$ IU	255			3.5	NA	NA	NA	NA
Boogaerts et al[34]								
ITR oral sol 200 mg	144	66% AML	9/0	5	3†		11.8	4.1
AmB caps 1500 mg + NYS 2 $\times 10^6$ IU	133			5	4		12.8	4.5
Morgenstern et al[31]								
ITR oral sol 5 mg/kg	288	53% AML, 12% ALL, 35% other hematol	NA	0.3	3.1		NA	0
FLU 100 mg	293			2	2.4		NA	2.4
Annaloro et al[83]*								
ITR caps 400 mg + NYS, dose NA	31	NA	35/65	12.9	3.2		6.4	0
FLU 300 mg + NYS, dose NA	28			3.6	7.1		7.1	0
FLU 50 mg + NYS, dose NA	30			3.3	6.6		3.3	0
Timmers et al[65]								
ABCD 2 mg/kg IV	12	25% AML, 8% ALL, 67% other hematol	0/0	0	NA	NA	17	0
FLU 200 mg	12			0	NA	NA	0	0
Schwartz et al[32]								
AmB 20 mg inhalation	227	74% AML, 9% ALL/NHL relapse	0/17	1.8	2.2	0.4	13	8
No prophylaxis	155			0.6	5.8	0.6	10	7
Buchanan et al[49]								
NYS 6 $\times 10^6$ IU PO	104	30% AML, 7% ALL, 29% NHL/HD	NA	NA	NA	NA	NA	NA
No prophylaxis	60			NA	NA	NA	NA	NA

MCZ indicates miconazole; CLO, clotrimazole; and ABCD, amphotericin B colloidal dispersion. Other abbreviations are defined in Tables 2 and 3 notes.

*Annaloro et al[83] used a randomized control design and a historic control group; all other authors used a randomized design.

†Data between "Probable" column and "Possible" column indicate cases deemed "probable or possible" in studies in which no distinction was made between the two categories of likelihood.

Itraconazole should be used for the prophylaxis of invasive fungal infections only if plasma level monitoring is conducted at least twice a week for control purposes and only if levels more than 500 ng/mL are reached within a few days. Clinical pharmacology studies underline the necessity of plasma levels of at least 500 ng/mL.[39] Evidence suggests that this level is achieved with a 90% probability 1 week after starting prophylaxis, if patients take 400 mg, that is, 40 mL oral solution daily and another eight 100-mg capsules in addition.[40]

Intravenous itraconazole was licensed in the United States in 2000, but only preliminary study data on intravenous prophylaxis have yet emerged.[90] Parenteral administration may be helpful in achieving effective plasma levels for prophylaxis in cases where it is not possible to raise oral dosage. Experience with this sequence of intravenous/oral procedure is limited and no evidence-based recommendations exist. Parenteral and oral itraconazole prophylaxis needs close monitoring of plasma levels, which is essential but has been used in *Aspergillus* species infections only. In a small population of 31 patients with invasive

Table 5. Historically controlled and uncontrolled clinical trials of primary antifungal prophylaxis

Prophylactic regimen and daily dose/study arm	No.	Underlying disease	Allo/auto SCT, %	Invasive fungal infections/ study arm, %			Mortality, %	
				Proven	Probable	Possible	Overall	Attributable
Böhme and Hoelzer[57]*								
AmB 0.5 mg/kg 3x/wk IV	61	87% AML, 9% ALL, 4% other hematol	NA	0	9.3	1.6	NA	NA
ITR oral sol 400 mg	72			16.7	8.3	4.1	NA	NA
Karthaus et al[56]*								
AmB 1 mg/kg/48 h	104	100% AL	NA	0	18.3	12.5	NA	NA
No prophylaxis	104			4.8	34.6	19.2	NA	NA
Rousey et al[84]*								
AmB 20 mg IV + LAF	110	24% AML, 8% ALL, 44% CML,	100/0	9	NA	NA	20	6
LAF	48	24% other hematol		23	NA	NA	35	13
No prophylaxis	28			25	NA	NA	46	18
Alangaden et al[85]*								
FLU 100/200 mg	112	50% AL, 36% NHL/HD, 15% other	67/33	3.6	NA	NA	8.9	0.9
No prophylaxis	79			10.1	NA	NA	17.7	3.8
Takatsuka et al[86]*								
FLU 200 mg + AmB oral sol 300 mg + AmB inhalation, dose NA	54	46% AML, 18% ALL, 19% NHL, 5% CML	NA	0	NA	NA	NA	NA
AmB 300 mg PO + oral sol 300 mg + inhalation, dose NA	70			7	NA	NA	NA	NA
Glasmacher et al[39]*								
ITR caps 400/600 mg + AmB oral sol 2400 mg or NYS 24 $\times 10^6$ IU	47	≈85% AML, ≈15% ALL, ≈22% AL relapse	NA	NA	NA	NA	17.9	0.9
AmB oral sol 2400 mg or NYS 24 $\times 10^6$ IU	76	NA		NA	NA	NA	25	8.8
Böhme et al[42]*								
ITR caps 400 mg	241	65% AML, 12% ALL, 23% other hematol	NA	4.6	0.5	1.5	NA	NA
AmB 800 mg PO	223			5.4	0.9	1.3	NA	NA
Tricot et al[87]*								
ITR caps 400 mg	45	68% AML, 26% ALL, 6% other hematol	NA	24	5.5	NA	24	15.5
KTC 400 mg	52			44.5	8.5	NA	40.5	36.5
Thunnissen et al[88]*								
ITR caps 400 mg	47	75% AML, 25% ALL/NHL	NA	0	NA	NA	8.5	0
NYS 10 $\times 10^6$ IU	47			9	NA	NA	26	13
Annaloro et al[83]†								
ITR caps 400 mg + NYS, dose NA	31			12.9	3.2‡		6.4	0
FLU 300 mg + NYS, dose NA	28	NA	35/65	3.6	7.1		7.1	0
FLU 50 mg NYS, dose NA	30			3.3	6.6		3.3	0
Hertenstein et al[50]§								
AmB 20 mg inhalation	303	55% AML, 26% CML, 19% other	89/9	3.6	NA	NA	20.5	2.6
Erjavec et al[51]‡								
AmB 30 mg inhalation	42	52% AML, 41% ALL, 7% other hematol	NA	14	14	NA	NA	7.1
Lamy et al[89]‡								
ITR caps 400 mg + LAF	96	45% AML, 10% ALL, 45% other hematol	NA	2	3	NA	NA	0

KTC indicates ketoconazole. Other abbreviations are defined in Tables 2, 3, and 4 notes.

*Authors used a historic control design.

†Annaloro et al[83] used a randomized historic control design.

‡Data between "Probable" column and "Possible" column indicate cases deemed "probable or possible" in studies in which no distinction was made between the two categories of likelihood.

§Authors used no control in their design.

pulmonary aspergillosis, 91% attained a level more than 250 ng/mL after 2 days on this regimen. It is necessary to point out that the level of more than 500 ng/mL recommended for effective prophylaxis was reached in this study only after 14 days.[41]

Whatever the route of administration, caution should be exercised in the prophylactic use of itraconazole in patients with acute lymphoblastic leukemia because symptoms of neurotoxicity, notably extremely severe cases of paralytic ileus, have occurred in patients taking a combination of vinca alkaloids and itraconazole.[42-44] Recently published data from the US Food and Drug Administration's Adverse Event Reporting System indicate that itraconazole may be negatively inotropic, and itraconazole labeling was modified as a result.[45] In addition, numerous interactions of several drugs with itraconazole due to a P450-3A4 metabolism are well known. The most common inducers of itraconazole metabolism are the anticonvulsives phenytoin, carbamazepine, and phenobarbital and the tuberculostatic drugs isoniazid, rifampin, and rifabutin. In addition, potent inhibitors of cytochrome P450-3A4, such as the macrolides erythromycin and clarithromycin, can increase the bioavailability of itraconazole. Doses need to be adapted due to an interference of the metabolism of the following drugs: terfenadine, astemizole, midazolam, statins, oral anticoagulants, and notably cyclosporin A.[46]

Amphotericin B

Amphotericin B has the broadest spectrum of activity of all antifungal agents available. It is in widespread use as an oral suspension (1.5-3 g/d). Local amphotericin B administration as

lozenges or suspension reduces colonization and lowers the incidence of superficial fungal infections (level BI).[23,47] However, there is no evidence that oral administration can prevent invasive pulmonary aspergillosis. Effective systemic levels of amphotericin B are not reached and after all *Aspergillus* spores are acquired aerogenically. Oral nystatin use is worthy of criticism because its efficacy has not been demonstrated in a recent meta-analysis.[48] In earlier trials topical nystatin seemed to reduce the fungal colonization rate.[49] There is no evidence from a randomized trial to support topical intranasal dosing with polyenes.

Amphotericin B inhalation was associated with a benefit in uncontrolled single-arm studies (level CIII).[50,51] A large multicenter trial did not provide a benefit for amphotericin B inhalation (level CI).[52] Adverse events included coughing, bad taste, and nausea, but no serious side effects.

Intravenous prophylaxis with conventional amphotericin B at a dose of 0.1 mg/kg/d demonstrated no benefit versus placebo (level CI).[53] Wolff et al[54] prospectively compared fluconazole 400 mg orally versus low-dose amphotericin B (0.2 mg/kg) in patients undergoing either allogeneic or autologous stem cell transplantation. They concluded that low-dose amphotericin B prophylaxis was as effective as fluconazole prophylaxis, but more toxic. Bodey et al[55] observed an increase in serum creatinine to more than 2 mg/dL in 22% of patients taking amphotericin B 0.5 mg/kg intravenously when administered 3 times weekly. Prophylaxis was discontinued in 11% of this population, but patients did not receive a sodium chloride loading to prevent nephrotoxicity. Efficacy could not be assessed because of the small sample size. A recently presented case-control study suggested efficacy of intravenous prophylaxis with amphotericin B 1 mg/kg administered every other day in reducing proven and probable invasive fungal infections, but had a historic control group only (level CII). Although amphotericin B therapy is reported with an infusion-related toxicity of up to 90%, it can safely be administered to the majority of patients. Amphotericin B had to be stopped because of adverse effects in 4% of patients receiving prophylactic treatment.[56] Prophylaxis was discontinued in 10% of patients in another study with historic controls because of uncontrollable chills and allergic exanthema.[57] No adequately large, placebo-controlled trials have been carried out to date to evaluate the efficacy of low-dose amphotericin B (eg, 0.5 mg/kg) for primary prevention.[58]

Because nephrotoxicity and infusion-related side effects of amphotericin B can be minimized by making full use of supportive measures, an experienced team is needed. The most important action taken in this context is nephroprotective loading with sodium chloride, which should be administered in the form of an intravenous dose of 1000 mL 0.9% saline in a timely fashion prior to administering amphotericin B.[59]

Prophylactic use of lipid-based amphotericin B products seems to be promising due to lower toxicity compared with conventional amphotericin B desoxycholate. Only in a murine model was prophylaxis with liposomal amphotericin B 5 mg/kg found to be effective and superior to treatment.[60]

Liposomal amphotericin B was administered at a dose of 1 mg/kg/d in a double-blind placebo-controlled study. The trial involved a small population mainly consisting of recipients of allogeneic transplants, but no significant effect was seen.[61-63] Another study in a population with various underlying malignant diseases disclosed no difference between placebo and liposomal amphotericin B 2 mg/kg administered 3 times weekly.[64]

Apart from liposomal amphotericin B, the use of amphotericin B lipid complex (ABLC) and amphotericin B colloidal dispersion (ABCD) would be conceivable.[65] Widespread use is unlikely owing to the high cost of liposomal amphotericin B formulations. At present, due to a lack of study data on the efficacy of lipid formulations, no evidence supports the use of these agents for prophylaxis (level CI).

Unfortunately, the above-cited studies were not powered to detect a clinically significant difference.

New drugs

Newly developed drugs worth mentioning include the new triazoles voriconazole,[66] posaconazole,[67] and ravuconazole,[68] liposomal nystatin,[69] and the new class of echinocandins.[70] Representatives of the latter include caspofungin, micafungin, and anidulafungin, of which caspofungin has been licensed in the United States and the European Union since 2001 for second-line treatment of invasive aspergillosis. The broad spectrum of action of the oral allylamine terbinafine suggests its suitability for prophylactic use,[71] especially given that allylamines are not used for treating invasive fungal infection. As far as prophylaxis is concerned, except micafungin,[9] these drugs have to date only been studied on an individual case basis, so that there is no evidence-based recommendation for their prophylactic use against systemic fungal infections at present.

In addition to safety and efficacy aspects, daily dosage costs will be a decisive factor in determining the feasibility of clinical use for prophylaxis.

Conclusion

A significant benefit versus placebo has been shown for fluconazole at a daily dose of 400 mg, but this superiority has only been demonstrated for recipients of allogeneic transplants (level AI). To date data advocating the prophylactic use of itraconazole are less conclusive (level BI). Evidence for the use of antifungal agents in patients not undergoing transplantation is poor to support prophylaxis (level CI). Based on the assessment of the literature and regarding efficacy there is no clear evidence-based indication against the use of any kind of antifungal prophylaxis (levels D and E).

The rising incidence of invasive fungal infections and the currently problematic early diagnosis call for the intensive exploration of new drugs and further developments in diagnosis and treatment of invasive fungal infection.

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