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Fluconazole for the management of invasive candidiasis: where do we stand after 15 years?

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***Candida* spp. are responsible for most of the fungal infections in humans. Available since 1990, fluconazole is well established as a leading drug in the setting of prevention and treatment of mucosal and invasive candidiasis. Fluconazole displays predictable pharmacokinetics and an excellent tolerance profile in all groups, including the elderly and children. Fluconazole is a fungistatic drug against yeasts and lacks activity against moulds. *Candida krusei* is intrinsically resistant to fluconazole, and other species, notably *Candida glabrata*, often manifest reduced susceptibility. Emergence of azole-resistant strains as well as discovery of new antifungal drugs (new triazoles and echinocandins) have raised important questions about its use as a first line drug. The aim of this review is to summarize the main available data on the position of fluconazole in the prophylaxis or curative treatment of invasive *Candida* spp. infections. Fluconazole is still a major drug for antifungal prophylaxis in the setting of transplantation (solid organ and bone marrow), intensive care unit, and in neutropenic patients. Prophylactic fluconazole still has a place in HIV-positive patients in viro-immunological failure with recurrent mucosal candidiasis. Fluconazole can be used in adult neutropenic patients with systemic candidiasis, as long as the species identified is a priori susceptible. Among non-neutropenic patients with candidaemia fluconazole is one of the first line drugs for susceptible species. Cases reports and uncontrolled studies have also reported its efficacy in the setting of osteoarthritis, endophthalmitis, meningitis, endocarditis and peritonitis caused by *Candida* spp. among immunocompetent adults. In paediatrics, fluconazole is a well tolerated and major prophylactic drug for high-risk neonates, as well as an alternative treatment for neonatal candidiasis. Importantly 15 years after its introduction in the antifungal armamentarium, fluconazole is still a first line treatment option in several cases of invasive candidiasis. Its prophylactic use should however be limited to selected high-risk patients to limit the risk of emergence of azole-resistant strains.**

Keywords: *Candida* spp., neutropenia, intensive care unit, bone marrow transplantation, solid organ transplantation, systemic candidiasis

Introduction

Fluconazole was discovered by Richardson *et al.*[1,2] working at Pfizer in Sandwich, UK in a programme initiated in 1978. The original patent covering its structure had been filed by Riley and colleagues at ICI Pharmaceuticals, who discontinued antifungal research prior to fluconazole's launch. Fluconazole was identified because of its *in vivo* activity, and only many years later were *in vitro* systems found to measure *in vitro* activity. Phase 2 studies commenced in 1988 and were focused on *Candida*, cryptococcal and coccidioidal infections, initially using doses of 50 mg daily.[3–6] Prophylaxis studies in neutropenia followed. The increasing need for orally active azoles because of the AIDS epidemic, and respectable efficacy despite low doses of the drug, led to rapid Foods and Drugs Administration and European licensures in 1990 (http://www.fda.gov/bbs/topics/ANSWERS/ANS00051.html; 21

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September 2005, date last accessed). Fears of severe idiosyncratic liver failure akin to ketoconazole effects did not materialize, and larger doses of fluconazole were explored for more seriously ill patients, especially for those with cryptococcal and coccidioidal meningitis and invasive candidiasis. The last is the focus of this review.

The aim of this article is to review the current prophylactic or curative use of fluconazole in the management of invasive candidiasis 15 years after its introduction in the anti-infective armamentarium. Probably in excess of 100 million patients have received fluconazole worldwide between 1990 and 2005.

Pharmacokinetics and pharmacodynamics

Mechanism of action

Fluconazole is a semi-synthetic azole designated an imidazole due to the presence of three nitrogen atoms on the azole ring, which is active against numerous yeasts, but not filamentous fungi. It acts by the inhibition of C-14 α demethylase which is required for ergosterol synthesis, an essential building block of fungal cell membrane. C-14 α demethylase is part of the fungal cytochrome P450 complex and as such can also have an effect on the human cytochrome P450 complex leading to potential drug interactions and side effects. Fluconazole is a fungistatic drug against *Candida* spp.[7]

Pharmacokinetics

Fluconazole is well absorbed with a bioavailability of over 80%. Peak levels are reached in 1–2 h in healthy fasting adults and gastrointestinal absorption is not influenced by the gastric pH. Its volume of distribution is reported to be 0.7–1.0 L/kg, and 11% is protein bound.[8] The majority is excreted via the kidneys (60–75%) with a further 8–10% being recoverable from the faeces. It is also removed by haemodialysis. The half-life is 27–34 h in adult population, allowing for once-a-day administration.

The pharmacokinetics of fluconazole vary with age. Neonates have a 2- to 3-fold higher volume of distribution than adults (~2 L/kg) that falls to 1 L/kg by 3 months of age.[9] The mean volume of distribution is greater and more variable in premature neonates. It is therefore necessary to double the fluconazole dose for neonates in order to achieve comparable plasma levels. Because of reduced glomerular filtration and reduced activity of hepatic enzymes, the half-life is increased in neonates compared with adults (55–90 h). It is thus recommended to administer the drug every 72 h in neonates during the first 2 weeks of life, and then every 48 h in weeks 2–4 of life. Following this period, daily dosing would be appropriate.[10,11]

The diffusion in tissues and body fluids is excellent, with CSF concentrations reaching at least 70% of blood levels even in the absence of inflamed meninges (see Table 1).[8]

A small study of four patients looking at the penetration of fluconazole into brain tissue found that brain levels closely paralleled plasma levels with a daily dose of 400 mg suggesting that this dose may be appropriate for those with brain abscesses caused by susceptible yeasts.[12] A case report of acute cholecystitis due to *Candida albicans* found higher biliary concentration of fluconazole with oral dosing compared with intravenous dosing.[13] Fluconazole penetrates well into joint fluids for the treatment of septic arthritis. Fluconazole can also be administered intraperitoneally for candidal peritonitis in patients on continuous ambulatory peritoneal dialysis with good bioavailability (87%) and plasma levels.[14] The ocular penetration is also good.[15] Indeed, aqueous humour concentrations are reported to reach over 80% of the serum concentration within the day following administration of a single oral dose of 200 mg fluconazole.[16]

Table 1. Diffusion of fluconazole in body tissues and fluids (http://www.pfizer.com/pfizer/download/uspi_diflucan.pdf; 29 September 2005, date last accessed)

Tissue	Ratio of tissue fluconazole concentrations to plasma fluconazole concentrations
CSF	0.5–0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister skin	2
Vaginal tissue	1
Vaginal fluid	0.4–0.7
Eye	0.8

Formulations

Different formulations are available for the treatment or prophylaxis of systemic candidiasis: tablets, capsules, oral solution and intravenous formulation. The intravenous formulation is a simple solution in water.

Dosing

In adults (prophylaxis or treatment). A dose of 200–400 mg/day is recommended in prophylactic setting. For the treatment of systemic candidiasis, a loading dose of 800 mg/day is recommended on the first day, followed by a 400 mg/day dose.

In children. A wide range of doses has been used in children. Recommended doses are of 3 mg/kg/day after the age of 1 year. Neonates with invasive candidiasis should receive 3–6 mg/kg every 72 h during the first 2 weeks of life, every 48 h during 2–4 weeks of life and then once a day at the same dose.[11,17]

In pregnancy. Owing to good bioavailability and volume of distribution, fluconazole is found in breast milk. Fetal abnormalities have been reported after long-term usage among pregnant women.[18] Manufacturers recommend that fluconazole is to be avoided if breast feeding, and that it should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

In renal failure. As fluconazole is mainly renally excreted some dose alterations are recommended for those with a decreased creatinine clearance: see Table 2.

In other settings. In a small review of 14 surgical patients hospitalized in the intensive care unit (ICU) with fluconazole-susceptible deep mycoses, enteral fluconazole was found to give similar levels in urine and exudates from the site of infection as did parenteral fluconazole. Levels in patients with thermal burns vary considerably from normal to shorter half-lives possibly due to the greater volume of distribution.[19] Patients on fluconazole prophylaxis during bone marrow transplantation (BMT) who develop haemorrhagic cystitis secondary to chemotherapy excrete more fluconazole in their urine than those who do not.[20]

Drug interactions

Owing to fluconazole's metabolism via the liver and the CYP450 family of enzymes, the potential exists for many drug interactions. Table 3 lists some of the more important drug interactions.

Table 2. Fluconazole dose reduction in case of renal failure (http://www.pfizer.com/pfizer/download/uspi_diflucan.pdf; 29 September 2005, date last accessed)

Creatinine clearance	Percentage of recommended dose
>50 mL/min	100
11–50 mL/min	50
Haemodialysis patients	100 after each dialysis
Haemofiltration	200

Case reports also include an individual with raised carbamazepine levels during concomitant fluconazole use presumed to be due to cytochrome P450 inhibition.[21] However decreased fluconazole and other azole levels have also been reported in four patients receiving concomitant antiepileptic therapy leading to antifungal failure.[22,23] As a weak inhibitor of cytochrome P450-3A, fluconazole at the standard dose does not inhibit clearance of the H-1 antagonist terfenadine. Higher doses (>200 mg/day) are contraindicated with terfenadine, because of the risk of impairment of the clearance of the drug, and exposing the patients to severe side effects, including QTc-interval prolongation.[24] (http://www.pfizer.com/pfizer/download/uspi_diflucan.pdf; 29 September 2005, date last accessed).

Side effects

Fluconazole displays an excellent profile of tolerance in the range of doses recommended in invasive candidiasis. Side effects do occur especially with doses >400 mg/day. They have been reported to occur more often in those with the human immunodeficiency virus (HIV).[25] Common side effects include headache, nausea and abdominal pain. Raised transaminase serum levels may occur in some cases: from 1% of cases in preventive use for BMT to 10% in preventive use for patients with acute leukaemia and even 20% in the setting of ICU.[26–28] Although generally mild, elevation of liver transaminases can eventually lead to the stopping of fluconazole. Patients with AIDS might be at higher risk for hepatotoxicity with fluconazole.[29] Rare cases of fulminant hepatitis have been reported.[30] Hair loss, which is reversible on stopping the drug, and anorexia have also been reported.[31,32]

Table 3. Major drugs interactions with fluconazole (21-4)

Drug	Mechanism/effect	Action
Ciclosporin	increased ciclosporin AUC	monitor ciclosporin levels, may be enhanced antifungal activity
Hydrochlorothiazide	40% increase in fluconazole levels (D. Denning, unpublished data)	
Glimepiride	via CYP2C9, increased AUC with high doses of fluconazole >400 mg	dose reduction may be necessary
Losartan	via CYP2C9, losartan accumulates	consider an alternative antifungal, monitor blood pressure
Methadone	via CYP3A4, increased AUC	consider an alternative, monitor for increased narcotic effects
Midazolam	increased AUC	monitor for increased sedation
Phenytoin	increased AUC	monitor for phenytoin toxicity, consider using ketoconazole
Rifabutin	via CYP3A4, increased AUC	consider alternative rifamycin, monitor for rifabutin toxicity
Rifampicin	via CYP3A4, accelerates fluconazole metabolism	dose increase fluconazole by 25% may be necessary
Tacrolimus	via CYP3A4, increased risk of interaction if doses of fluconazole >100 mg/day	monitor tacrolimus levels, reduction in dose may be necessary
Warfarin	via CYP2C9, doses of fluconazole >100 mg, reduced warfarin metabolism	monitor INR as possible increase
Cyclophosphamide and CYP450 associated antineoplastic agents	via CYP3A4 and 2C9, doses of fluconazole >200 mg may accelerate cyclophosphamide metabolism	no specific recommendation

CYP, cytochrome P; INR, international normalized ratio.

Neurotoxicity can occur with very high doses above 1200 mg/day.[33] Very unusually anaphylaxis and Stevens Johnson syndrome have been reported.[34]

Safety and tolerability have been also clearly assessed in the paediatric population, mirroring the excellent profile of tolerance observed in adult population.[35] In 1999, Novelli and Holzel reviewed data from 562 children treated with fluconazole: 10.3% presented with treatment-related side effects including 7.7% involving gastrointestinal tract disturbances and 1.2% involving the skin.[35]

Monitoring of levels

There are no routine indications for measuring fluconazole levels. Patients with short bowel who require long-term therapy may require confirmation of absorption. Drug monitoring should be performed among neonates (especially premature infants) with invasive candidiasis to ensure therapeutic plasma concentrations of fluconazole within a range between 4 and 20 mg/L. Salivary concentrations are proportional to plasma levels after 1 week and could potentially be used to monitor compliance.[36]

Pharmacodynamics

Dose-fractionation studies demonstrated that the pharmacodynamic parameter of fluconazole that best predicted outcome in experimental systemic candidiasis was the AUC/MIC ratio.[37] However, clinical response is also related to the immune status of the patient and presence of foreign materials or vegetations.[38]

Activity of fluconazole against *Candida* species

It should be noted that breakpoints have been defined for the susceptibility of *Candida* species to fluconazole using the M27 NCCLS method.[39] *Candida* isolates are qualified as susceptible if MIC values are ≤8 mg/L, S-DD (susceptible dependent upon dose) if at 16 or 32 mg/L and resistant if ≥64 mg/L. When considering the relevance of these breakpoints, they have been well validated for the management of mucosal candidiasis in HIV-infected patients, but much less for the treatment of systemic candidiasis.

Generally, first isolates of *Candida* spp. are susceptible to fluconazole when they are first isolated from a patient who has not been treated with an azole, with the exception of all *Candida krusei* and occasional isolates of other species. When examining the susceptibility of *Candida* species currently isolated from blood cultures, it indeed appears that ≥95% of *C. albicans* isolates remain susceptible to fluconazole. This is also the case for *Candida tropicalis* and *Candida parapsilosis* (refs 40, 41; Observatoire des levures and F. Dromer, unpublished data). The worldwide percentage of *Candida glabrata* susceptible to fluconazole according to geography ranges between 62.1% in Latin America and 80.9% in the Asia-Pacific region.[42]

The susceptibility data are much different in the populations receiving long-term fluconazole prophylaxis. These data will be presented later in the article.

Fluconazole for prophylaxis of systemic candidiasis in transplanted patients

Solid organ transplants

Liver transplants. Among solid organ transplantation, liver transplantation has conveyed the highest risk of fungal infection, *Candida* species accounting for at least 60% of them.[43,44] *C. albicans* is the most frequently involved, followed by *C. glabrata* and *C. tropicalis*. The subsequent associated mortality of these infections is high, ranging between 30 and 100%.[43,45] Invasive candidiasis is strongly related to several conditions: haemodialysis or a creatinine level of ≥2 mg/dL, fungal colonization, ICU hospitalization, exposure to >3 antibiotics, acute hepatic failure, surgical events (urgent surgery, a long procedure >11 h, biliary digestive anastomosis and the need for substantial intraoperative transfusions) and several post-operative events. These include re-intervention, haemodialysis, early colonization (from ≤2 days before to ≥3 days after transplantation), retransplantation, biliary leaks, infarcted tissue, bacterial, and cytomegalovirus and HHV-6 infections.[46–52] Enhanced immunosuppression with steroids, OKT3 monoclonal antibody treatment of rejection as well as antimicrobial prophylaxis to prevent ascites infection may also facilitate the development of invasive candidiasis. Thus, subgroups presenting a high risk of invasive candidiasis have been individualized and are the appropriate targets of fluconazole prophylaxis. The annual incidence of invasive candidiasis among liver transplant recipients has been estimated to range between 6 and 15%, but is now decreasing due to significant technical developments, surgical improvements and the wide use of fluconazole as fungal prophylaxis in this subset of high-risk patients. Indeed, Singh *et al.* in a retrospective study documenting the evolving trends in liver transplantation practices and their impact on fungal infections observed a significant decline in the incidence of invasive candidiasis. *Candida* infections occurred in 9% of the patients between 1990 and 1992, in 1.5% between 1993 and 1995, and in 1.7% of the patients from 1996 onwards.[44]

Three randomized double-blind studies have shown the efficacy of fluconazole in the prevention of candidiasis in this setting (see Table 4). In 1996, Lumbreras *et al.*[53] compared the efficacy of nystatin (4×10^6 U every 6 h, $n = 67$) versus fluconazole (oral 100 mg/day, $n = 76$) administered during the first 4 weeks after transplantation. Fluconazole significantly reduced the rate of *Candida* sp. colonization (7% versus 17%), and proven superficial infection (10% versus 25%), with a trend towards a reduction of invasive candidiasis (2% versus 9%). At that dose, fluconazole was safe and well tolerated, without any interference with ciclosporin. In 1999, Winston *et al.*[46] studied fluconazole (oral 400 mg/day, $n = 119$) compared with placebo ($n = 117$) given for 10 weeks after transplantation. Fluconazole significantly reduced the incidence of fungal colonization (34% versus 78%), superficial infection (4% versus 28%) and invasive infection (6% versus 23%). Of interest, fluconazole also reduced the mortality associated with invasive fungal infection (2% versus 13%) although global mortality rate was not reduced among fluconazole-treated population (11% versus 14%). However, significantly higher serum ciclosporin levels were reported in the fluconazole-treated group. In 2002, Winston *et al.*[54] compared the efficacy of fluconazole (oral 400 mg/day, $n = 108$) versus itraconazole (oral 200 mg twice a day, $n = 104$) given for the first 10 weeks after transplantation. Both equally reduced the rate of colonization (from first to last day of treatment):

Table 4. Studies on prophylactic fluconazole in liver transplant recipients

Reference	Study design	Regimen	Duration of treatment	Number of patients	Proven *Candida* sp. infections (%)	Superficial infections	Invasive infections	*Candida* sp. colonization at the EOT	Death
Winston *et al.*[54]	R, DB, PC, SC	FLC 400 mg/day po versus itraconazole 200 mg/12 h	D0 to W10	91 97	4% 9% ($P = 0.25$)	1% 2%	3% 7%	30% 25%	8% 12%
Winston *et al.*[46]	R, DB, PC, SC	FLC 400 mg/day po versus placebo	D0 to W10	108 104	**9%** **43% ($P < 0.001$)**	**4%** **28% ($P < 0.001$)**	**6%** **23% ($P < 0.001$)**	**34%** **78% $P < 0.001$)**	11% 14% at W10
Lumbreras *et al.*[53]	R, DB, vs tt, MC	FLC 100 mg/day po versus nystatin 4×10^6 U/day	D0 to D28	76 67	**12%** **27% ($P = 0.022$)**	**10%** **25% ($P = 0.034$)**	1% 9% ($P = 0.12$)	**7%** **17% ($P < 0.001$)**	13% 13% at D90
Tortorano *et al.*[56]	R, NB, vs tt, SC	FLC 200 mg/day po versus amphotericin B po 1500 mg /6 h	D0 to D28	38 37	0 3%	ND	ND	24% 32%	ND
Kung *et al.*[57]	HC, SC	FLC 100 mg/day versus no treatment	duration not precise	45 72	ND	ND	0 8%	ND	35% 42% at 12 months
Decruyenaere *et al.*[226]	Retr, SC	FLC 200 mg/day + amphotericin B po in high-risk patients versus amphotericin B po in low-risk patients	D0 to discharge from ICU	45 30	ND	ND	2% 0%	ND	ND

R, randomized; Retr, retrospective; DB, double blind; NB, not blind; PC, placebo controlled; D, day; W, week; vs tt, versus treatment; SC, single centre; MC, multicentre; HC, historical comparison; FLC, fluconazole; po, oral; EOT, end of treatment; ND, not done. Values given in boldface are statistically significant.

from 77 to 30% for fluconazole, and from 67 to 25% for itraconazole. Rates of invasive candidiasis were similar to those described in the author's former study. Other studies have also looked to the contribution of fluconazole in the prophylaxis of invasive candidiasis in liver transplant recipients.

Tortorano *et al.*[55] in 1995 observed a better prevention and clearance of *C. albicans* colonization with fluconazole than with oral amphotericin B, although clearance of *Candida* spp. was not found to be different, because of fluconazole inefficiency on non-*albicans* species. Finally, Kung *et al.*[56] in a historical comparison reported a higher survival rate among patients receiving fluconazole as prophylaxis ($n = 45$, 100 mg/day) compared with untreated patients ($n = 72$): 75% versus 58%. As highlighted by the recently published Infectious Diseases Society of America (IDSA) guidelines, fluconazole-based prophylaxis is therefore recommended among high-risk liver transplant recipients (with ≥2 previously defined risk factors), during the early post-operative period.[57] This practice has been shown to be efficient in decreasing the incidence of invasive candidiasis. However, a shift towards non-*albicans Candida* species in colonization or invasive infections has occurred during the past 10 years with a rise from 15 to 39% after widespread use of fluconazole.[49] This trend emphasizes that the use of fluconazole as prophylaxis should be strictly targeted to high-risk patients and not be generalized to all liver recipients.

Kidney transplants. Given the low incidence of severe *Candida* sp. infections in this population and the lack of specific studies, the use of fluconazole is not recommended in this setting, in Europe and North America.[58,59]

Pancreas and pancreas–kidney transplants. Intra-abdominal and urinary tract infections are the most common sites of fungal infections among pancreas and pancreas–kidney transplant recipients. In a retrospective survey of 445 consecutive pancreatic and pancreas–kidney transplantations, fungal intra-abdominal infections occurred in 41/445 (9.2%) patients and were associated with three times higher risk of death.[60] 87% of all invasive fungal infections following pancreas transplantation are caused by *Candida* species.[61] Enteric drainage procedures, living relative donor as well as previous or simultaneous kidney transplantation are associated with a higher incidence of fungal infection.[60] Underlying diabetes mellitus is a predisposing condition. A consistent characteristic of pancreas-transplanted patients with candidiasis is colonization of the urine with *Candida* species.[62] Benedetti *et al.*[60] observed that patients receiving fluconazole prophylaxis ($n = 108$, 400 mg/day for 7 days) had lower rate of fungal infection than those who did not ($n = 327$): 6% versus 10%. It should be noted that randomized comparative studies of antifungal prophylaxis in pancreas transplantation are lacking. However, data from the Benedetti study suggest that fluconazole might be administered prophylactically in that setting, especially in patients who experienced high-risk procedures or those colonized by *Candida* spp.

Small bowel transplantation. In a retrospective study of 29 patients with small bowel transplantation, Kusne *et al*.[63] reported 20 cases of invasive fungal infections, 16 of them due to *Candida* species, which was involved in 9% of all positive blood cultures. Although never evaluated, current recommendations advocate that fluconazole might be administered in that setting.[57] The use of new biological immunosuppressants such as almetuzumab which is associated with severe T cell cytopenia and high risk of opportunistic infections might convey higher risk of infection and could justify the use of preventive fluconazole.[64]

Heart, lung and heart–lung transplantation. Aspergillus is the main fungal pathogen involved in that setting. Taken its lack of efficacy on moulds, fluconazole as any prophylaxis targeting *Candida* sp. is not relevant.[43,60,66]

Bone marrow transplantation

Invasive fungal infections are still a major cause of morbidity and mortality among recipients of bone marrow or peripheral stem cell transplantation. Allogeneic BMT recipients are at special risk.[66] In the pre-engraftment phase (day 0–day 30), the two major identified risk factors for invasive fungal infections are (i) prolonged neutropenia and (ii) breaks in the mucocutaneous barrier.[67] The most prevalent fungal pathogens are yeasts, especially *Candida* spp., and, as neutropenia continues, *Aspergillus* sp. Post-engraftment from day 30 to day 100 is characterized by impaired cell-mediated immunity. Susceptibility to fungal infections is then related to factors suppressing the T lymphocyte immune response: existence of graft-versus-host disease, use of corticosteroids or anti-T lymphocyte antibodies, and use of T-depleted grafts. This period is more likely associated with mould infections, especially with *Aspergillus* sp., and also to some extent to chronic disseminated candidiasis.[68] Two main randomized double-blind studies have demonstrated the benefit of fluconazole among BMT recipients (allogeneic + autologous) as shown in the Table 5.[69,70] At the dose of 400 mg/day, fluconazole was able to significantly decrease the risk of superficial and invasive candidal infections and the overall number of deaths related to fungal disease. Furthermore, fluconazole was able to reduce the fungal colonization at the endpoint of evaluation. Slavin *et al.* showed a significant decrease of overall mortality at day 110 post-allogeneic transplantation after a 75 day regimen of fluconazole.[70] Confirmation and extension of this benefit was shown by Marr *et al.*[71] on the same cohort with the survival benefit persisting after up to 8 years of follow-up. Indeed, administration of placebo was shown to be an independent factor for poor survival.

Fluconazole has also been compared with other antifungal drugs in allogeneic and autologous BMT (see Table 6). It has been shown to be as efficient as intravenous amphotericin B (0.2 mg/kg/day) for lowering *Candida* colonization and superficial and invasive fungal infections in randomized non-blinded trials.[73] Three randomized non-blinded studies have compared the efficacy of itraconazole and fluconazole in bone marrow recipients, with conflicting results.[74–76] Annaloro *et al.*[74] did not observe any difference in infection-related death, invasive candidiasis or in the need for curative doses of amphotericin B. Winston *et al.*[75] observed statistically more invasive fungal infections in the fluconazole group than in the itraconazole one ($n = 138$, 25% versus 9%), all of them related to non-*albicans Candida* species and moulds (*Aspergillus* sp., *Fusarium* sp. and *Rhizopus* sp.). However, no difference in survival could be detected. Tolerance of itraconazole was lower than that of fluconazole. Marr *et al.*[76] failed to show any superiority of itraconazole in an intention-to-treat analysis, whereas on-treatment analysis revealed a higher rate of invasive fungal infection in the fluconazole group (mostly invasive mould infections). However, only one study has shown increased incidence of infections due to *Aspergillus* species or other moulds in patients treated with fluconazole.[79] Therefore, although with a spectrum of activity

Table 5. Studies on prophylactic fluconazole versus placebo or no treatment in allogeneic and autologous bone marrow transplant patients

Reference	Study design	Regimen	Duration of treatment	Number of patients (auto)	*Candida* sp. colonization at the EOT	Superficial infections	Invasive infections	Death related to IFI	Overall mortality
Marr *et al.*[71]	R, DB, PC, SC	FLC po 400 mg/day	first day with PMN <500/mm^3	152 (18)	ND	ND	**C3%**	**9% C 1%, F 8%**	**55%**
		versus placebo	until D+75	148 (17)			**C20% (*P* < 0.001)**	**14% C 8%, F 6% (*P* = 0.001)**	72% (*P* = 0.0001)
Slavin *et al.*[70]	R, DB, PC, SC	FLC po 400 mg/day	First day with PMN <500/mm^3	152 (18)	**77%**	**0%**	**7%**	**7% C <1%, F 7%**	**20%**
		versus placebo	until D+75	148 (17)	**86% (*P* = 0.037)**	**7% (*P* < 0.001)**	**18% (*P* = 0.004)**	**13% C 9%, F 4%**	**35% (*P* = 0.004)**
Alangaden *et al.*[72]	HC	FLC po 100 or 200 mg/day	2 weeks before BMT until	112 (28)	**70%**		**4%**		9%
		versus no treatment	PMN >500/mm^3	79 (40)	**82%**	**ND**	**10% (*P* < 0.05)**	ND	18%
Goodman *et al.*[69]	R, DB, PC, MC	FLC po 400 mg/day	first day conditioning regimen	179 (86)	**30%**	**8%**	**3% C 2%, F 1%**	**1%**	**31%**
		versus placebo	until engraftment (PMN > 10^3/mm^3)	177 (100)	**67% (*P* < 0.001)**	**33% (*P* < 0.001)**	**16% C 14%, F 2% (*P* < 0.001)**	**6%**	**26%**

R, randomized; Retr, retrospective; DB, double blind; PC, placebo controlled; D, day; SC, single centre; MC, multicentre; HC, historical comparison; auto, autologous bone marrow; FLC, fluconazole; po, oral; EOT, end of treatment; IFI, invasive fungal infection; ND, not done; C, *Candida* sp.; F, filamentous fungi; PMN, polymorphonuclear cells; BMT, bone marrow transplantation. Values given in boldface are statistically significant.

Table 6. Studies on prophylactic fluconazole versus other antifungals in allogeneic and autologous bone marrow transplant patients

Reference	Study design	Regimen	Duration of treatment	Number of patients (auto)	Superficial *Candida* sp. infections	Invasive fungal infections	*Candida* sp. colonization at the EOT	Death related to IFI	Overall death
van Burik *et al.*[79]	R, DB, MC	FLC po 400 mg/day	48 h before conditioning	457 (201)	ND	2.4% C 0.4%, F 2%	34%	<1%	6%
		versus micafungin (50 mg/day)	regimen until engraftment	425 (203)		1.6% C 0.9%, F 1.7%	52%	<1%	4%
Marr *et al.*[76]	R, NB, SC	FLC po or iv 400 mg/day versus	conditioning regimen to D-120 (n = 187)	148	ND	19% C 3%,F 16%	ND	7%	31%
		itraconazole 7.5 mg/kg po 200 mg/day	D-0 to D-120 (n = 102)	151		18% C 3%, F 15%		8%	39%
Winston *et al.*[75]	R, NB, MC	FLC po or	D-1 to D-100	68	3%	**25%**	ND	ND	42%
		iv 400 mg/day versus itraconazole iv 200 mg/day or po 2.5 mg/kg/day ×3/day	after BMT	72	4%	**9% (P = 0.01)**			45%
Koh *et al.*[227]	R, NB, SC	FLC po 200 mg/day	24 h before conditioning	100 (26)	1%	12%	ND	6%	22%
		versus amphotericin B iv 0.2 mg/kg/day	regimen until engraftment (PMN > 500/mm^3>3 days)	86 (20)	5%	13%		7%	30%
Wolff *et al.*[73]	R, NB, MC	FLC po 400 mg/day	D-1 preconditioning regimen	196 (142)	ND	2.6%	27%	3%	12%
		versus amphotericin B iv 0.2 mg/kg/day	until engraftment (PMN >500/mm^3)	159 (110)		2%	43%	1%	12%
Annaloro *et al.*[74]	R, NB, SC	FLC po 300 mg/day	D-1 preconditioning	28	ND	4%	ND	no difference	ND
		versus FLC po 50 mg day versus itraconazole 400 mg/day	regimen until engraftment (PMN >500/mm^3)	30		3%			
				31		13%			
Gluckman *et al.*[228]	R, NB, SC	FLC po/iv 100 mg/day	D–8 to D+90 after BMT	30	3%	10%	47%	ND	ND
		versus ketoconazole 400 mg/day		29	11%	7%	41%		

R, randomized; DB, double blind; NB, not blind; PC, placebo controlled; SC, single centre; MC, multicentre; FLC, fluconazole; po, oral; iv, intravenous; EOT, end of treatment; ND, not done; C, *Candida* sp.; F, filamentous fungi; PMN, polymorphonuclear cells; BMT, bone marrow transplantation; D, day. Values given in boldface are statistically significant.

limited to yeasts, fluconazole has been widely adopted as an effective and safe therapy. Its use is now recommended from the day of haematopoietic stem cell transplantation until engraftment in guidelines for prevention of opportunistic infections among allogeneic bone marrow recipients.[67] The optimal dose of fluconazole in that setting is not clearly determined. The posology of 400 mg/day is recommended by the IDSA. However, lower doses have been shown to be similarly effective in reducing the risk of invasive infections and candidal colonization.[71,76] MacMillan *et al.*[77] in a large cohort of 253 patients demonstrated similar efficiency of high and low dosages of fluconazole (200 and 400 mg/day) on the rate of fungal colonization and infection. No increase of reduced susceptibility in isolates of *Candida* was seen at the low doses. The adoption of fluconazole as prophylactic regimen in BMT has raised concern about a shift of colonization towards azole-resistant strains of *Candida* sp. Indeed, Marr *et al.*[78] observed that out of 585 patients undergoing BMT with prophylactic fluconazole 44% were colonized with *Candida* sp. during the procedure, half of them with a species other than *C. albicans*. However, no increase in invasive candidiasis or in deaths related to non-*albicans Candida* infections could be observed. Very recently, van Burik *et al.*[79] in a large randomized double-blind multicentre study on 882 patients observed superior efficacy of the echinocandin micafungin (50 mg/day) over fluconazole (400 mg/day) on the prevention of invasive fungal infection among bone marrow recipients: 80% of success versus 73%. Further cost–benefit studies are required to determine whether micafungin could be an alternative to fluconazole in that setting, particularly as fluconazole is now generic.

Fluconazole for prophylaxis of Candida infections in neutropenic patients

Neutropenic patients with haematological malignancies are at high risk for developing invasive and superficial mycoses. However, all of them do not share the same risk of fungal infection.

Prolonged deep neutropenia as observed in intensive induction or salvage regimens for acute leukaemia, use of corticosteroids and exposure to high-dose cytosine arabinoside or to monoclonal antibodies (anti-CD52) are deeply immunosuppressing conditions facilitating the emergence of invasive fungal infections.[80]

Studies versus placebo. Seven studies have shown the efficacy of fluconazole in the setting of fungal prophylaxis among neutropenic patients (excluding BMT), including five randomized, double-blind placebo-controlled trials.[81–87] Indeed, fluconazole has been shown to significantly reduce *Candida* species colonization, superficial infections, invasive proven candidal infections as well as fungal-related mortality. A broad range of doses were used in these studies ranging from 50 to 400 mg/day. However, no benefit on overall mortality has been observed (see Table 7).

Comparative studies. Fluconazole has also been compared with other antifungal agents (see Table 8). When compared with oral polyenes, it was at least equivalent in terms of prevention of superficial infection, except in the study by Rozenberg *et al.* suggesting that amphotericin B (400 mg × 4/day) might more efficiently reduce superficial candidal colonization.[88–98] Egger *et al.*[88] also suggested that fluconazole might reduce the need for curative amphotericin B among neutropenic patients, but taken the absence of consensus about the use of amphotericin B in the case of persistent fever, these results are of low clinical pertinence. Fluconazole has an excellent tolerance profile in that population, with similar efficiency and fewer side effects than intravenous polyene prophylaxis.[98]

Optimal dose is not clearly defined in neutropenic patients. Dosages ranging from 100 to 400 mg/day were used with apparently the same efficacy. Low doses of 50 mg/day prevent superficial candidiasis but not invasive disease. Oral administration was apparently as efficient as the intravenous one, although this point had never been extensively studied in appropriate comparative studies, especially as more recent studies allowed either route of administration.

Recently two meta-analyses reviewed the data extracted from all major studies on fluconazole prophylaxis in neutropenic patients with or without BMT.[99,100] Comparators were fungal-related deaths, superficial and invasive candidal infections, use of parenteral antifungal therapy, and infection and colonization with fluconazole-resistant species. In 2000, Kanda *et al*. reviewed 16 controlled studies involving 3734 patients.[99] Superficial infections were clearly reduced by the use of fluconazole (combined OR 0.23; 95% CI 0.17–0.31). In trials involving neutropenic patients without BMT, the benefit of fluconazole on invasive infections appeared only in studies in which the incidence of fungal infection was >15%: with a combined OR at 0.23 (95%CI 0.15–0.36). There was also no difference in the incidence rate of invasive aspergillosis between control and study groups. Colonization by *C. krusei* was more frequent in fluconazole-treated patients (OR 2.01; 95% CI 1.3–3.12). Colonization by *C. glabrata* was more frequent among patients with low-dose (50–200 mg/day) regimen (OR 2.04; 95% CI 1.18–3.53). However, there was also no difference between test and control groups in the incidence rate of invasive proven infections with *C. krusei*, *C. glabrata* or *Aspergillus* sp. Fungal-related mortality was not reduced in fluconazole-treated patients. In 2002, Bow *et al.*[100] similarly reviewed 38 trials, including 14 involving fluconazole (4062 patients with malignant disease and severe neutropenia). Fluconazole regimen was associated with benefit on superficial and invasive fungal infections and also on fungal infection-related mortality (weighted OR 0.53; 95% CI 0.34–0.83). Overall mortality was not reduced, and no excess of invasive aspergillosis could be evidenced. One negative issue was subsequently identified in a retrospective study including 3002 patients, Viscoli *et al.* found that absorbable antifungal prophyl axis in neutropenic patients was associated with an increased rate of bacteraemia, with an estimated OR of 1.42 (95% CI 1.07–1.88).[101]

There is no clear international recommendation about the use of fluconazole or other antifungal drugs in the non-BMT profoundly neutropenic setting. The IDSA 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer indicate that 'routine use of fluconazole or itraconazole for all cases of neutropenia is not recommended. However, in certain circumstances in which the frequency of systemic infection due to *C. albicans* is high and the frequency of systemic infection due to other *Candida* species and *Aspergillus* species is low, some physicians may elect to administer antifungal prophylaxis (D-II).[102] In German guidelines, fluconazole prophylaxis (400 mg/day) among patients undergoing conventional chemotherapy is a grade C-I recommendation (poor evidence).[103] French guidelines on the care of invasive candidiasis in adults were recently updated. The use of fluconazole prophylaxis (400 mg/day) is a high

Table 7. Studies on prophylactic fluconazole versus placebo or no treatment in neutropenic patients

Reference	Study design	Regimen	Duration of treatment	Number of patients	Proven *Candida* sp. infections	Superficial infections	Invasive infections	*Candida* sp. colonization at the EOT	Death
Laverdière *et al.*[81]	R, DB, PC, MC	FLC 400 mg/day po versus placebo	within 72 h post-initiation of chemotherapy until PMN >500/mm^3	135 (60 BMT) 131 (58 BMT)	ND	ND	**3%** **17% *P* < 0.001**	**31%** **75%**	ND
Rotstein *et al.*[84]	R, DB, PC, MC	FLC 400 mg/day po versus placebo	within 72 h post-initiation of chemotherapy until PMN >500/mm^3	141 (62 BMT) 133 (58 BMT)	ND	**7%** **18% (*P* = 0.02)**	**3%** **16% (*P*=0.0001)**	**0.15 ± 0.23** **0.39 ± 0.30** **fungal index colonization (*P* < 0.0001)**	ND
Kern *et al.*[86]	R, DB, SC	FLC 400 mg/day po versus no treatment		36 32	ND	ND	6% 6%	ND	no difference
Schaffner *et al.*[87]	R, DB, PC, SC	FLC 400 mg/day po/iv versus placebo	admission until sustained PMN >500/mm^3	75 76	ND	1% 12% (*P* = 0.018)	8% C0%, F8% 9% C5%, F4%	**8%** **36% (*P* < 0.0001)**	6% 7%
Yamaç *et al.*[85]	R, NB, SC	FLC 400 mg/day po versus no treatment	D0 chemotherapy until PMN >2 × 10^3/mm^3	41 29	ND	ND	**9%** **31% (*P* < 0.05)**	ND	ND
Chandrasekar[83]	R, DB, PC, SC	FLC 400 mg/day po versus placebo	D0 chemotherapy or conditioning or regimen until D+7 after PMN > 10^3/µl	23 (11 BMT) 24 (11 BMT)	ND	34% 79% (*P* = 0.0002)	10% C0%, F10% 5% C5%, F0%	ND	17% 13%
Winston[82]	R, DB, PC, MC	FLC po 400 mg/day po/iv versus placebo	D0 chemotherapy until PMN > 10^3/µl	124 132	9% 21% (*P* = 0.02)	6% 15% (*P* < 0.01)	4% C1%, F3% 8% C4.5%, F3.5%	29% 68% (*P* = 0.001)	21% 18%

R, randomized; DB, double blind; NB, not blind; PC, placebo controlled; SC, single centre; MC, multicentre; FLC, fluconazole; po, oral; iv, intravenous; EOT, end of treatment; ND, not done; C, *Candida* sp.; F, filamentous fungi; PMN, polymorphonuclear cells; BMT, bone marrow transplantation; D, day. Values given in boldface are statistically significant.

Table 8. Comparative studies on prophylactic fluconazole versus other antifungals in neutropenic patients

Reference	Study design	Regimen	Duration of treatment	Number of patients	Proven *Candida* sp. infections	Superficial infections	Invasive infections	*Candida* sp. colonization at the EOT	Death
Morgenstern *et al.*[89]	R, SB, MC	FLC 100 mg/day po versus itraconazole 2.5 mg/kg twice a day po	beginning conditioning regimen until PMN $>10^3/mm^3$>1 week	227 (120 BMT)	ND	5%	3% C1%, F2%	ND	4%
				218 (110 BMT)		2%	1% C1%		1%
Egger *et al.*[88]	R, NB, SC	FLC 400 mg/day iv/po versus nystatin 24×10^6 U ×3/day po	from hospitalization in isolation unit until end of neutropenia	43 (14 BMT)	2%	0%	2%	ND	ND
				46 (19 BMT)	4%	0%	4%		
Bodey *et al.*[98]	R, NB, SC	FLC 400 mg/day po versus AMB 0.5 mg/kg ×3/week iv	from D0 chemotherapy until PMN $>10^3/mm^3$	41	4%	0%	4%	18%	15%
				36	8%	0%	8%	15%	9%
Ellis *et al.*[90]	R, DB, SC	FLC po 200 mg/day versus clotrimazole (10 mg qid) + mycostatin 500 000 IU qid	admission until PMN $>10^3/mm^3$	42 (10 BMT)	9.5%	2%	5%	ND	**19%**
				48 (13 BMT)	35% ($P < 0.01$)	13%	21%		**35% ($P < 0.04$)**
Menichetti *et al.*[93]	R, NB, MC	FLC 150 mg/day po versus AMB 500 mg ×4/day po	D-3 to D-1 before chemotherapy until PMN $>10^3/mm^3$	420	3.5%	2%	1.5%	ND	10%
				400	5%	3%	2%		10%
Ninane *et al.*[92]	R, NB, MC, children	FLC po 3 mg/kg/day versus nystatin po 50 000 U/kg qid or AMB 25 mg/kg qid po	48 h within initiation of chemotherapy until PMN $>10^3/mm^3$	245	**2%**	**1%**	1% C0.5%, F0.5%	no difference in reduction and control of colonization	ND
				257	**8% ($P = 0.002$)**	**6% ($P = 0.004$)**	2% C2%		
Akiyama *et al.*[94]	R, NB, SC	FLC 200 mg/day po versus AMB 800 mg ×3/day po	D0 chemotherapy until PMN $>500/mm^3$	71	ND	ND	1%	2%	ND
				59			3%	9%	
Philpott-Howard *et al.*[91]	R, NB, MC	FLC 50 mg/day po versus AMB 2 g/day po or nystatin 4×10^6 U/day	before chemotherapy until PMN $>10^3/mm^3$ or 4 weeks	269	**4%**	**2%**	2% C1%, F1%	similar	ND
				267	**12% ($P = 0.001$)**	**9% ($P < 0.001$)**	4% C3.5%, F0.5%		
Meunier *et al.*[95]	R, NB, SC	FLC po 200 mg/day versus AMB po 430 mg/day	D-2 neutropenia until PMN $>10^3/mm^3$	30 (9 BMT)	7%	0	14% C7%, F7%	ND	17%
				29 (9 BMT)	13%	3%	17% C10%, F7%		21%
Rozenberg-Arska *et al.*[96]	R, NB, SC	FLC 50 mg/day po versus AMB 400 mg ×4/day po	D0 neutropenia until PMN $>500/mm^3$	25	ND	0	4% C0%, F4%	52%	ND
				25		4%	4% C4%, F0%	16%	
Brammer *et al.*[97]	C, NB, MC	FLC 50 mg/day po versus oral polyenes	NR	126	27%				
				122	45% (suspected fungal infections)	ND	ND	ND	ND

R, randomized; DB, double blind; NB, not blind; SB, single blind; SC, single centre; MC, multicentre; FLC, fluconazole; po, oral; iv, intravenous; EOT, end of treatment; ND, not done; C, *Candida* sp.; F, filamentous fungi; PMN, polymorphonuclear cells; BMT, bone marrow transplantation; D, day; qid, four times a day. Values given in boldface are statistically significant.

grade recommendation (A-I) among allogeneic bone marrow recipients, but not in the setting of autologous BMT or acute leukaemia (http://www.srlf.org/Data/Documents/HTML/O2_refenticls_OA-recommendations/20040513.asp date last accessed 26 December 2005). Thus, in the light of the previously described meta-analysis, fluconazole might be appropriate in neutropenic patients with a high risk of fungal infection, i.e. those with long duration of neutropenia, prolonged corticosteroid therapy, but probably other drugs will be better choices.

Fluconazole as prophylaxis for systemic candidiasis in ICU adults

The extent of the problem. There is an increasing incidence of both bacterial and fungal sepsis occurring in ICU patients. A US study found that the absolute number of deaths due to invasive mycoses rose from 1557 in 1980 to 6534 in 1997.[104] Although much of this increase was associated with fungal infections related to HIV, there were also marked increases in deaths due to candidiasis, aspergillosis and other mycoses in the non-HIV population. A UK study looking at the outcome of candidaemia infections reported 18.7 episodes of candidaemia per 100 000 finished consultant episodes. Of them, 45.4% occurred in an ICU setting, and *C. albicans* was isolated in 65% of cases.[105] A Swiss study found that two-thirds of episodes of candidaemia occurred in ICU or on surgical wards, with invasive candidiasis occurring 5–10 times more frequently in an ICU setting than on other wards.[106] Strikingly, in spite of all therapeutic innovations in the field of antifungal therapy, the crude and attributable mortality of nosocomial fungaemias have not decreased over the past 15 years (38%).[107]

How are patients at risk of invasive candidiasis identified? The diagnosis of invasive candidiasis may be difficult due to the high frequency of colonization, especially in patients who are on broad spectrum antibiotics. A prospective study of non-neutropenic patients in whom *Candida* species were isolated found that digestive and respiratory samples and the isolation of non-*albicans* species were risk factors for invasive candidiasis.[108] Additionally the most significant risk factors for invasive candidaemia identified in a surgical ICU in those who had undergone surgery were prior surgery, acute renal failure, receipt of total parenteral nutrition and the presence of a central venous catheter.[109] This study also found that administration of an antifungal agent was associated with decreased risk for invasive candidal infection. For critically ill surgical patients, Pittet *et al.*[110] proposed a *Candida* colonization index based on the ratio between the number of colonized sites and the number of sites tested. Although its use in hospital practice is complex, expensive and time-consuming, this index was highly predictive of invasive candidiasis: indeed a threshold of 0.5 or more correctly identified the infected patients an average of 6 days before the documented candidiasis. An alternative approach has been considered using both anti-*Candida* antibody and antigen titres.[111] A high concordance between the two has been observed for patients with invasive candidal disease compared with patients who were only colonized with *Candida*. Sensitivity and specificity reached 100 and 83.3% respectively when the two tests were combined.[112]

Studies that have been done. A recent paper has highlighted the importance of appropriate trial design of antifungal prophylaxis and the need for appropriate assessment of risk factors to identify those patients who are at higher risk.[113] Fluconazole has previously been assessed as a prophylactic agent in ITU settings with contradictory results.

Concerns over a shift in *Candida* isolates that are less susceptible or resistant to fluconazole may be balanced against the justification of using it in appropriately identified high-risk patients.[114]

For. Three prospective randomized placebo-controlled trials have emphasized the efficacy of fluconazole in that setting (see Table 9). In one study, 260 critically ill surgical patients staying in ICU for >3 days, mainly pre-hepatic transplantation patients, were randomly assigned to either placebo or 400 mg of fluconazole per day. The risk of fungal infection was reduced by 55% in the fluconazole group, compared with the control group who experienced 15% of invasive infections.[115] In a small study of 43 surgical patients with recurrent gastrointestinal leaks or perforations, the use of fluconazole prophylaxis resulted in decreased isolation of *Candida* in surveillance cultures and in a decrease in candidal peritonitis: 4% versus 35%, with a decrease in global invasive candidiasis (9% versus 35%).[116] A slightly different approach was used in a study of 204 critically ill patients in surgical and medical ICU where fluconazole was used as part of a selective digestive decontamination regimen.[28] These patients appear to more closely represent a typical group of ICU patients. Invasive *Candida* infections occurred less frequently: in 8% of the fluconazole group compared with 20% of the placebo group, and no shift towards non-*albicans* species was observed.

Several reviews of historical cohorts have provided similar results. A recent retrospective review in a surgical ICU comparing the use of fluconazole prophylaxis versus a historical cohort found that prophylaxis decreased the incidence of candidaemia and did not find an increase in non-*albicans* species.[117] No reduction of mortality with fluconazole was observed. Secondary *Candida* infections in high-risk patients with trauma occurred in 9/62 (14.5%) patients who did not receive fluconazole prophylaxis compared with 3/145 (2%) of a historical cohort who did.[118]

In another randomized prospective study of bacterial septic shock, fluconazole had a measurable positive impact on survival, although no fungal infection was diagnosed. This unclear beneficial effect might be related to fluconazole's observed ability to enhance the bactericidal activity of neutrophils, or to prevent *Candida* spp. infection which was not diagnosed by standard blood cultures which are known to be relatively insensitive.[119,120]

Against. One group of patients at increased risk of invasive candidiasis includes those who have undergone recent liver transplantation. In a previously cited prospective study of 35 post-liver-transplantation patients, patients with *C. albicans* infections were less likely to have received antifungal prophylaxis than those with non-*albicans Candida* infections (13.6% versus 50%, $P = 0.04$). Non-*albicans Candida* infections and prior antifungal prophylaxis correlated with poorer outcome.[49] A further study looked at 125 critically ill patients who received either fluconazole prophylaxis or placebo during their entire stay in ICU.[121] There were no significant differences in the incidence of candidal infections nor any difference in the mortality or length of stay on ICU. In the study performed by Pelz *et al.*[115] among pre-liver-transplantation patients, no benefit of fluconazole on survival could be noticed, although a clear reduction of fungal infection was observed.

There are however concerns that the use of prophylactic fluconazole in critical care patients favours the emergence of

Table 9. Controlled randomized prospective studies on fluconazole prophylaxis in ICUs

Reference	Risk factor	Mean APACHE 2 score	Regimen	Number of patients	New *Candida* sp. colonization	Invasive candidiasis	Death rate
Garbino *et al.*[28]	mechanical ventilation for >48 h with >72 h expected	21	100 mg iv	103	**53%**	8%	39%
			versus placebo	101	**78% ($P < 0.001$)**	20%	41%
Pelz *et al.*[115]	ICU stay >3 days pre-hepatic transplantation	63	400 mg po	130	ND	**8.5%**	14%
			versus placebo	130		**15% ($P < 0.01$)**	16%
Eggimann *et al.*[116]	abdominal surgery recurrent gastrointestinal perforation or anastomotic leakages	17	400 mg iv	23	**15%**	**9%**	30%
			versus placebo	20	**62% ($P = 0.04$)**	**35% ($P = 0.02$)**	50%

ICU, intensive care unit; po, oral; iv, intravenous; ND, not done. Values given in boldface are statistically significant.

non-*albicans* species, some of which are less susceptible or resistant to fluconazole. One review paper in 2002 suggested that there was no evidence of therapeutic benefit with prophylactic fluconazole used in this manner.[122] In a small retrospective review of critically ill patients on ITU who did or did not receive fluconazole, the mortality was higher in the fluconazole group and this group also demonstrated increased bacterial resistance. There was a trend towards increasing *Candida* resistance to fluconazole over the period of the study.[123]

Tortorano *et al.*[124] recently reported a 20 year study on the evolving trends of candidiasis in an Italian ICU. When comparing the data from 2000 and the data from the 1980s, the rate of *Candida* spp. invasive infections and colonization appeared stable. However, the authors reported an increased number of mixed colonization (39% versus 6%), with a reduction of colonization by *C. albicans* (78% versus 93%) and a flare up of *C. glabrata* involvement (35%). Two cases of acquired resistance to fluconazole in *C. glabrata* strains were documented. MICs to other azoles were also elevated in both cases, with one case resistant to itraconazole and less susceptible to voriconazole.

In summary, fluconazole prophylaxis in the ICU has been shown to reduce the incidence of invasive candidal infections in some high-risk patients, such as those with a perforated viscus, major trauma and possible pancreatitis. The role of acquired resistance to fluconazole in this setting is however unclear, and prophylaxis has not been shown to reduce mortality. Even if the epidemiology of *Candida* sp. infections in ITU does not display the shift towards azole less-susceptible strains observed in the AIDS population, the regular use of fluconazole prophylaxis may lead to selection of resistant organisms. Larger trials with appropriate selection of patients are needed. This view has been reported in detail previously.[125,126]

Fluconazole for prophylaxis of oesophagitis in HIV-infected patients

Mucosal candidiasis had markedly contributed to the morbidity of HIV-infected patients worldwide, until the era of highly active antiretroviral therapy (HAART), which led to a drastic reduction of both colonization and infection by *Candida* spp.[127] However, *Candida* is still one of the most common fungal pathogens observed in the HIV-infected population who do not have access to HAART, and candidiasis is still a concern in Europe and in United States among patients with poor adherence to antiviral treatment or viro-immunological failure.

Primary prophylaxis. Mucosal infections are not targeted for primary prophylaxis, because of the effectiveness of curative antifungal therapy in that setting, the low mortality associated with mucosal candidiasis and potential for resistant *Candida* spp. to develop as well as of the possibility of drug interactions.

However, in the pre-HAART era, Powderly *et al.*[128] demonstrated in 1995, in a randomized multicentre unblinded trial, that oral fluconazole (200 mg/day), compared with clotrimazole troches, was associated with fewer episodes of oesophageal and oropharyngeal candidiasis.

Secondary prophylaxis. When recurrences are frequent or severe, long-term oral azole use may be considered to improve quality of life. Seven randomized placebo-controlled studies performed during the pre-HAART era have clearly demonstrated the efficacy of

fluconazole in that setting, with doses ranging from 50, 100 or 200 mg/day to 150 and 400 mg/week.[129–135] Three of them included more than 20 patients per arm[132,133,135] (see Table 10). Fluconazole decreased the rate of mucosal infections caused by *Candida* (vaginal, oropharyngeal and oesophageal). Daily regimens of fluconazole probably convey better protection against new superficial infection events. Indeed, Havlir *et al.*[134] observed significantly higher rates of thrush among weekly treated population than among daily treated (19.9% versus 12.3%), with shorter time to onset of the initial episode. The tolerance of fluconazole was good. Such long-term strategies raise the concern about emergence of fluconazole-resistant *C. albicans* and non-*albicans* strains.

Pagani *et al.*[135] identified *in vitro* fluconazole resistance in 12 patients within their cohort of 135 patients. Of them, eight were receiving the fluconazole regimen and four were placebo-treated and five presented with clinical failure at the endpoint of study (four receiving fluconazole and one placebo-treated). The incidence of resistant candidiasis was not found significantly different in these two small groups. However, microbiological resistance was significantly associated with the cumulative dose of fluconazole before entry in a multiple regression analysis, and patients with clinical failure had received larger cumulative doses of fluconazole before study entry (mean value 8.7 g versus 2.9 g). In a similar approach, Vazquez *et al.*[136] observed that 17% of the fluconazole-treated patients had fluconazole-resistant C*andida* sp. isolated in the mouth, versus only 8% in the placebo group. However this difference was not significant.

The best prophylaxis for mucosal candidiasis relies on HAART. For patients with immuno-virological failure, fluconazole appears to be an effective prophylactic drug. Noting the probable long-term emergence of resistant strains, its use should be limited to the setting of severe frequent recurrences, as suggested in the recently updated French guidelines for HIV care.[137]

Fluconazole in adult neutropenic patients with systemic candidiasis

Fluconazole is an alternative treatment to amphotericin B in neutropenic patients if the infecting strain is susceptible to it. This conclusion is based on three already dated main studies, of which only one was randomized and consisted of a small number of affected patients.[138–140] De Pauw *et al.*[138] showed that fluconazole at a dose of 400 mg/day cured six out of nine patients, namely four of the six patients with candidaemia, one of the two patients suffering from generalized candidiasis and the fourth patient suffering from *Candida*-induced meningitis. The other two studies showed that fluconazole at a dose of 400 mg/day (in adults) was just as effective and better tolerated than deoxycholate amphotericin at a dose of 0.6–0.7 mg/kg/day. Fluconazole in neutropenic patients is often used successfully at higher doses such as 800 mg/day (even 1200 mg/day), but this is not supported by published data. The combination of fluconazole (800 mg/day) and amphotericin B (0.7 mg/kg/day) has not been studied in neutropenic patients. The IDSA is cautious not to recommend the use of fluconazole as a first line treatment if the patient's condition is not stable and/or if the strain has not been identified.[57] In practice, this limits the indication of fluconazole as initial treatment. In theory at least, only patients colonized by a strain that is usually susceptible to fluconazole (*C. albicans*, *C. tropicalis*, *C. parapsilosis*) and who have not received azole prophylaxis can be treated by first line fluconazole.[141] As long as the yeast is identified as fluconazole susceptible and the patient is stable, fluconazole is indicated in neutropenic patients.

Chronic disseminated candidiasis is mostly observed in neutropenic patients with haematological malignancies. Its incidence ranges from 3 to 7% and is decreasing following the common practice of fluconazole as a prophylactic regimen in haematology patients.[26,142] The efficacy of fluconazole in that setting was evaluated only in observational or retrospective studies.[143,144] Anaissie *et al.*[143] reported an 88% rate of cure in a series of 20 patients either resistant or intolerant to amphotericin B after prescription of fluconazole (100–400 mg/day, median 30 weeks). Kauffman *et al.*[144] similarly reported 100% success in six patients resistant to amphotericin B (200–400 mg/day for 2–14 months). Several authors believe that the daily dosage should be raised to 600–800 mg/day.[145] In conclusion, fluconazole cannot be used as first line treatment in the setting of systemic candidiasis among neutropenic patients. It is recommended when switching initial amphotericin B therapy to oral maintenance regimen, if the patient was not previously on fluconazole prophylaxis and was not known to be colonized/infected with a less-susceptible or resistant strain. Treatment should be maintained for months, until disappearance of calcification of the lesions, especially if further antineoplastic drugs courses have to be administered.

Fluconazole in adult non-neutropenic patients with candidaemia

Fluconazole has often been used for treatment of fungal infections in non-neutropenic patients (see Table 11). Early trials using fluconazole looked at different doses. A paper from the early 1990s compared doses of 5 mg/kg versus 10 mg/kg to treat candidiasis in ICU patients. The clinical response rate was better in the 10 mg/kg group and deaths were reduced in this group (24% versus 3%) with fluconazole being well tolerated at both doses.[146] Six studies compared the efficacy of fluconazole and amphotericin B in non-neutropenic patients with invasive candidiasis.[139,140,147–150] Of them three were randomized, double-blind multicentre studies.[140,147,148] All confirmed the similar efficacy of both drugs with better tolerance of the fluconazole regimen. In 1994, Rex *et al.*[148] compared in a randomized prospective multicentre study fluconazole (400 mg/day) and amphotericin B (0.5–0.6 mg/kg/day) among 237 patients. Both displayed the same clinical and microbiological efficacy and the same mortality rate at 2 weeks. In 1996, Anaissie *et al.*[140] performed in the same year a prospective, randomized, multicentre study of 164 patients (including 104 non-neutropenic patients) with more consistency in the fluconazole and amphotericin B doses (fluconazole 400 mg/day, amphotericin B 25–50 mg/day). Although clinical response rates were similar, there was significantly less toxicity in the fluconazole group. Philips *et al.*[147] in 1997, in a prospective randomized study confirmed the pattern of efficacy (resolution of fungaemia and death at day 14) of fluconazole (400 mg/day) and amphotericin B (0.6 mg/kg/day). Other kinds of studies were also performed. Nguyen *et al.*[150] in 1995 failed to find any difference of mortality between the fluconazole-treated (100–800 mg/day) and amphotericin B-treated groups in an open, prospective multicentre trial. In 1996 Abele-Horn *et al.*[149] compared patients hospitalized in ICU treated either with fluconazole (400 mg/day on day 1 then 200 mg/day) or amphotericin B (1–1.5 mg/kg/day) plus flucytosine in a randomized prospective trial: no difference in clinical/microbiological

Table 10. Studies on secondary prophylactic fluconazole among HIV-infected patients

Reference	Study design	Regimen	Duration of treatment	Number of patients	Rate of infections
Leen *et al.*[129]	R, DB, SC	FLC po 150 mg week versus placebo	24 weeks	14	22%
					100%
Stevens *et al.*[130]	R, NB, SC	FLC po 200 mg/day versus placebo	12 weeks	12	0
				13	62%
Just-Nubling *et al.*[131]	R, NB, SC	FLC po 50 mg/day or 100 mg/day versus placebo	6 months	18	11%
				19	21%
				21	95%
Marriott *et al.*[132]	R, DB, PC, SC	FLC po 150 mg/week versus placebo	6 months	35	42%
				38	96%
Schuman *et al.*[133]	R, DB, PC, MC	FLC 200 mg/week versus placebo	29 months	162	44%
				161	58%
Havlir *et al.*[134]	R, DB, MC	FLC 400 mg/week versus 200 mg/day	528 days	318	20%
				318	12%
Pagani *et al.*[135]	R, DB, PC, SC	FLC po 150 mg/week versus placebo	37 months	67 71	**61%**
				71	**90% ($P < 0.0001$)**

R, randomized; DB, double blind; PC, placebo controlled; SC, single centre; MC, multicentre; FLC, fluconazole; po, oral; OPC, oropharyngeal candidiasis; OC, oesophageal candidiasis. Values given in boldface are statistically significant.

Table 11. Studies on fluconazole as curative treatment among non-neutropenic patients

Reference	Study design	Kind of infection	Regimen	Duration of treatment	Number of patients	Evaluation items	Efficacy
Phillips *et al.*[147]	R, MC, PC	candidaemia	FLC 400 mg/day iv versus AMB 0.6 mg/kg/day iv	4–8 weeks	50 53	clinical microbiological 6 months survival	FLC 57% AMB 62%
Anaissie *et al.*[140]	R, MC, PC	invasive candidiasis	FLC 400 mg/day iv versus AMB 25–50 mg/day iv	9 days	75 67	clinical microbiological EOT	FLC 66% AMB 64%
Anaissie *et al.*[139]	O, SC	candidaemia	FLC 200–600 mg/day versus AMB 0.3–1.2 mg/kg/day	13 days 10 days	45 45	clinical microbiological D0, D5, EOT	FLC 73% AMB 71%
Abele-Horn *et al.*[149]	R, SC	invasive candidiasis	FLC 200 mg/day iv versus AMB 1–1.5 mg/kg every other day + 5FC 3 × 2.5 g/day	14 days	36 36	clinical microbiological EOT	FLC 64% AMB + 5FC 63%
Nguyen *et al.*[150]	O, MC, PC	candidaemia	FLC 100–800 mg/day versus AMB	13 days	67 227	death/EOT	no difference in mortality at D+7,D+14, D+21
Rex *et al.*[148]	R, DB, MC	candidaemia	FLC 400 mg/day iv versus AMB 0.6 mg/kg/day iv	4–8 weeks	103 103	clinical microbiological W12	FLC 70% AMB 79%

R, randomized; DB, double blind; SB, single blind; PC, placebo controlled; SC, single centre; MC, multicentre; FLC, fluconazole; AMB, amphotericin B; 5FC, flucytosine; po, oral; D, day; W, week; EOT, end of treatment; iv, intravenous.

response or death could be found. In 1996 Anaissie *et al.*[139] compared the same drugs in cancer patients with candidiasis and enrolled 90 patients. Doses of both fluconazole and amphotericin were highly variable (fluconazole 200–600 mg/day, amphotericin B 0.3–1.2 mg/kg/day). The two cohorts were well matched and response rates at day 5 for each cohort were similar, overall response rates were slightly better for fluconazole and there were significantly fewer toxic effects in the fluconazole group.

A more recent comparison of fluconazole versus fluconazole plus amphotericin B in non-neutropenic subjects compared 800 mg/day of fluconazole versus the same dose plus 0.7 mg/kg/day of amphotericin B in a randomized blinded multicentre trial involving 219 patients.[151] Success rates were slightly higher and there was a faster clearance rate of candidaemia in the combination group compared with fluconazole alone. This suggests that the two drugs are not antagonistic and may perhaps act synergistically.

Although fluconazole may be the preferred agent in non-neutropenic patients because of its low toxicity, the recent introduction of caspofungin challenges this place, particularly as it has a broader spectrum of action. A randomized study comparing caspofungin versus amphotericin B for the treatment of candidaemia in both neutropenic and non-neutropenic patients has been completed, but there is no direct comparison with fluconazole.[152] Results of a prospective randomized controlled multicentre trial comparing anidulafungin, a new echinocandin, and fluconazole in patients with candidaemia should be available soon.

Fluconazole for the treatment of specific Candida organ infections

All randomized studies using fluconazole to date have been undertaken in oesophageal candidiasis or candidaemia, none in *Candida* organ infection, although some patients with invasive candidiasis have been included in the randomized studies. Therefore, the data presented here come from non-comparative open-label studies.

Osteoarticular infections due to Candida sp

Very few data are available on the efficacy of fluconazole as first line therapy in osteoarticular infections due to *Candida* sp. Some observations associated with spondylodiscitis have been published and have been summarized in Table 12.[153–162] Fluconazole (200–400 mg/day initially, >2 months) proved to be efficacious in three cases of knee infections due to *C. parapsilosis*.[163–165] A prosthetic joint infection and osteomyelitis of the knee due to *C. albicans* were cured with high doses of 800 mg/day of fluconazole for 2 months in combination with repeated surgical debridement, after a 10 day course of fluconazole 400 mg/day which seemed to be inefficient.[166] Fluconazole (400–800 mg/day for 6 months) was also effective for the treatment of *C. albicans* post-surgical mediastinitis in two cases.[167,168] Fluconazole (400 mg/day for 7 months) successfully treated an old patient with acute myeloid leukaemia who presented with *C. tropicalis* arthritis of the knee.[169] The latest IDSA guidelines recommend surgical debridement and initial course of amphotericin B for 2–3 weeks, followed by fluconazole for a total duration of 6–12 months.[57]

Endophthalmitis due to Candida sp.

A combination of partial or complete vitrectomy, intraocular amphotericin B and antifungal drugs is the usual therapeutic approach to *Candida* sp. eye infections. Several documented

Table 12. Reports of patients with spondylodiscitis due to *Candida* sp. and treated with fluconazole

Reference	Localization of infection	*Candida* species	Number of patients	Dose of fluconazole (mg/day)	Treatment duration	Associated treatments	Efficacy (follow-up duration)
Garbino *et al.*[162]	lumbar	*C. albicans*	1	400	3 months (relapse) then 6 months	–	recovery (16 months)
	lumbar	*C. tropicalis*	1	800		followed by itraconazole	recovery (4 months)
Seravalli *et al.*[161]	lumbar	*C. glabrata*	1	800	3 weeks	replaced by AMB (70 days) then lipid complex (56 days)	failure with fluconazole, then recovery (16 months)
El-Zaatari *et al.*[160]	dorsal	*C. albicans*	1	400	3 months	–	recovery (1 year)
Turner *et al.*[159]	dorso-lumbar	*C. albicans*	1	200 (1 month) then 100	12 months	after failure of AMB, liposomal AMB and 5FC (9 weeks)	recovery (3 years)
Rössel *et al.*[158]	dorsal	*C. albicans*	1	400 (14 days) then 200	7 months	after failure of AMB (21 days)	recovery (1 year)
Jonnalagadda *et al.*[157]	dorsal	*C. albicans*	1	200	6 months	AMB (3 g) + 5FC	recovery (8 months)
Hennequin *et al.*[156]	lumbar	*C. albicans*	1	400	6 months	–	recovery (47 months)
	lumbar	C. albicans	1	200	6 months	–	recovery (17 months)
Lafont *et al.*[155]	lumbar	*C. albicans*	1	400	4 weeks	–	recovery (18 months)
Tang *et al.*[154]	dorsal	*C. albicans*	1	200	1 year	–	recovery (16 months)
Sugar *et al.*[153]	dorsal and lumbar	*C. tropicalis*	1	100–150	1 year	AMB (380 mg)	recovery (26 months)

AMB, amphotericin B; 5FC, flucytosine.

clinical cases reported the efficacy of fluconazole, alone or in combination with other treatments, in cases of endophthalmitis due to *Candida* spp.[16,170–173] Finally, several recent series confirmed fluconazole efficacy in cases of severe ocular infections due to susceptible *Candida* sp. in non-neutropenic patients.[174–180] Their results are summarized in Table 13. Most cases are due to *C. albicans*, and fluconazole-resistant species causing endophthalmitis is extremely rare. On the basis of these data, the IDSA recommends the use of fluconazole in this indication, particularly as follow-up therapy.[58]

Meningitis due to Candida sp

Very few data exist on fluconazole's efficacy for the initial treatment of *Candida* sp. meningitis in adults, although this drug has a very good CSF penetration. Oral fluconazole (800 mg/day for 3 months then 200 mg/day) was successful for the treatment of a *C. albicans* meningitis in an HIV-infected patient with a CD4 cell count of 35 cells/mm^3 who refused intravenous therapy.[181]

Endocarditis due to Candida sp

No series has documented the efficacy of fluconazole in endocarditis due to *Candida* sp. Only a few clinical cases have been published and most of these are summarized in Table 14.[182–198] These cases illustrate the efficacy of fluconazole (sometimes with no surgical treatment) in endocarditis due to *C. albicans* and also in endocarditis related to some non-*albicans Candida* spp., especially *C. parapsilosis*. However, no study has demonstrated the superiority of fluconazole over amphotericin B in this indication, and there are insufficient data to recommend fluconazole as the first line treatment for endocarditis due to *Candida* spp.[58,199] The echinocandins might have a place as primary therapy in these cases. Fluconazole (200–400 mg/day) is often employed as part of a long-term suppressive regimen, especially if valve replacement is not possible because of the high propensity for delayed relapse of candidal endocarditis.[200,201]

Peritonitis due to Candida sp.

Peritonitis due to *Candida* sp. may develop in patients with peritoneal dialysis catheters, or in those with surgical or traumatic injury to the gut wall. In this latter situation, *Candida* spp. are usually part of a polymicrobial infection. Isolation of *Candida* by direct examination of peritoneal fluid is an independent factor for a severe outcome,[202] and recent small studies suggest that prompt, effective, adequate and safe antifungal therapy should be given in all cases of *Candida* sp. peritonitis in order to lower the mortality rate and shorten the hospital stay.[113,116] In a recent study of 23 cases secondary to peptic ulcer perforation, the mortality rate in patients receiving fluconazole (200 mg intravenously, twice daily for 2–4 weeks) was high (five of eight cases), probably related to inadequate or too late initiation of antifungal therapy.[203] Some cases showing fluconazole efficacy have been reported in patients with continuous ambulatory peritoneal dialysis, either alone or in combination with flucytosine.[204–207] Catheter removal is crucial in these cases.

Urinary infections due to Candida spp.

Candida is by far the most frequent agent of urinary fungal infections. The line between colonization and real infection is generally blurred. Candiduria usually present as nosocomial infections,

Table 13. Reports of patients with endophthalmitis due to *Candida* sp. and treated with fluconazole

Reference	Methodology of study	*Candida* species	Number of patients	Dose of fluconazole (mg/day)	Treatment duration	Associated treatments	Efficacy (follow-up duration)
Martinez-Vazquez *et al.*[180]	prospective	*C. albicans*	11	400	2–8 weeks	AMB iv (n = 9) or no treatment (n = 1) until vitrectomy (n = 10, 2–180 days after diagnosis)	9/11 (6 months)
Essman *et al.*[179]	retrospective	*C. albicans, C. tropicalis*	5	unspecified	unspecified	vitrectomy ± local AMB	5/5 (2.5–11.5 months)
Christmas *et al.*[178]	prospective	*C. albicans, C. tropicalis*	5	100–200	3–6 weeks	vitrectomy	5/5 (4–11 months)
Akler *et al.*[177]	retrospective	unspecified	6	total median dose = 9975 mg	median = 52 days	AMB iv <500 mg + vitrectomy: 1	5/6, relapse: 1 (≤6 weeks)
Luttrull *et al.*[176]	retrospective	*C. albicans* (n = 2) unspecified (n = 2)	4	200–400	4 weeks (n = 3)	vitrectomy: 1	4/4 (3–25 months, n = 3)
del Palacio *et al.*[175]	retrospective	*C. albicans*	7	400 (1 day) then 200	3 weeks	–	6/7 (vitrectomy refusal in 1 patient) (≥6 months)
Kauffman *et al.*[174]	retrospective, lens implants	*C. parapsilosis*	4	400 (200 in patients with renal failure)	1 year	failure of local AMB	relapse if no lens ablation (2 years after stopping)

AMB, amphotericin B; iv, intravenous.

Table 14. Reports of patients with endocarditis due to *Candida* sp. and treated with fluconazole

Reference	Valvular involvement	*Candida* species	Number of patients	Dose of fluconazole (mg/day)	Treatment duration	Associated treatments	Efficacy (follow-up duration)
Inoue *et al.*[182]	aortic valve	*C. parapsilosis*	1	600 then 400	18 months	surgery	recovery (18 months)
Lejko-Zupanc *et al.*[197]	mitral prosthesis	*C. parapsilosis*	1	400 (14 days) then 100	8 months	AMB (3.9 g) ABCD (1.5 g) no replacement	recovery (>3 years)
Joly *et al.*[198]	pacemaker	*C. albicans*	1	400 (6 days) then 200	7 months	surgery	recovery (18 months)
Nguyen *et al.*[196]	aortic prosthesis	*C. albicans*	1	400 then 200	4.5 years	AMB + 5FC, 12 weeks no replacement	recovery (5.5 years)
Gilbert *et al.*[195]	aortic prosthesis	*C. albicans*	1	200	8 months	surgery AMB (2 g) + 5FC, 40 days	recovery (9 months)
Wells *et al.*[194]	mitral and tricuspid valves	*C. albicans*	1	200–400 (14 days) then 400 then 50	6.5 months (400 mg) and 10 months (50 mg)	no replacement	recovery (4.5 years)
Zahid *et al.*[193]	mitral valve (probable)	*C. parapsilosis*	1	400	18 months	AMB (5 g) + 5FC ketoconazole (800 mg/day, 4 months) no replacement	recovery (5 years)
Cancelas *et al.*[192]	mitral valve	*C. parapsilosis*	1	200	4 months	surgery, AMB (2 g)	recovery (4 months)
Thakur *et al.*[191]	aortic prosthesis	*C. albicans*	1	200	6 weeks	AMB (30 mg/day), 6 weeks no replacement	recovery (26 months)
Czwerwiec *et al.*[190]	aortic prosthesis	*C. parapsilosis*	1	400	26 months	AMB (725 mg) no replacement	recovery (26 months)
Otaki *et al.*[189]	mitral prosthesis	*C. parapsilosis*	1	unspecified	68 days	no replacement	failure (death due to cerebral haemorrhage and fever)
Wallbridge *et al.*[188]	mitral prosthesis	*C. parapsilosis*	1	200-400	>7 weeks	AMB (300 mg) no replacement	recovery (6 months)
Venditti *et al.*[187]	interatrial septum	*C. albicans*	1	200 (28 days) then 600 (11 days) then 400	6 months	no replacement	recovery (14 months)
Hernandez *et al.*[186]	mitral valve	*C. albicans*	1	200	3 months	AMB failure no replacement	improvement (3 months)
Roupie *et al.*[185]	aortic valve	*C. tropicalis*	1	400	50 days	no replacement	recovery (11 months)
Martino *et al.*[184]	interatrial septum	*C. parapsilosis*	1	3 mg/kg (7 days) then 6 mg/kg	>3 months	GM-CSF (>6 weeks) no replacement	recovery (5 months)
Isalska *et al.*[183]	mitral prosthesis	*C. parapsilosis*	1	100–200	11 months	no replacement	recovery (1 year)

AMB, amphotericin B; 5FC, flucytosine; ABCD, amphotericin B colloidal dispersion; GM-CSF, granulocyte–monocyte colony-stimulating factor.

favoured by indwelling urinary catheters, immunosuppressive drugs or antibiotic prescriptions, diabetes mellitus and extreme ages. *C. albicans* is involved in half of the cases, followed by *C. glabrata* in 15% of the cases. In 10% of cases, infection involves more than one species.[208] Fluconazole achieves a 10 times higher concentration in urine than in blood with powerful effect even on *C. glabrata* infections. Therefore, it represents a first line treatment of any *Candida* urinary tract infection.

In a randomized placebo-controlled multicentre study among patients with asymptomatic candiduria, Sobel *et al.*[209] found that fluconazole (200 mg/day) hastened the time to negative results of urine cultures. However, the rate of negative urine cultures 2 weeks after the end of therapy was similar in the fluconazole- and placebo-treated groups, showing the minimal utility of treatment in that setting. Indeed, asymptomatic candiduria should be treated only in high-risk situations, namely patients with neutropenia, infants with low birth weight, patients with renal allografts, and patients who will undergo urologic manipulations (recommendation of grade B-III from the IDSA). The optimal regimen in that setting is not known. Short courses regimen are not recommended and therapy for 1–2 weeks should be efficient.

Ascending pyelonephritis treatment should also include adequate urinary drainage and removal of obstructive fungus balls.[210] Urinary tract devices should be optimally removed or at least replaced.

Haematogenous renal involvement should be treated with high-dose parenteral fluconazole (6 mg/kg/day) in accordance with the recently published IDSA guidelines.[57]

Fluconazole in children/infants

No specific approval of fluconazole has been obtained in young children before the age of 6 months, but a few studies have evaluated its use in several settings.

Prophylaxis of systemic candidiasis in neonates

Few studies have focused on the use of fluconazole as a prophylactic agent against invasive candidiasis in neonates. Kaufman *et al.*[211] demonstrated in 2001 the efficacy and safety of fluconazole (3 mg/kg every 3 days during the first 2 weeks, then every 2 days during the following 2 weeks and then every day until the sixth week of life) in extremely low birth weight and high-risk infants (<1000 g) in preventing both colonization and invasive fungal infection. High risk was defined as the presence of a central vascular catheter or endotracheal tube. Indeed, among the 50 infants randomly assigned to fluconazole, the rate of colonization (22%) was significantly lower than in the 50 placebo-treated ones (60%); no invasive fungal infection developed in the fluconazole group compared with a 20% rate of infection in the placebo group. No adverse effect of fluconazole was documented.

Kicklighter *et al.*[212] similarly observed the safety of fluconazole at 6 mg/kg (for 6 weeks) and its efficacy among neonates with low birth weight (<1500 g) in the prevention of rectal colonization (however, occurrence of invasive candidiasis was similar in both groups). A Cochrane review of fluconazole prophylaxis in preterm infants demonstrated a reduced risk of invasive infection (related risk 0.20) and mortality (related risk 0.44) in fluconazole-treated patients compared with placebo-treated patients.[213] Although concerns about resistance to azoles have been raised, the vast majority of *Candida* spp. strains have remained susceptible to fluconazole over the past decade in this population.[40]

Fluconazole in systemic candidiasis in children/infants

Neonatal candidaemia. Candidaemia is a major cause of sepsis in neonatal ICU, representing up to 16% of all sepsis cases. The related mortality rate is high, often nearly 50%.[214] Most cases are related to *C. albicans* and *C. parapsilosis*, with a recent rise in cases related to *C. tropicalis*. The main risk factors for invasive candidiasis among neonates are low birth weight, intravascular catheters, intratracheal intubation, total parenteral nutrition and administration of intralipid solution and recent administration of broad-spectrum antibiotics and corticosteroids.[10]

Treatment with amphotericin B and 5-flucytosine has been the gold standard for years. However amphotericin B has some serious side effects, which makes it mandatory to consider its use in that setting. With good profile of tolerance, good diffusion in all tissues and body fluids, and reliable oral absorption, fluconazole has been studied as an alternative (see Table 15). In 1994, Fasano *et al.*[215] reported the compassionate use of fluconazole among 40 newborns, including 11 who presented with *Candida* sp. meningitis. They were treated with a mean daily dosage of 5 mg/kg/day for a mean duration of 26 days. Of the 32 patients with evaluable outcome, 31 experienced clearance of infection. Other studies have confirmed these results in the recent years.[11,216–220] In a multicentre prospective randomized study, Driessen *et al.*[220] compared the efficacy and safety of either amphotericin B ± 5-flucytosine or fluconazole (oral or intravenous dose of 10 mg/kg as initial dose, and then 5 mg/kg/day) in neonates with candidaemia. In the fluconazole group 8/12 (67%) survived versus 6/11 (55%) in the other group.[220] Among the four patients who died in the fluconazole group, two had treatment failure versus one in the amphotericin B group. Cytolytic hepatitis was less frequent in the fluconazole-treated group. Two isolated case reports also suggest that the association of fluconazole and flucytosine might be synergistic in the treatment of neonatal candidaemia.[222,223]

Very recently, Mondal *et al.*[229] compared the efficacy and safety of oral itraconazole versus oral fluconazole (both doses of 10 mg/kg/day) in newborns and paediatric patients with candidaemia. Similar cure rate (81 and 82%), mortality rate (9.5 and 13.5%) and number of side effects were observed.[224] Fluconazole thus appears as a safe and effective systemic antifungal agent in the setting of neonatal candidiasis.

Children with systemic candidiasis. Excluding the setting of neonatal candidiasis, very few studies have however focused on the paediatric population when studying the efficiency of fluconazole for the treatment of invasive candidiasis.

In 1991 Viscoli *et al.* reported the outcome of 24 immunocompromised children treated with fluconazole (6 mg/kg/day) for 34 episodes of proven invasive candidiasis. A total of 30/34 clinical and microbiological cures were achieved. Two patients with fungaemia due to *C. parapsilosis* required an increase in dosage of up to 12 mg/kg. Transient drug-related increases of liver transaminases occurred in two cases (6%).[225] In 1994 Fasano *et al.* reported the outcome of 63 children with AIDS, cancer or transplantation prospectively receiving fluconazole as compassionate treatment (dose regimen ranging from 0.16 to 11 mg/kg/day, mean 3.4 mg/kg/day).[215] Half of them had fungaemia, while the others had respiratory, urinary tract or superficial oropharyngeal infections.

Table 15. Non-comparative studies on fluconazole as curative treatment of neonatal candidaemia

Reference	Number of patients	Regimen	Microbiological cure	Side effects
Driessen *et al.*[220]	21 very low birthweight	5 mg/kg for 1–42 days mean 16	90%	30% cytolytic hepatitis
Fasano *et al.*[215]	40	5 mg/kg for 2–80 days mean 26	97%	5% cytolytic hepatitis
Wainer *et al.*[216]	19	10 mg/kg on day 1 then 5 mg/kg	63% surviving 32% fungal free deaths	NS
Huang *et al.*[217]	18 very low birthweight	3–10 mg/kg for 15–173 days mean 34	6 first line treatment: 83% 13 after AMB failure: 62%	29% cytolytic hepatitis
Huttova *et al.*[218]	40 very low birthweight	6 mg/kg for 6–48 days	65% cure without relapse	5% cytolytic hepatitis 5%-elevated serum creatinine
Gurpinar *et al.*[219]	24	2–16 mg/kg for 5–72 days mean 25	96%	8% anaemia or cytolytic hepatitis
Schwarze *et al.*[11]	53	5–6 mg/kg for 3 weeks mean 21	78%	4% cytolytic hepatitis

AMB, amphotericin B; very low birthweight <1500 g; NS, statistically not significant.

Clinical cure or improvement was achieved in 52/63 (83%) and pathogen eradication was achieved in 43/59 (73%).[17] Huttova *et al.*[218] reported in 1998 the outcome of 10 children with nosocomial fungal meningitis, including 8 cases of candidal meningitis treated using fluconazole. Five of them survived with clinical and microbiological cure.

Conclusions

Almost 15 years after its launch, fluconazole remains a cornerstone of antifungal prophylaxis and therapy of invasive candidiasis. It has an excellent pharmacokinetic and safety profile even in debilitated patients, with good tissue penetration and a lack of major drug interactions particularly with immunosuppressive agents. It can be prescribed in patients with renal failure if daily dosages are adapted to the creatinine serum level. Its spectrum of antimicrobial efficacy is reasonable and it remains active against most intrinsically susceptible *Candida* spp. encountered in systemic disease, with <5% of *C. albicans* resistant to fluconazole in that setting. Although *C. krusei* is intrinsically resistant to fluconazole, it is rarely reported as a cause of systemic infection outside neutropenic patients. Thus *C. glabrata* is the only species which might now limit the use of fluconazole for the first line therapy of yeast fungaemia when the species is not identified. Similarly, patients who recently received fluconazole as antifungal prophylaxis should not be treated with fluconazole for the curative treatment of a presumed or proven episode of systemic candidiasis. The fungistatic effect of fluconazole against *Candida* spp. does not appear to influence the outcome of candidaemic episodes at least in comparison with amphotericin B, which is apparently fungicidal against *Candida* spp. Finally, when summarizing its valuable properties, the strong demonstration of its efficacy in large randomized controlled trials and selected clinical series, its availability in various commercial presentations and its current low cost, fluconazole still remains a leading antifungal drug against susceptible *Candida* species.

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