Working Party Report

Chemoprophylaxis for candidosis and aspergillosis in neutropenia and transplantation: a review and recommendations

Working Party of the British Society for Antimicrobial Chemotherapy

Introduction
Antifungal drugs are used in immunosuppressed patients in several ways other than for the treatment of defined episodes of fungal infection. Chemoprophylaxis may be initiated as soon as a risk factor, such as profound neutropenia, becomes evident—primary chemoprophylaxis; antifungal drugs may be continued (possibly in a reduced dosage or with an alternative drug) after an episode of proven mycosis has been treated—suppressive therapy of relapse or reinfection. Also antifungal drugs may be started some time after the risk period begins, often when fever occurs and particularly after it has failed to respond to antibiotics, and sometimes without subsequent definitive proof of fungal infection—delayed antifungal use. The results of studies of all these various approaches are relevant to the consideration of drug choice in antifungal prophylaxis against invasive aspergillosis or candidosis in the prolonged immunosuppression associated with HIV infection, transplantation or neutropenia. This article confines its attention to non-AIDS related immunosuppression, and to aspergillosis and candidosis although infections with other fungi are increasingly described in the immunosuppressed. Almost all the studies have been carried out in patients with haemic malignancy and the dearth of studies in solid organ transplantation is striking. Nevertheless, we consider that recommendations for solid-organ transplant recipients are important and have included some recommendations until substantive studies are reported.

Risk factors
Invasive candidosis and aspergillosis may occur in the patient whose immune system is not grossly compromised. For example, disseminated infections and fungaemia with Candida parapsilosis and Candida albicans are well described in infection related to intravascular cannulae and prosthetic replacement surgery in non-neutropenic patients.
However, invasive candidosis and invasive aspergillosis are much more common in patients with compromised immune systems.

Risk factors for all invasive fungal infection include in leukaemia and lymphoma the nature of the primary malignant disease and its associated chemotherapy. Duration of neutropenia, particularly after first fever is an important determining factor (Wiley et al., 1990). In invasive aspergillosis, the major risk factors are occupation of rooms not supplied with HEPA-filtered air (Sherertz et al., 1987), and building work in the vicinity (Weber et al., 1990). Historical controls are therefore inadequate for studies of antifungal chemoprophylaxis for invasive aspergillosis since exposure may vary with changes in these important environmental factors. Additional less important factors include graft-versus-host disease and graft rejection requiring treatment, and perhaps the total dosage of steroids prescribed.

Candidosis arises usually from an endogenous source. Colonization of the mouth or gut with Candida tropicalis in neutropenic patients has been associated with a very high incidence of disseminated candidosis (Sandford et al., 1980; Wingard et al., 1980; Pfaller et al., 1987) but there is no information on this after solid organ transplantation. The presence of C. albicans in surveillance cultures in neutropenic patients is said not to be predictive of invasive candidosis, reflecting the low incidence of disseminated candidosis in those colonized (Wingard et al., 1980; Fainstein et al., 1981a; Kostiala et al., 1982; Pfaller et al., 1987). Nevertheless, recovery of candida from the mouth certainly predicts the subsequent development of oropharyngeal candidosis (Yeo et al., 1985; Bodey, Samonis & Rolston, 1990). In patients receiving placebo in comparative studies, 30–50% of those with positive cultures for candida at the onset of the trial, but no features of clinical candidosis, developed clinically overt mucosal candidosis (Yeo et al., 1985; Bodey et al., 1990; Samonis et al., 1990). In some short-term studies disseminated candidosis was confined to those from whom earlier cultures from mucosal sites were positive (Buchanan et al., 1985). Opinions differ as to whether the presence of the organisms in more than one non-contiguous surveillance site increases the predictive value for disseminated candidosis (Sandford et al., 1980; Martino et al., 1989a,b). Absence of C. albicans in surveillance site cultures has a high predictive value for the absence of disseminated candidosis in patients with lymphoma, leukaemia, or marrow transplantation (Sandford et al., 1980; Pfaller et al., 1987).

Candida overgrowth (or indeed presence and persistence) may be more likely with particular antibacterial regimens in cancer patients but this has not been systematically and prospectively investigated. A retrospective study in acute lymphocytic leukaemia suggested that administration of vancomycin (route unspecified) in the absence of antifungal prophylaxis was a major risk factor for disseminated candidosis and was associated with increased colony counts of candida in the gastrointestinal tract (Richet et al., 1991). In another study the addition of oral vancomycin to oral nystatin and gentamicin prophylaxis was also associated with new persistent oral colonization with yeasts (Bender et al., 1979). Oral vancomycin suppresses oral Gram-positive bacteria (Borthen-Svinhufvud, Heimdal & Nord, 1988) and this may have relevance to the development of candidosis. Yeast colonization has not been studied prospectively with parenteral vancomycin or related antibiotics, such as teicoplanin.

There is no convincing evidence that increased counts of candida in the faeces is predictive for those who will develop candidaemia (Karabinis et al., 1988), despite experimental evidence that large inocula of candida given by mouth are associated with persorption (translocation) across the gastrointestinal mucosa (Seelig 1966; Krause,
Matheis & Wulf, 1969). Other factors may be important in persorption, as in animal studies, persorption is reduced if animals are fed by mouth on a single occasion, rather than being starved (Inoue et al., 1989).

We consider that, in view of the evidence that previous fungal colonization determines the chances of subsequent invasion and the lack of data on factors controlling this, trials of prophylaxis against candida should contain groups of patients with a similar prevalence of initial candida colonization and subsequent exposure to antibacterial chemotherapy. In the case of invasive aspergillosis, there is some evidence that episodes of fungal pneumonia, even if not proven to be caused by aspergillus spp., predispose to recurrence in subsequent episodes of neutropenia (Robertson & Larson, 1988). There is also some retrospective evidence that prior nasal colonization with Aspergillus spp. predisposes to fungal pneumonia (Aisner et al., 1979; Martino et al., 1989). Hence these factors also need to be controlled in the design of any trial.

Not all patient groups have been fully assessed as having a risk of invasive mycosis that can be prevented by chemoprophylaxis. Primary antifungal chemoprophylaxis has been judged to be beneficial in preventing disseminated candidosis in concurrent placebo controlled trials in bone-marrow transplant recipients, neutropenic leukaemic patients (Williams et al., 1977; Hughes et al., 1983; Estey et al., 1984; Buchanan et al., 1985; Hansen et al., 1987; Goodman et al., 1992), patients with solid tumours and lymphoma undergoing remission induction chemotherapy (Yeo et al., 1985), renal transplant recipients (Owens et al., 1984), patients in surgical intensive care units (Slotman & Burchard, 1987), and pre-term neonates weighing < 1250 g (Sims et al., 1988). Its use in hepatic transplant recipients, including those in acute hepatic failure, and in burn patients (Desai & Herndon, 1988), has only been examined against historical controls, and, in the former, in combination with antibacterial drugs, as part of selective gut decontamination (Wiesner, 1990).

We regard the use of prophylaxis as established only in solid tumour, lymphoma and leukaemia remission induction therapy, and this is largely on the basis of efficacy against oral candidosis. Independent confirmation of the efficacy of prophylaxis is required for other indications although the high incidence of invasive candidosis in some of these groups, such as liver transplant recipients, is accepted. All studies involving prophylaxis against disseminated mycoses proven by culture or histology have been individually small and the assessment of prophylactic efficacy against culture-proven systemic mycosis is impaired by the likelihood of a statistical Type II error. Future studies of chemoprophylaxis should be considered as being intended either for oral or for both oral and disseminated mycosis and both study types must be adequately assessed statistically for sample population size.

**Resistant strains and timing of prophylaxis**

A potential disadvantage of a chemoprophylactic programme is selection for antimicrobial-resistant species. Ketoconazole may select for *Candida (Torulopsis) glabrata* (Acuna, Winston, & Young, 1981; De Jongh et al., 1982; Shepp et al., 1985) although this does not always occur (Kauffman et al., 1984). Clotrimazole resistance emerging in this species on serial in-vitro passage is also well recorded (Plempel et al., 1974). Fluconazole does not eliminate the rarer *Candida krusei* which usually becomes the predominant cause of disseminated yeast infection (Brammer 1991; Winston 1991; Goodman et al., 1992). There are no data on the role of *C. krusei* in local mucosal
infection. In one prospective study there was no significant increase in colonization with \textit{C. krusei} or \textit{C. glabrata} in patients receiving fluconazole when compared with those receiving placebo (Goodman \textit{et al.}, 1992). \textit{C. krusei} colonization and fungaemia occurred before fluconazole was introduced and an association of fungaemia with severe gastrointestinal cytotoxic damage was suggested (Merz \textit{et al.}, 1986). Some of the patients had been receiving miconazole. Recent retrospective reports suggest that disseminated candidosis caused by \textit{C. krusei} increases in incidence substantially with fluconazole use. One reports an incidence of 8.3\% of patients on fluconazole developing \textit{C. krusei} sepsis compared with 1.2\% in those not receiving the drug. This compares with an incidence of 3\% of patients receiving no fluconazole who developed \textit{C. albicans} fungaemia and 3\% \textit{C. tropicalis} fungaemia and the absence of these fungaemias in those receiving fluconazole (Wingard \textit{et al.}, 1991). There is, as yet, little information on selection of fluconazole- or itraconazole-resistant strains of \textit{C. albicans} other than in AIDS patients. There is no evidence that ketoconazole selects for the more pathogenic species, \textit{C. tropicalis}, but in one trial it was notably ineffective against fungaemia due to this species (Fainstein \textit{et al.}, 1987). Parenteral polyene antifungal agents apparently do not select for amphotericin B resistance but such resistant invasive strains do occur in patient populations in which topically applied polyenes are used (Powderly \textit{et al.}, 1988). There is some experimental evidence \textit{in vitro} and in animals that the use of clotrimazole, ketoconazole, or miconazole prophylaxis may lead to resistance to amphotericin B in aspergillus (Schaffner & Frick, 1985) and yeasts (Beggs, Sarosi & Steele 1976; Sud & Feingold 1983). Prophylaxis with the newer triazole antifungal drugs, fluconazole and itraconazole, has not been reported to select for amphotericin B resistant strains and there is no information on apparent antagonism in clinical use. Trials to assess whether combinations of oral polyenes with triazoles or imidazoles would prevent or promote appearance of resistant species or strains are needed and are particularly important in the light of fluconazole selection for \textit{C. krusei} which remains amphotericin B susceptible (Wingard \textit{et al.}, 1991). Examination of the data from a small study in patients with leukaemia and positive oral yeast cultures before chemoprophylaxis started suggested that addition of oral amphotericin to ketoconazole reduced the amount of 'yeast overgrowth' but did not affect the need for empirical parenteral amphotericin B (Donnelly \textit{et al.}, 1984). We recommend that yeast speciation and susceptibility testing in a reference centre should be undertaken when invasive infections arising from failures of chemoprophylaxis or chemotherapy are assessed.

Studies in experimental animals suggest that chemoprophylaxis for yeasts may fail if completing bacteria have previously been eliminated. We therefore recommend that antifungal chemoprophylaxis should begin in time to be effective locally before bacterial elimination takes place. If oral antibacterial decontamination is used in neutropenic patients, we believe that antifungal prophylaxis should always be used and started with (or before) antibacterial agents, some 3 to 4 days (or 5–6 days in the case of itraconazole) before anticipated neutropenia. If oral digestive tract decontamination is not used but broad-spectrum antibacterial drugs are needed it is not clear when prophylaxis against candida should be started. The integration of immediate use of antifungal drugs with empirical antibacterial chemotherapy has not been compared with delayed use of antifungal drugs started after failure of the antibacterial regimen. Immediate use may affect evaluation of the initial empirical antibacterial regimen for fever, however candidosis is common with prolonged use of broad spectrum antibiotics. Between courses of cytotoxic drugs in neutropenic patients when neutrophil
counts recover, antifungal prophylaxis against yeasts is not required and preferably should be stopped to reduce the risk of selection of resistance. In allogeneic bone marrow and solid-organ transplantation, the risk of invasive aspergillosis extends beyond the period of neutropenia (if any). In centres where filamentous fungal infections are common, extended prophylaxis based on whether high steroid doses are given, or active graft versus host disease or CMV infection occur is probably required. The optimal duration and precise criteria for prophylaxis are unknown. In the absence of clear data, we believe that a 3-month period of prophylaxis after grafting is reasonable, although potentiation of cyclosporin nephrotoxicity would also be an important factor for consideration.

Prophylaxis against candidosis

Antiseptics

Topical chlorhexidine mouth rinse may reduce oropharyngeal candidosis and candidaemia in bone marrow transplant recipients (Ferretti et al., 1988; Weisdorf et al., 1989) but does not affect the incidence of mucositis or oral ulceration (Ferretti et al., 1988; Raether et al., 1989). Chlorhexidine dental gels have not been adequately assessed.

Non-absorbed polyene suspensions and tablets and clotrimazole

Candidaemia may occur from persorption across the gastrointestinal mucosa. Invasion across the oropharyngeal mucosa and spread from localized infection also occurs and non-absorbed oral drugs were used initially in prophylaxis against candidaemia. It is thought that antifungal prophylaxis may be more necessary when combined with antibacterial prophylaxis but this has not been examined in controlled studies comparing polyene antifungal drugs with placebo, although it has for ketoconazole. Topical nystatin suspension was not a very effective prophylactic agent against either oropharyngeal candidosis (Bodey & Rosenbaum, 1974) or disseminated candidosis in leukaemic patients (Dekker et al., 1981; DeGregorio, Lee, & Ries 1982; Barrett 1984; Buchanan et al., 1985). Poor efficacy seems to be dose-independent in the case of disseminated candidosis, even 26 megaunits/day (Wade et al., 1981) (combined with oral gentamicin) being ineffective in prophylaxis against disseminated candidosis. Nystatin is almost insoluble and amphotericin B is inactivated in faeces so that high oral doses of either are needed to produce detectable antifungal activity in those sites (Hofstra et al., 1979; Hofstra, de Vries-Hospers & van der Waaij 1982; van Saene et al., 1985).

There is little evidence that oral amphotericin B suspension or 10 mg lozenges are substantially better as prophylaxis against disseminated candidosis, although the findings at autopsy in one otherwise unreported and consequently poorly-defined, placebo-controlled study did suggest that the large dose of 200 mg/day, as tablets, was effective (Ezdinli et al., 1979). Little data are provided in this and other studies on compliance with alternative regimens and poor compliance is likely to have a major impact on outcome. Better efficacy in prophylaxis and treatment of oropharyngeal candidosis may be achieved with sucked pastilles, tablets and troches but comparative formulation data are scanty (de Vries-Hospers et al., 1982) and the patient with severe cytotoxic-induced mucositis may not be able to suck or swallow tablets. The value of
both nystatin and amphotericin B suspensions and swallowed tablets in prophylaxis is, at best, unimpressive and the Working Party do not recommend their use alone.

Clotrimazole troches (available in the USA) prevented oropharyngeal candidosis in the short-term in leukaemic patients undergoing remission induction, but were not particularly effective in eliminating culture-proven candida colonization present at the outset (Yeo et al., 1985; Cuttner et al., 1986). A similar observation was made with topical miconazole (Brincker 1978). Another study reports that the overall impact of extended use of clotrimazole troches was unimpressive in leukaemic patients (Owens et al., 1984), perhaps because the drug induces enzymes responsible for its own destruction. In patients with solid tumours assessed over short periods, clotrimazole seemed more effective in preventing symptoms (Yeo et al., 1985). In a dosing study, nystatin pastilles (containing 400,000 units) were more effective at clearance of candida after therapy for candida stomatitis than clotrimazole troches applied equally frequently, but the difference was small (Conrad, Lentnek, & Bendush 1988). Polyene and clotrimazole tablets, troches, and pastilles have not been compared with triazole antifungal drugs in prophylactic regimens.

Ketoconazole

Systemically absorbed drugs that maintain adequate serum levels may be more effective in chemoprophylaxis. Antifungal chemoprophylaxis with ketoconazole has been studied with and without concurrent co-trimoxazole. A small, four-armed, double-placebo controlled, comparative study showed that the use of co-trimoxazole to prevent bacterial infection was associated with an increased incidence of invasive fungal infection but this was prevented by addition of 200 mg ketoconazole once daily to the regimen. Ketoconazole in the absence of co-trimoxazole also prevented major fungal infection (Estey et al., 1984). Similar studies of prophylaxis should be undertaken using more recently introduced antifungal agents given concomitantly with fluoroquinolone prophylaxis. In a number of small placebo-controlled trials ketoconazole (400 mg/day) prevented oral and usually oesophageal, but not necessarily disseminated, candidosis (Brincker 1983; Donnelly et al., 1984; Hansen et al., 1987). A dosing study suggested that 400 mg od ketoconazole was more effective than 200 mg od in preventing colonization, but not infection (Scrimgeour & Anderson, 1985). This result does not justify the use of the higher dose in chemoprophylaxis. Little difference in efficacy was seen when ketoconazole (200 mg/day) and oral miconazole (250 mg qds) were compared in neutropenic patients (Meunier-Carpentier, Cruciani & Klastersky, 1983). Ketoconazole (200-mg/day) was no more effective than 0·5 megaunits 6-hourly of nystatin suspension in preventing oropharyngeal candidosis but did protect better against oesophagitis and vaginitis, as might be expected (Jones et al., 1984).

Ketoconazole (400 mg/day) when compared with nystatin in patients receiving vancomycin, gentamicin and colistin antibacterial chemoprophylaxis reduced the incidence of oral mucositis and the isolation of \textit{C. albicans} from the mouth, genital tract and rectum but increased significantly isolation of \textit{C. glabrata} from the rectum and to some extent from the vagina (Shepp et al., 1985). Compliance was better with ketoconazole than nystatin. In patients receiving neomycin, colistin, and co-trimoxazole, ketoconazole was compared with a combination of amphotericin B and nystatin tablets and nystatin suspension. Although yeasts persisted in the faeces in more patients on polyenes, the incidence of culture-proven invasive mycosis was equally low in both groups. Gas liquid chromatographic detection of presumed fungal products in serum is
of uncertain significance but positive results were rarer in the ketoconazole group. The clear effect demonstrated was reduction in oropharyngeal candidosis and genital candidosis in the ketoconazole treated group in those who were neutropenic and had not received an allogenic transplant (Hann et al., 1982). Allogenic marrow transplantation was associated with low serum levels of ketoconazole and no better effect than was achieved with the oral polyenes (Hann et al., 1982). Ketoconazole is also poorly absorbed in those taking antacids and \( H_2 \) histamine antagonists but there are no data with cytoprotectives such as sucralfate. Drug absorption has not been assessed in recipients of bone-marrow autografts or with differing cytotoxic regimens. As well as causing rare hepatic adverse drug reactions, ketoconazole interacts with mammalian \( P_450 \) cytochrome oxidase enzymes increasing cyclosporin levels and the incidence of associated nephrotoxicity (Morgenstern et al., 1982). We cannot therefore recommend the use of ketoconazole in allogenic transplantation of any organ and its role in prophylaxis in neutropenic patients must be reconsidered as fluconazole and itraconazole have now been introduced.

**Triazole antifungal drugs**

Data from animal experiments suggest that fluconazole is more effective in prophylaxis and early treatment than in therapy of advanced disseminated candidosis (Walsh et al., 1990a,b). In a placebo-controlled study in prophylaxis in cancer patients only 2% of patients receiving 50 mg/day fluconazole developed oropharyngeal candidosis compared with 28% of controls. This difference was largely associated with the many patients with initially positive cultures for candida but no evidence of candidosis, who were cleared of the organisms by fluconazole but not placebo (Bodey et al., 1990; Samonis et al., 1990). This clearance is a significant difference from previous experience with ketoconazole and miconazole and might be expected to be associated with delayed relapse when antifungal drugs are stopped. Delayed relapse has been described in another study of cancer patients which otherwise demonstrated only equal efficacy of ketoconazole and fluconazole in oropharyngeal candidosis (Meunier, Aoun, & Gerard 1990). Most experience in comparing ketoconazole and fluconazole has been gained in patients with AIDS where ketoconazole absorption is poor and there is some evidence that suggests that fluconazole is more effective (de Wit et al., 1989). The minimal adequate prophylactic dose of fluconazole, which has a long plasma half-life and may be suitable for less than daily use, is not established in neutropenic patients. It has also not been established whether infrequent dosage is more likely to be associated with colonization and infection with resistant strains. In one study in non-neutropenic patients with AIDS weekly prophylaxis with 150 mg fluconazole proved effective (Leen et al., 1990). Comparison with a range of polyene regimens suggested that 50 mg/day fluconazole was an effective prophylactic regimen for oropharyngeal candidosis (Brammer, 1990). Absorption has been assessed in a limited number of patients undergoing marrow autografting and is satisfactory, though excretion may be delayed with resulting reduction in dosage requirements (Milliken et al., 1989). Absorption is not pH dependent (Thorpe, Baker, Bromet-Petit, 1990) but absorption studies have not been reported in allograft recipients. In the presence of dysphagia due to cytotoxic drugs' suspensions or parenteral prophylaxis may be needed but these have not been assessed.

A higher dose of 400 mg/day fluconazole, combined with a very liberal policy for
employing empirical intravenous amphotericin B, has been assessed in a large study (Winston, 1991) of prophylaxis in neutropenic patients and shown to be effective in reducing the incidence of disseminated candidosis, oral and faecal colonization and local infection with all yeasts except *C. krusei*. No effect on the incidence of infection with filamentous fungi was seen (Winston, 1991). A similar randomized multicentre trial in marrow transplant recipients reported a reduction in systemic fungal infection from 28/177 (15.8%) receiving placebo to 5/179 (2.8%) receiving 400 mg fluconazole (Goodman* et al.*, 1992), and reduced associated deaths from 10 to 1. Lower doses of chemoprophylaxis (50 mg/day fluconazole) were assessed in comparison with oral polyenes against systemic candidosis and candidaemia in 536 patients undergoing remission induction therapy and showed a less convincing reduction because of a higher incidence of filamentous fungal infection (Brammer, 1991). This study, however, did show complete prevention of infection due to *C. albicans* and *C. glabrata*, although as in the two previous studies *C. krusei* infection was seen (Brammer, 1991). The inactivity of fluconazole against *C. krusei* is offset by its more reliable action against *C. tropicalis* and *C. glabrata* when compared with ketoconazole. Nevertheless, the incidence of *C. krusei* colonization may rise to 40% in those taking fluconazole and a substantial incidence of candidaemia may occur with this previously uncommon species (Persons* et al.*, 1991; Wingard* et al.*, 1991). Fluconazole does induce and inhibit different hepatic drug-metabolizing enzymes (Lavrijsen* et al.*, 1990) but the rise in cyclosporin levels is not consistent nor frequently clinically toxic if constant dosing is used (Krüger* et al.*, 1988; Canafax* et al.*, 1991). The Working Party therefore recommends a dose of 50 mg/day fluconazole for prophylaxis against yeast infection in neutropenic patients. Combining fluconazole with polyenes might be effective in preventing overgrowth with *C. krusei* but this has not yet been investigated and cannot be confidently recommended.

Reported experience with itraconazole in comparative studies is much smaller (Prentice & Bradford 1989). In a large open study in patients with solid tumours and lymphoma itraconazole 100 mg/day given prophylactically for a mean time of two years, oropharyngeal candidosis was reported in 15% of patients (Mühl Dorfer & König 1990) It is not clear if this is due to the impact of poor absorption from the formulation of itraconazole used. Fluconazole and itraconazole have not been compared directly.

*Delayed antifungal drug usage*

An alternative approach to primary oral chemoprophylaxis is use of antifungal drugs as both delayed antifungal prophylaxis and parenteral ‘therapy’ in febrile episodes, which are not documented as fungal in aetiology. This is widely used but seldom assessed for its prophylactic component. It is usual to withhold antifungal treatment until the patient has failed to respond initially to antibacterial agents and then use amphotericin B (Pizzo* et al.*, 1982). Against historical controls, this empirical antifungal drug use appears to reduce the rate of systemic fungal infection detected at autopsy (Zimmerman-Hösli* et al.*, 1989). The distinction between therapy and prophylaxis can be blurred. Systemic prophylaxis with intravenous miconazole started at the onset of first fever and continued for the duration of neutropenia has been shown to prevent invasive candidosis in adult (Wingard* et al.*, 1987) and paediatric leukaemic patients (Fainstein, Elting & Bodey 1981a), although the studies are small. Parenteral miconazole may have adverse effects associated with the vehicle of administration
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(Fainstein, et al., 1981a) and alternative antifungal agents and routes should be assessed. Oral triazole antifungal drugs have not been assessed as additional therapeutic components of regimens for fever in neutropenia, nor for continuation chemoprophylaxis.

In experimental animals, parenteral liposomal amphotericin B exerts a prophylactic effect against candidosis in animals which, unlike that of non-liposomal amphotericin B, endured for a 7-day period, an effect not explained by serum levels (Lopez-Berestein et al., 1984). There are no corresponding data on human use.

**Prophylaxis for aspergillosis**

*Amphotericin B*

Use of intravenous amphotericin B 30 mg thrice weekly as prophylaxis has been shown not to prevent aspergillus infection in unselected neutropenic patients (Bodey & Anaissie, 1991) or bone marrow autograft recipients (Warren et al., 1990) and unless amphotericin B were given in one of its lipid formulations toxicity problems might preclude general prophylactic use at a higher dosage. The place of aerosols of topical agents has also been reconsidered recently in invasive aspergillosis and mucormycosis which are usually acquired from the air and had been thought to require systemically active drugs. The use of a thrice-daily topical nasal amphotericin B spray or aerosol as prophylaxis in leukaemic patients was reported as being successful in three studies (Meunier-Carpentier et al., 1984; Conneally et al., 1990; Jeffrey et al., 1991) but failed in another (Jorgensen et al., 1989). Unfortunately all used historical controls and although additional data suggested that aspergillus exposure had continued (Jeffrey et al., 1991) only studies with concurrent matched controls, with data on episodes and recurrences of pneumonia and fever unresponsive of antibiotics, would be clearly interpretable. Aerosols of amphotericin B are protective in animal models of invasive aspergillosis (Schmitt et al., 1988) although there is no work on the optimum particle sizes of the aerosol (which is known to be important in pentamidine prophylaxis against *Pneumocystis carinii* infection. More work in this area with concurrent controls is a major priority and would be justified in units without HEPA filtration. Although it has not been subjected to a controlled clinical trial, systemic amphotericin B prophylaxis started two days before anti-leukaemia therapy seems successful in preventing reactivation in most patients with prior invasive aspergillosis and tomographic evidence of continuing pulmonary infection (Karp, Burch & Merz, 1988). The Working Party recommend this approach in patients with proven invasive aspergillosis or patients where a presumptive diagnosis was made and there are residual cavities. Itraconazole or liposomal amphotericin B should also be assessed formally for this indication.

*Itraconazole*

Newer absorbed antifungal agents are now being assessed in prophylaxis of invasive aspergillosis. Published clinical trials of itraconazole therapy or prophylaxis in the immunocompromised patient are few. Itraconazole 200 mg bd was compared with ketoconazole 200 mg bd as a prophylactic agent in patients with prolonged neutropenia who had not received bone marrow transplants but had been given antibacterial chemoprophylaxis and nursed without HEPA filtration (Tricot et al., 1987). The trial compared patients given itraconazole with a group of historical controls given ketoco-
nazole and was acknowledged by the authors to be flawed as there was no formal control for exposure to *aspergillus* spp. The major finding was reduced mortality from biopsy and culture proven invasive aspergillosis in the itraconazole group. Amongst patients neutropenic for > 25 days 57% of those receiving ketoconazole and 9% of those receiving itraconazole died of invasive mycoses, predominantly invasive aspergillosis. This high incidence suggests nosocomial acquisition. Surprisingly there was no reduction in empirical amphotericin B usage. Patients with itraconazole levels measured by HPLC as < 250 ng/mL for > 7 days were more than twice as likely to have invasive mycoses with itraconazole-susceptible strains. Only one patient with adequate serum concentrations developed invasive aspergillosis compared with five in the group with inadequate levels, an internal control that suggests that differences in patient exposure to aspergillus was not the sole, although a possible, reason for differences between the two trial periods (Tricot *et al.*, 1987). However, low concentrations were reported in 50% of assessed patients. The dose of itraconazole for prophylaxis requires assessment. Our starting dose is low. Itraconazole absorption from a single dose was reduced but not to an extent distinguishable from intersubject variation after H₂ receptor antagonists (Stein *et al.*, 1989). More infections due to *C. albicans* occurred in the ketoconazole group and more due to *C. glabrata* in an itraconazole group gives 200 mg/day but the numbers of invasive yeast infections were small (Boogaerts *et al.*, 1989).

It will be important to carry out further prospective comparative adequately controlled trials with itraconazole to define more clearly the indications for its use and any potential disadvantages such as invasive yeast infection. An improved formulation which overcomes the problems of erratic absorption is needed. Meanwhile we note that the current licensed formulation of itraconazole may be of benefit in patients nursed without HEPA filters, where there is a proven high incidence of invasive aspergillosis or where building works are being undertaken. Itraconazole should also be substituted for other antifungal prophylaxis in such institutions in patients neutropenic for more than 20 days. With current formulations, itraconazole levels should be regularly measured whenever used. It seems prudent to measure them one week after commencing the drug and thereafter weekly if there is dysphagia, any chance of cytotoxic drug-induced gastrointestinal damage, evidence of GVHD, or the use of antacids, H₂ receptor antagonists, or drugs with capacity to enhance hepatic drug metabolism. If none of these predisposing factors is evident and levels are satisfactory then assays can be less frequent, perhaps monthly in solid organ allografts. It should be noted that intrapatient variation in levels is substantial (Bradford *et al.*, 1991) and measurements must be repeated including during subsequent periods of neutropenia. It is not clear whether additional prophylaxis against yeasts is ever required but this seems likely if the drug is not absorbed. If serum levels of itraconazole are inadequate in patients susceptible to yeast infection, we recommend that fluconazole should be substituted. In such patients who are additionally susceptible to aspergillosis, the use of nebulized amphotericin B, in addition to fluconazole, should be considered, at least until discharge from hospital. In allograft recipients no longer susceptible to yeast infection but susceptible to aspergillosis nebulized amphotericin B may be used alone if itraconazole levels are inadequate. Itraconazole is said to induce and inhibit hepatic drug-metabolizing enzymes and renal toxicity may occur in allograft recipients receiving cyclosporin (Kramer *et al.*, 1990), although the drug may be particularly valuable in this group of patients because of their susceptibility to invasive aspergillosis. Cyclosporin dosage should be reduced at once if itraconazole is used in therapy and levels of both drugs
measured. There are no published data on the prophylactic use of itraconazole after solid organ transplantation, although this may seem sensible if there is a high risk of invasive aspergillosis.

HEPA filtration of air substantially reduces the risk of invasive aspergillosis although occasional cases presumably associated with incubating or recrudescent infection may occur. Substantial problems with this condition always call for urgent investigation into possible sources of nosocomial infection (as outbreaks are now being commonly described), or for improved ventilation systems. Our view is that itraconazole is usually not required as prophylaxis whilst neutropenic patients are nursed in HEPA filtered air. The lack of substantial published clinical trials of itraconazole prophylaxis or clearance of candida together with the problems with its absorption should limit its use at the outset of neutropenia, when the extensive data on prevention of yeast infections with fluconazole are considered. Until such data are published for itraconazole, we cannot advocate its general prophylactic use in neutropenia. Nevertheless, ultimately itraconazole may prove preferable to fluconazole in prophylaxis, because the latter appears not to have activity against invasive aspergillosis at economic doses and because of the high

Table. Summary of the recommendations of the Working Party of the BSAC on chemoprophylaxis of fungal infections in immuno-compromised patients

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<th>1. Prophylaxis in neutropenia</th>
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<td>With selective digestive tract decontamination—primary prophylaxis</td>
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<tr>
<td>Commence fluconazole* 50 mg/daily with prophylactic antibacterials four days before anticipated neutropenia [ &lt; 1.0 x 10^9/L].</td>
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<td>Stop if patient is given empirical intravenous amphotericin B for duration of infusion.</td>
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<td>Stop* when neutrophils &gt; 0.5 x 10^9/L.</td>
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<td>Without selective digestive tract decontamination</td>
</tr>
<tr>
<td>Commence fluconazole* 50 mg/daily with initiation of first course of antibiotics during neutropenia [ &lt; 1.0 x 10^9/L] or if yeasts grown from oral flora earlier.</td>
</tr>
<tr>
<td>Stop if given empirical intravenous amphotericin B (for duration of infusion).</td>
</tr>
<tr>
<td>Finish course* when neutrophils &gt; 0.5 x 10^9/L.</td>
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</tbody>
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<thead>
<tr>
<th>2. Prophylaxis in allogenic solid organ transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic transplantation</td>
</tr>
<tr>
<td>Consider prophylaxis with fluconazole in first postoperative month unless high institutional incidence of aspergillosis when consider prophylaxis with itraconazole*.</td>
</tr>
<tr>
<td>Other solid organ transplantation</td>
</tr>
<tr>
<td>General prophylaxis not recommended.</td>
</tr>
</tbody>
</table>

*Ketoconazole 200 mg/day may be substituted for fluconazole in patients who are not receiving antacids, cyclosporin A, or H2 receptor antagonists but may be less effective in prophylaxis of disseminated candidosis.

*Use, or change to, itraconazole 200 mg/day at once if:—
(i) neutropenic > 20 days AND
(ii) not in HEPA filtered air AND
(iii) not allogenic transplant.

OR

(i) not in HEPA filtered air, AND
(ii) building works in close vicinity.

If serum levels are adequate, continue. If levels are inadequate substitute nasal amphotericin B spray and oral fluconazole.

*If allogenic transplant AND either GVHD or CMV infection occurs, change to itraconazole 200 mg daily and, if serum levels are adequate, continue for 3 months. If levels are inadequate substitute nasal amphotericin B spray.
fatality rate of that disease. Itraconazole has little activity in mucormycosis which can occasionally be seen in similar airborne outbreaks associated with fatalities.

Conclusion

The Working Party summarizes its views in the Table. It considers the evidence suggests that absorbed antifungal agents appear more effective than clotrimazole, miconazole, and oral amphotericin B or nystatin in prophylaxis and prevention of relapses of oropharyngeal candidosis. It is likely but not proven that this extends to disseminated candidosis and more rigorous clinical trials should be undertaken. There appear to be advantages to using fluconazole rather than ketoconazole in allogenic transplant recipients requiring prophylaxis and receiving cyclosporin, or in susceptible patients receiving antacids or H₂-histamine receptor blockers. Only preliminary data for itraconazole are available, despite the time that has elapsed since its introduction, so its role is uncertain in prophylaxis of either candidosis or invasive aspergillosis. The preliminary evidence of efficacy against Aspergillus spp., suggests that itraconazole may be useful where effective control of the quality of air supply to a unit caring for susceptible patients cannot be ensured. More data are required in solid organ transplants. For all chemoprophylactic antifungal agents, careful consideration should be given to the prevalence of invasive mycosis (for which there are inadequate surveillance and autopsy data in Europe) and the timing of prophylaxis in relation to periods when the patient is most susceptible. Prophylactic antifungal regimens can then be restricted to minimize the selection of resistant fungi.

References


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trimethoprim, ketoconazole, and a combination of the two. *Archives of Internal Medicine* **144**, 1562-8.


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