Antifungal prophylaxis with azole derivatives

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ABSTRACT

In recent years, several reports have underlined the increasing role of fungal infections as a cause of morbidity and mortality in hospitalised patients. For this reason, and also in light of the high mortality rate associated with these infections, chemoprophylaxis has been advocated by several authors. The available evidence suggests that both fluconazole and itraconazole are able to decrease candida colonisation and infection, when compared with placebo or with nonabsorbable antifungals. Data seem also to suggest that a decrease in fungus-related mortality can be achieved with prophylaxis, although with little effect on overall mortality, probably because of the importance of severe underlying diseases. Itraconazole proved to be effective in the prevention of fungal infections, including invasive aspergillosis, although with increased incidence of side-effects, often leading to treatment discontinuation. The other side of the coin is that antifungal prophylaxis might have untoward effects, such as the selection of triazole-resistant *Candida* strains or the induction of resistance. In addition, some authors have suggested that the use of triazoles might modulate the pattern of infecting organisms in cancer patients, increasing the risk of both aspergillosis and bacteremia. In conclusion, antifungal prophylaxis with triazole antifungals should be used with caution, only in patients at high risk for invasive fungal infections. These include allogeneic bone marrow transplant patients (especially those with mismatched or unrelated donors), acute myeloid leukaemia patients treated with high-dose cytarabine (C-ara), very-low-birth-weight infants, patients with chronic granulomatous disease, and high-risk surgical and intensive-care unit patients.

Keywords Fluconazole, itraconazole, prophylaxis

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BACKGROUND

In recent years, several reports have underlined the increasing role of fungal infections as a cause of morbidity and mortality in hospitalised patients. For example, a national survey of nosocomial fungal infections in American hospitals (Hospital Infection Program, Centers for Disease Control, Atlanta, GA) showed that the incidence of these infections increased from 2.0 to 3.8 infections/1000 discharges from 1980 to 1990, with the incidence of nosocomial candidemia increasing from 1.0 to 4.9 infections/1000 discharges [1]. There are studies (including autopsy studies) performed on both sides of the Atlantic Ocean showing a well-documented increase in fungal infections in cancer patients [2,3], especially in leukaemic patients and in those undergoing bone marrow or stem cell transplantation [4]. In American hospitals, *Candida* now represents the fourth most frequent pathogen isolated in blood culture [5]. The incidence of fungal infections varies according to the underlying condition and is higher in burn/trauma intensive-care units [6]. Patients undergoing major abdominal surgery are also at risk for fungal infection, with an incidence approaching 40% [7]. The frequency of fungal

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infection in solid organ transplant recipients has been recently reviewed by Singh *et al*. [8]. They found a decreasing incidence of invasive candidiasis, and an increasing incidence of invasive aspergillosis over the last 10 years. In intensive-care units, epidemiological data concerning incidence and prevalence are much less clear, because of some confusion between colonisation and infection. For example, in a classic prevalence study performed on 21 April 1992, Vincent *et al*. found that 24% of the patients were infected and that fungi accounted for 17% of the isolated pathogens [9]. More recently, however, Blumberg *et al*. reviewed 4276 admissions in intensive-care units in America and found that candidemia was observed in 1% of the patients [10]. Very-low-birth-weight infants admitted to intensive-care units are also at high risk for developing fungal infections [11].

There are indications that the pattern of infecting fungal organisms is changing. Among fungal pathogens, moulds are certainly increasing more than yeasts. For example, Groll *et al*., in a large autopsy study, clearly showed that the overall increase in fungal infection was mainly the result of an increase in infections by filamentous fungi, including species that were never known to be a cause of human infections in the past [3]. Among yeasts, for years, *Candida albicans* was the most frequently isolated species among candida isolates. Recently, a surveillance study of fungemia in cancer patients conducted by the Invasive Fungal Infection Group of the EORTC revealed that non-*albicans Candida* had become prevalent among patients with leukaemia and lymphoma [12]. This phenomenon seems to be common to almost all compromised patients, although its proportions in other patient populations may not be as evident as in cancer patients [13]. Although fungal infections usually do not represent more than 10% of all infections, the mortality they cause remains very high. There is general agreement that from 80% to 95% of patients with cerebral aspergillosis die from the disease [14], while the mortality rate from candidemia may vary from 25% to 50%, according to the underlying condition [12].

In the light of the high mortality rate, preventing invasive fungal infections has always been considered a desirable approach. Unfortunately, until about a decade ago, the antifungal armamentarium was very limited. Both the polyenes and the azoles available at that time were not absorbed by the oral route and their use was limited to intestinal decontamination. Intravenous administration was not practical and was associated with important toxicity. When the triazole became available, several investigators started clinical trials to examine the effects of these drugs for prophylactic purposes.

In the following text we will summarise advantages and disadvantages related to the use of antifungal prophylaxis in patients at risk for fungal infections, excluding patients infected with human immunodeficiency virus (HIV). Because fluconazole and itraconazole, the two triazole drugs that have been extensively used in prophylaxis, have a different spectrum of action and different pharmacological properties, we will deal with them separately. The purpose of this article will be not only to review the most important studies performed in this field but also to put their results in perspective compared to other studies that showed or suggested the possibility that prophylaxis might also carry some untoward, undesirable effect.

FLUCONAZOLE

According to Bow *et al*., 69 trials of antifungal prophylaxis in cancer patients were found in a literature search from 1966 to 2000 [15]. Among them, 38 were comparative trials, having placebo, no treatment or a polyene as control regimen, and were therefore evaluable for the purpose of the analysis. Most of the trials (17 of 38 or 58% of patients in randomised trials) included fluconazole as study regimen. Eight fluconazole studies included at least 100 patients per arm. With the exception of the very early studies, fluconazole was almost always given at the relatively high dose of 400 mg/day or 3–15 mg/kg/day. The first randomised, double-blind placebo-controlled study was published by Goodman *et al*. in 1992 [16]. In a population of patients undergoing autologous and allogeneic bone marrow transplantation (BMT), a statistically significant advantage of fluconazole was shown in the reduction of invasive candidiasis. In this study, fluconazole was given from the day of initiation of the transplant-conditioning regimen to engraftment. Shortly after, Slavin *et al*. published another large study in a slightly different patient population, including only recipients of allogeneic grafts.

The administration of the study drugs was not discontinued at engraftment but was continued until day 75 after transplant, to cover the acute graft-versus-host disease period. In this study the administration of fluconazole was associated not only with a reduction of invasive candidiasis, but also with improved survival [17]. Very interestingly, the same group performed an 8-year follow-up of the patients randomised in the Slavin study. The results of the long-term follow-up were surprising because a statistically significant survival advantage was still present among patients who 8 years before had been randomised in the fluconazole arm, with a reduction in the overall number of invasive candidiasis and candidiasis-related deaths as well as severe intestinal graft-versus-host disease [18]. From the same group, another confirmation of the positive effects of fluconazole prophylaxis in allogeneic BMT came from a study on the effect of BMT from unrelated donors in patients with chronic myeloid leukaemia. In these patients, administration of fluconazole was significantly associated with improved survival [19].

In patients with acute leukaemia, the positive effects of fluconazole prophylaxis were less impressive. Winston *et al.* failed to demonstrate a significant advantage of fluconazole in preventing invasive infections or reducing mortality [20]. Menichetti *et al.*, who published the largest clinical trial of fluconazole vs. a nonabsorbable antifungal drug in acute leukaemia patients, did not show any difference between fluconazole and oral amphotericin B. In this study, fluconazole was given at the relatively low dose of 150 mg daily [21]. In a placebo-controlled study in adults with acute leukaemia [22], Rotstein *et al.* showed that fluconazole at a dose of 400 mg/day reduced the incidence of probable or documented invasive fungal infections, especially among patients with acute myelogenous leukaemia receiving remission-induction chemotherapy with cytarabine plus anthracycline regimens (administerd for 7 and 3 days, respectively) and high-dose cytarabine-containing regimens. Finally, in a very recent study fluconazole at 200 mg/day was compared with low-dose amphotericin B (0.2 mg/kg/day) in 186 haematopoietic stem cell transplant recipients [23]. No difference was observed in terms of study discontinuation for persistent fever, proven, suspected, or superficial fungal infections, or survival at day 100 after transplant.

Fluconazole has been administered as antifungal prophylaxis in other compromised patients. A placebo-controlled study performed by Eggiman *et al.* [24], in a very select group of high-risk surgical patients (those undergoing a second laparatomy), showed that the administration of 400 mg of fluconazole significantly reduced the incidence of invasive candidiasis. Similar results were obtained by Pelz *et al.* in critically ill surgical patients, staying in the intensive-care unit longer than 3 days [25], and by Garbino *et al.*, who showed an advantage of low-dose fluconazole (100 mg daily) in reducing *Candida* colonisation and candidemias, with no effect on either invasive candidiasis or overall mortality [26].

Very-low-birth-weight infants represent another group of patients at risk for severe *Candida* infection [11]. In a recent randomised double-blind placebo-controlled study, fluconazole administered at 3 mg/kg and administered according to an age-adapted schedule, reduced both fungal colonisation and invasive fungal infections in neonates weighing less than 1000 g, requiring a vascular access or endotracheal intubation [27].

Fluconazole could not be expected to be effective against filamentous fungi, such as *Aspergillus*, which represent an important cause of morbidity and mortality, especially in patients with acute leukaemia and in those undergoing BMT. Indeed, no study showed any advantage for fluconazole in the prevention of invasive aspergillosis, although the incidence of these infections was seldom reported.

ITRACONAZOLE

With respect to fluconazole, itraconazole possesses a broader spectrum of action, which includes some *Candida* strains that are intrinsically resistant to fluconazole (*C. kruzei*) and *Aspergillus.* According to Bow *et al.* [15], five randomised trials are available in which itraconazole was compared with placebo or polyenes. Of them, four studies included at least 100 patients per arm [28–31]. In a double-blind placebo-controlled study performed by the GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) with 405 neutropenic patients [28] itraconazole oral solution administered at 5 mg/kg/day resulted in effective reduction of the incidence of candida infections in leukaemic adults. Unfortunately, no effect was shown on the incidence of invasive aspergillosis.

In a similar trial with 557 patients, comparing itraconazole oral solution with placebo [29], the incidence of proven systemic fungal infections, the number of deaths due to invasive mycoses and the use of empiric antifungal therapy seemed to be lower in the itraconazole group, but no statistically significant difference could be documented. In another double-blind placebo-controlled study in 210 patients with haematological malignancies or receiving autologous BMT [30] itraconazole capsules administered at 100 mg twice daily showed a redution in the use of empiric antifungal therapy and a reduced incidence of fungal infection in the subgroup of patients with severe (< 100/mm^3) and prolonged (> 7 days) neutropenia. Finally, a trend in the reduction of deep fungal infections, especially in patients with severe (< 100/mm^3) and prolonged (> 2 weeks) neutropenia, was documented in a trial comparing itraconazole oral solution with amphotericin B plus nystatin in 277 patients [31]. Unfortunately, no significant difference in major end points, such as incidence of invasive mycoses or mortality, could be detected.

In contrast, in a recent meta-analysis Glasmacher and colleagues [32] studied the pooled effect of itraconazole prophylaxis on several markers of efficacy, including the incidence of aspergillosis. They included all kinds of itraconazole studies, and not only placebo or no-treatment-controlled studies. Itraconazole (any formulation) significantly reduced the incidence of invasive fungal infection, invasive yeast infections, and fungal-associated mortality. The incidence of invasive aspergillosis was only reduced when the oral solution was used, with a clear dose-dependent (and concentration-dependent) effect, and at the price of a higher incidence of drug-related adverse events and drug discontinuations.

Itraconazole has also been tested in patients with rare diseases, such as chronic granulomatous disease. In a prospective, open-label study with 30 patients, administration of itraconazole reduced the incidence of pulmonary aspergillosis from 11.5/100 patients-year, observed in historical controls not receiving prophylaxis, to 3.4 in subjects treated with 5 and then 10 mg/kg/day of itraconazole [33]. Despite the severity of invasive fungal infections in chronic granulomatous disease patients and the availability of convincing data in favour of prophylaxis, a randomised, double-blind and placebo-controlled clinical trial was deemed necessary [34]. In this controversial trial, which enrolled 39 patients, there were seven serious fungal infections in placebo recipients compared with only one in itraconazole recipients.

EFFECTS OF ANTIFUNGAL PROPHYLAXIS IN METANALYSES

At least three large metanalyses of the effects of antifungal prophylaxis in cancer patients have been published [15,35,36]. The control areas in these studies were placebo, no treatment or a non-absorbable polyene. The Cochrane study [34] was clearly biased by the inclusion of both antifungal prophylaxis and empiric therapy, showing that clinical expertise should always support the statistical work. The study by Kanda *et al.* [36] showed positive effects of prophylaxis only in studies in which the incidence of systemic fungal infections was higher than 15%. Finally, the study by Bow and colleagues reviewed 38 randomised, controlled studies including more than 7000 patients. The study found that the use of antifungal prophylaxis, mostly with azole drugs (94% of the patients), was associated with a reduction in the use of parenteral antifungal therapy, in the occurrence of both superficial and invasive fungal infections and in fungal-related mortality, with a pooled-weighted odds ratio of 0.59 (0.50–0.67). In the subpopulations of patients with prolonged neutropenia and in recipients of allogeneic BMT there was also a reduction in the overall mortality. Another metanalysis of the effect of fluconazole prophylaxis in very-low-birth-weight infants was performed by the Cochrane group, with the aim of assessing whether intravenous prophylactic antifungal drugs reduced mortality and adverse neurodevelopmental outcomes [37]. Among the 203 patients enrolled into studies comparing fluconazole with placebo, infants who received fluconazole prophylaxis had a reduced risk of death prior to hospital discharge, suggesting efficacy of fluconazole prophylaxis in these patients, even if no data about long-term outcome was available.

FLUCONAZOLE VS. ITRACONAZOLE

In acute leukaemia and BMT patients Huijgens *et al.* found no difference in the incidence of fungal infections in the two arms of the study [38], while another study reported a slight, but not statistically significant, advantage for itraconazole

[39]. In an open-label study, Winston *et al.* compared intravenous and oral fluconazole with intravenous and oral itraconazole in BMT patients [40]. Both drugs were given for 100 days after transplant. Itraconazole performed better than fluconazole, with an incidence of invasive fungal infections of 9% vs. 25%. However, also in this context, there were relatively fewer cases of invasive aspergillosis (three in the itraconazole group vs. eight in the fluconazole group).

Finally, Marr and colleagues [41] compared itraconazole vs. fluconazole in the prophylaxis of infection in BMT patients. In this study the dose of itraconazole was adjusted to maintain serum levels to at least 0.5 μg/mL. This was obtained with a dose of 2.5 mg/kg two or three times a day. Among patients able to tolerate this high dosage, itraconazole effectively prevented fungal infection, with a significant effect on the incidence of aspergillosis as well. However, almost one-quarter of the patients discontinued itraconazole because of gastro-intestinal side-effects. In addition, an important toxic interaction between itraconazole and cyclophosphamide was detected in this study, leading to the recommendation of not administering the two drugs concomitantly [42].

In orthotopic liver transplant recipients, a patient population in which the incidence of fungal infections is relatively low, Winston *et al.* randomised 188 patients to receive either itraconazole or fluconazole. Again, the two drugs were shown to be equivalent in reducing fungal colonisation. As expected, no conclusion could be drawn, because the incidence of fungal infections was very low in both arms [43]. Finally, it is worthwhile to report the execution of two prophylactic clinical trials, in which patients were randomised to receive an unorthodox combination of antifungal drugs. Biancofiore *et al.* randomised 129 consecutive orthotopic liver transplant recipients to receive sequential treatment with intravenous liposomal amphotericin B + oral itraconazole, intravenous fluconazole + oral itraconazole, or intravenous and oral placebo [44]. Mattiuzzi *et al.* randomised 139 patients with newly diagnosed acute myeloid leukaemia or myelodysplastic syndrome to receive antifungal prophylaxis with liposomal amphotericin B or the association of itraconazole + fluconazole [45]. It is quite difficult to understand the rationale behind these choices and how the studies were planned from a statistical point of view. Needless to say, both studies showed no statistically significant difference between the study arms.

SECONDARY PROPHYLAXIS

Patients with a history of invasive aspergillosis (IA) appear to be at high risk for reactivation when undergoing further chemotherapy. This is probably because the fungal organisms remain viable in these lesions. Whether or not the risk of relapse depends on the persistence of lesions is a matter of controversy. According to Martino *et al.* [46], the risk is lower in the presence of a complete radiological response, while for Offner *et al.* [47], patients may relapse even in the absence of residual lesions. What everybody agrees upon is that a history of IA is not an absolute contraindication to further chemotherapy and BMT [48–51]. Ideally, patients needing further treatment for leukaemia should undergo surgical excision of the pulmonary lesions, but this is often impossible because of the impending risk of leukaemia relapse or because of the presence of multiple, bilateral lesions. In any case, even surgical excision does not guarantee complete cure, because aspergillosis is usually a multifocal disease, at least at the microscopic level [52]. Therefore, even if this indication has never been proved in large-scale clinical trials, secondary antifungal prophylaxis (or pre-emptive therapy) remains the only possible option for these patients. The drug of choice seems to be amphotericin B (in any formulation), but itraconazole (alone or in combination) has also been used [53–55]. Two reports have suggested that voriconazole might also be a suitable choice for secondary prophylaxis of invasive aspergillosis in BMT patients [56,57].

POSSIBLE UNTOWARD EFFECTS RELATED TO ANTIFUNGAL PROPHYLAXIS

Untoward effects related to the administration of antibiotics can be classified as toxic, allergic, idiosyncratic, related to the antimicrobial activity of the drug and related to other effects, independent of the antimicrobial activity. In the particular case of triazole drugs, toxicity and allergic reactions are of limited importance. Indeed, triazoles are usually well tolerated, and no severe side-effect has ever been reported, even when prophylaxis is administered for long periods. More

important are the effects unrelated to the antimicrobial activity, especially with itraconazole. Indeed, while fluconazole is poorly metabolised and is eliminated mainly by the renal route, itraconazole undergoes extensive metabolization, with some variability between subjects. Itraconazole is both a substrate and an inhibitor of the cytochome P450 enzyme system, and therefore tends to inhibit its own metabolism with a consequent trend to accumulation. More importantly, itraconazole may interact with other drugs that are metabolised through the same metabolic pathway, a phenomenon that must be recognised because of the increased risk of adverse reactions [42,58].

The prolonged and widespread administration of antifungal prophylaxis with triazoles in patients at risk for fungal infections has been correlated, with variable degrees of certainty, with possible untoward effects related to that very activity of antimicrobial agents which allows them to modify the micro-ecology of human beings. Indeed, the potential for these side-effects, which for obvious reasons are peculiar to antibiotics, should be recognised and carefully considered, when discussing the advantages and disadvantages of prophylaxis.

TRIAZOLE PROPHYLAXIS AND BACTEREMIA

The possible role of antifungal prophylaxis with azole compounds in increasing the rate of bacteremia among febrile and neutropenic patients was first raised by Palmblad *et al*. in 1992 [59]. In a small, randomised, double-blind trial of ketoconazole vs. placebo, they found that the incidence of febrile episodes was the same in both groups, but that the administration of ketoconazole was apparently affecting the type of fever documentation. Indeed, there were many more bacteremias among patients receiving ketoconazole than among those receiving placebo (74% vs. 37%), while clinically documented infections and unexplained fevers were prevalent in the placebo group. As a result of the small size of the study (107 patients), there is the possibility that this difference was chance. However, similar results were also reported by Shaffner *et al.* in a slightly larger study of fluconazole vs. placebo [60]. They reported a 36% incidence of bacteremia in fluconazole recipients, compared with 21% in placebo recipients. More recently, in a large prospective, randomised clinical trial of itraconazole oral solution against placebo, Menichetti *et al.* again found a higher rate of bacteremia among patients receiving prophylaxis [28]. Although the duration of neutropenia was the same in both groups, the rate of bacteremia was 23% in itraconazole recipients compared with 15% in placebo recipients ($P = 0.037$). As reviewed by Palmblad [61], other authors apparently did not find the same effect, although the incidence of bacteremia was rarely reported in these studies. In 1994, in a study aimed at identifying, at the onset of fever during neutropenia, those factors more likely to be associated with the risk of bacteremia, we also found administration of antifungal prophylaxis to be an independent prognostic factor for bacteremia, with an odds ratio estimate of 2.48 and a confidence interval at 95% ranging from 1.49 to 4.13 on a derivation set of 558 episodes [62]. Finally, in 2001 we published a retrospective study based on prospectively collected data to give further insight into this problem [63]. Starting from a database of 3002 febrile and neutropenic patients enrolled in four therapeutic trials performed by the International Antimicrobial Therapy Group of the EORTC from 1986 to 1994, we found that the rates of bacteremia were 20%, 26% and 27% ($P = 0.0001$) among patients not receiving antifungal prophylaxis, receiving nonabsorbable drugs, or receiving triazoles, respectively. In a multivariate model without including antifungal prophylaxis, factors associated with bacteremia were age, duration of hospitalisation, duration of neutropenia before fever, underlying disease, presence of an intravenous line, presence of a site of infection, shock, antibacterial prophylaxis, temperature and granulocyte count at onset of fever. When antifungal prophylaxis was included, the adjustment quality of the model improved slightly ($P = 0.05$), with an odds ratio of 1.19 (95% CI 0.92–1.55) for patients receiving nonabsorbable drugs and 1.42 (95% CI 1.07–1.88) for those receiving triazoles. Finally, very recently Cordonnier *et al*. [64] again found antifungal prophylaxis to be a factor independently associated with the risk of streptococcal bacteremia in febrile and neutropenic patients. In conclusion, although no causal relationship could be demonstrated and the role of antifungal prophylaxis on the rate of bacteremia might well be a marker for other variables not recorded in our database, the data were at least

suggested that every clinical trial of antifungal prophylaxis should record and report the rate of bacteremia among patients enrolled.

TRIAZOLE PROPHYLAXIS AND EMERGENCE OF NON-*ALBICANS* CANDIDA OR MOULD INFECTIONS

Several reports have focused on the increasing rate of colonisation and infection by the natively resistant *Candida* species (*C. krusei* and *C. glabrata*) in leukaemic or BMT patients receiving fluconazole [65–67]. Although this phenomenon was not confirmed in large prospective studies [17,20,21,68,69], it would be surprising if antifungal prophylaxis had no effect on the pattern of pathogens causing infection in patients receiving prophylaxis. Indeed, in a surveillance study of candidemia in cancer patients, we found that administering antifungal prophylaxis, not only with fluconazole, was one of the factors associated with an increasing risk of non-*albicans* candidemia [12]. The other factors identified were severity of the underlying disease and neutropenia.

Prior use of fluconazole has been associated with an increase in the incidence of mould infections, mainly invasive aspergillosis, both in BMT and other immunocompromised patients [69,70]. The explanation of this phenomenon is quite difficult and could range from a lack of 'colonisation resistance' (as described for bacterial infections) to a simple reduction of disease and mortality from candida infection allowing the 'emergence' of *Aspergillus*. An interesting point of view has been recently presented [71] with the suggestion that fluconazole, even if inactive against *Aspergillus* strains, could up-regulate the expression of some genes from these fungi with the consequent trasformation of a previous colonisation or locally invasive infection to a full-blown invasive aspergillosis, perhaps refractory to antifungal drugs.

TRIAZOLE PROPHYLAXIS AND EMERGENCE OF RESISTANCE

In addition to the increased frequency of infections by naturally fluconazole-resistant *Candida* strains (*C. krusei* and *C. albicans*), HIV-infected patients undergoing prolonged treatment with fluconazole presented infections caused by *Candida* strains which 'acquired' resistance to the new azoles [72]. Although this has been shown in other immunocompromised patients [73], the practical importance of this phenomenon is probably negligible and the emergence of clinical problems related to acquired resistance can be considered anecdotal.

CONCLUSION

There is clear evidence, in our opinion, that every approach to the prophylaxis of infectious complications in immunocompromised patients should be tailored to the individual patient risk, to local epidemiological factors and to the results of clinical trials. In this sense, as shown in Table 1, it is likely that triazole antifungal prophylaxis directed against the prevention of candida infections could be recommended in allogeneic BMT patients (especially those undergoing transplantation from unrelated donors and mismatch transplants), in acute myeloid leukaemia patients treated with high-dose cytarabine with or without anthracyclines, in very-low-birth-weight infants, in patients with chronic granulomatous disease, and in high-risk surgical and intensive-care unit patients. Both itraconazole and fluconazole have shown activity, although there is some concern about itraconazole's toxicity profile and the risk of drug interactions. Other patient populations that might deserve prophylaxis include liver and lung transplant recipients, especially if in high-risk conditions (re-transplantation, re-interventions, heavy candida colonisation). The adverse biological consequences of an excessive use of antibiotics for prophylaxis and treatment, both in the individual patient and in the environment, are of the utmost importance, and the consequences are even more serious when the effectiveness of these procedures has not been properly demonstrated. The risk of selecting for natively resistant *Candida* strains or moulds, the risk of inducing acquired resistance and the possible effect on the incidence of severe bacterial infections play against a widespread use of prophylaxis in other patient categories.

For reasons that have already been addressed, antifungal prophylaxis has almost never been targeted specifically at the prevention of invasive aspergillosis. Clinical trials that have evaluated the impact of prophylaxis on aspergillosis have failed to show any advantage. This is particularly disappointing, because nowadays aspergillosis represents the most important 'killer', at least in

Table 1. Patient populations which might deserve triazole antifungal prophylaxis

Patient population	Associated conditions	Drug of choice
Very-low-birth-weight infants	< 1 kg of body weight admission in neonatal ICU during first 6 weeks of life, requiring vascular catheterization or endotracheal intubation	fluconazole 3 mg/kg/dose with administration adjusted according to patients' age
Leukaemic patients	patients with AML treated with remission-induction chemotherapy with cytarabine plus anthracycline regimens (administered for 7 and 3 days, respectively) and high-dose cytarabine-containing regimens	fluconazole 400 mg/day
Bone marrow transplant recipients	patients receiving allogeneic bone marrow transplant, especially from matched unrelated or mismatched donors from day 6 to day 100 (if itraconazole is used, do not administer concomitantly to cyclophosphamide and check frequently for drug interactions)	fluconazole 400 mg/day itraconazole: i.v. 200 mg/day; per OS (oral solution) 2.5 mg/kg every 8–12 h, to keep serum concentrations at least at 0.5 μg/mL.
Patients in ICU	surgery for acute pancreatitis, patients with previous abdominal surgery in the presence of second laparatomy (recurrent gastrointestinal perforation or anastomotic leakages)	fluconazole 100–400 mg/day
	critically ill surgical patients with ICU stay of at least 3 days, patients mechanically ventilated for at least 48 h and expected to stay in ventilation for at least an additional 72 h	
Patients with chronic empty granulomatous disease	Primary prophylaxis of invasive aspergillosis	itraconazole oral solution 5–7 mg/kg/day with empty stomach
Patients with previous invasive mycosis who need further immunosuppression	Secondary prophylaxis conditions	according isolated pathogen (if available) and/or localization of the infection and/or other clinical

haematological patients. We look forward to new drugs that will be able to cope with this fundamental problem.

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