Chapter 17

Antifungal Agents: Resistance and Rational Use

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1. INTRODUCTION

For several years, almost every publication in the field of clinical mycology has begun by stating one or more of the following points. The incidence of invasive fungal disease continues to rise despite judicious antifungal prophylaxis and heightened clinical awareness of the risk of such disease in particular types of patient. There has been a shift among species causing invasive disease away from *Candida albicans* towards other *Candida* species with resistance to triazole antifungal agents such as fluconazole. There is an urgent need for new antifungal agents active against new molecular targets to combat the rising tide of infection and antifungal resistance. While such claims inevitably generate a climate of apprehension about mycoses, they tend to simplify and overstate the reality. This chapter will attempt to evaluate the true extent of antifungal resistance problems and suggest approaches to rational prophylactic and therapeutic use of antifungal agents.

2. EPIDEMIOLOGY OF INVASIVE FUNGAL INFECTIONS

Expressed concerns about a rising incidence of invasive *Candida* infection can be traced back at least to the 1950s (Keye and Magee, 1956). There is little doubt, however, that the greatest rise in invasive infections caused by

Antibiotic Policies: Theory and Practice. Edited by Gould and van der Meer
Kluwer Academic / Plenum Publishers, New York, 2005

Candida spp. and many other types of fungi began in the early 1980s, in parallel with rapidly increasing medical and surgical use of immunosuppressive procedures. The AIDS epidemic also began at this same time and AIDS became recognized as a factor predisposing not only to superficial fungal infections, but also commonly to potentially fatal deep-tissue mycoses such as cryptococcal meningitis and *Pneumocystis jiroveci* pneumonia worldwide, and disseminated histoplasmosis and *Penicillium marneffei* infection in geographical areas where these mycoses are endemic. By 1990, the major emphasis of clinical mycology had switched from infections of the skin and mucous membranes to the study of disseminated, invasive, and all too commonly lethal fungal diseases. While seriously immunosuppressed patients remain those most at risk of invasive mycoses, fungal infections have grown as a cause for concern in intensive care and after major surgical procedures.

Since 1990, the epidemiology of mycoses has been far from static, and a number of surveys have illustrated the major trends. These can be characterized as follows. There has been a decreasing incidence of invasive *Candida* infection and a steadily rising incidence of invasive infections caused by *Aspergillus* and other mould species. The species causing *Candida* infection differ between countries, regions, and even individual institutions, as well as between patients with different underlying diseases, making it difficult to generalize about temporal changes in the incidence of *Candida* species. The incidence of all types of mycoses associated with HIV infection has declined dramatically in countries where highly active anti-retroviral therapy (HAART) is used widely. The status of certain fungi with very low susceptibility to existing antifungal agents (*Fusarium* spp., *Scedosporium* spp., *Zygomycota*) has emerged from that of obscure case reports to routine mention in lists of opportunistic fungal risks in haematological malignancy.

2.1. *Candida* infections

The decrease in invasive *Candida* infections began during the 1990s and has been evidenced from US mortality records (McNeil *et al*., 2001), incidence data from US intensive care units (Trick *et al*., 2002) and neutropenic patients (Wisplinghoff *et al*., 2003), and from Japanese autopsy data (Yamazaki *et al*., 1999). Most of the decrease is attributable to a marked decline in infections caused by *C. albicans*, so it is not surprising that the proportion of other *Candida* species incriminated in disseminated disease has risen. However, evidence for a rising *incidence* of *Candida* infections due to species other than *C. albicans* is less impressive than data illustrating their increased *prevalence*. Only *Candida glabrata* infections may have increased in incidence in some areas in a manner and extent consistent with a general trend: infections caused by *Candida krusei, Candida parapsilosis,* and *Candida tropicalis* have

occurred at fairly consistent rates through the 1990s (Trick *et al*., 2002). In a particularly thorough analysis of publications detailing the epidemiology of candidaemia, Sandven (2000) showed how, in the United States, the prevalence of *C. glabrata* among *Candida* species isolated from blood cultures has risen from around 10% up to 1990 to around 20% in surveys done since that date; the change is at the expense of *C. tropicalis*, which has had a lower prevalence since 1990. The large survey by Pfaller *et al*. also shows *C. glabrata* representing 18% of *Candida* spp. blood isolations in the United States from 1992 to 1998 (Pfaller *et al*., 1999b). In European surveys, a similar overall doubling in the prevalence of *C. glabrata* (at the expense of *C. albicans*) is apparent between the 1980s and the 1990s, although the average current prevalence of *C. glabrata* in European surveys is lower (~15%) than in the United States (Sandven, 2000). By contrast, most data from Latin American countries, Japan, and elsewhere in Asia all show *C. glabrata* to be a relatively rare species, with *C. parapsilosis* highly prevalent and second to *C. albicans* as a cause of bloodstream infections (Pfaller *et al*., 2000; Sandven, 2000). These observations are slightly confused by results from the SENTRY prospective surveillance scheme, which covers the United States, Europe, and Latin America, and which puts *C. parapsilosis* as the second most common species in Europe (Pfaller *et al*., 1999a). With such mixed messages emerging from large surveys of bloodstream isolates, it is impossible to make confident statements about any particular trends or their causes.

2.2. *Aspergillus* infections

The almost continually rising incidence of aspergillosis worldwide is far more easy to discern. The same surveys that show a fall in *C. albicans* infections document a steady rise in aspergillosis, mainly due to *Aspergillus fumigatus*, but sometimes caused by other species such as *Aspergillus flavus* (McNeil *et al*., 2001; Yamazaki *et al*., 1999). The source of the increased incidence is easy to define: the number of patients undergoing procedures that predispose to invasive aspergillosis (primarily allogeneic haematopoietic stem cell transplantation and major solid organ transplantation) has grown steadily through the 1980s and 1990s (Denning, 1998; K. A. Marr *et al*., 2002a, b). Mortality in invasive aspergillosis is often very high, exceeding 80% in stem cell transplant recipients and patients with aspergillosis disseminated from a primary pulmonary site (Lin *et al*., 2001).

2.3. Other fungal diseases

The same clinical settings that predispose patients to aspergillosis also increase the risk of nosocomial infections by other filamentous fungi.

Groll and Walsh have extensively reviewed the threat posed by uncommon fungal diseases (Groll and Walsh, 2001). Among the fungi they discuss, *Fusarium* spp., *Scedosporium* spp., and members of the *Zygomycota* pose the greatest threat to life since they are commonly refractory to systemic antifungal agents.

The introduction of HAART has reduced HIV burdens so effectively that the incidence of most life-threatening AIDS-related mycoses has declined, sometimes dramatically (Ives *et al*., 2001; Raffaele *et al*., 2003). This change particularly affects *Pneumocystis* and *Cryptococcus* infections, where the high incidence and clinical consequences stimulated intensive research into both diseases through the 1980s and 1990s. Both are now encountered only occasionally in countries where HAART is readily available and affordable.

3. ANTIFUNGAL RESISTANCE: IS IT A GROWING PROBLEM?

The still-rising overall incidence of invasive fungal disease creates a particular concern that is easily expressed. Since the obvious and necessary action to combat a growing fungal infection problem is to increase prophylactic and therapeutic usage of antifungal agents, will this not inevitably lead to a rise in incidence of infections caused by antifungal-resistant strains and species? Should we not take precautionary steps to ensure that resistant fungi do not become a clinical problem comparable with multiresistant bacteria?

3.1. Antifungal resistance in *Candida* species

These are very reasonable questions, and some authors have already published alarming accounts that have engendered concerns without necessarily delivering accurate detail and evidence to support their claims. For example, the now almost universal use of the ugly term "non-*albicans Candida* species" in publications has created a widespread illusion that only *C. albicans* is susceptible to fluconazole and other azoles. The detailed reality is quite different. The only clinically important *Candida* species regarded as resistant to fluconazole *per se* is *C. krusei*, and this species remains susceptible to most other triazole antifungals, albeit with lower susceptibility than *C. albicans*. *C. glabrata* is less susceptible to triazoles than *C. albicans*, but to characterize this species as azole-resistant is a gross oversimplification of the data; *in vitro*, most isolates of *C. glabrata* fall within the "susceptible" range of triazole minimal inhibitory concentrations (MIC) (Pfaller *et al*., 2000) and resistance prevalence varies between age groups and geographical locations (Pfaller *et al*., 2003b). *Candida dubliniensis* can be readily induced to develop

resistance to fluconazole *in vitro*, although most fresh isolates of this species are susceptible in the absence of exposure to the drug (Moran *et al*., 1997; Quindos *et al*., 2000). Almost all other *Candida* species remain equally or more susceptible to triazoles than *C. albicans*, and occasional reports of widespread azole resistance among isolates of, for example, *C. tropicalis* (St Germain *et al*., 2001) may represent problems of interpretation of trailing end-points in azole susceptibility tests (Rex *et al*., 1998) since the majority of surveys have failed to show reduced azole susceptibility in species other than *C. krusei* and *C. glabrata* (Sanglard and Odds, 2002).

Resistance to triazole antifungals can result from alterations in the structure of the protein target for these agents, Erg11p, from upregulation of expression of this protein and from upregulation of multidrug efflux transporters in fungi (Sanglard and Odds, 2002). These mechanisms may be expressed in combination in some isolates (White, 1997). Fluconazole is unique among the triazole antifungal agents because it is a substrate for the major facilitator family of efflux transporters; all triazoles are exported by ABC-family transporters (Sanglard and Odds, 2002). This difference suggests that resistance to fluconazole may arise slightly more commonly than to other triazoles (at least in isolates of *C. albicans* where the mechanisms have been most thoroughly studied).

Regardless of details of resistance mechanisms, it is unquestionable that antifungal resistance can develop in normally susceptible fungal species and that resistance can lead to treatment failure. The high prevalence of resistance development among oral *C. albicans* isolates during the peak of the AIDS epidemic has been well documented (Canuto *et al*., 2000; Chryssanthou *et al*., 1995; Milan *et al*., 1998) and is clearly associated with treatment failures (Rex *et al*., 1995). Resistance to itraconazole and to voriconazole and concomitant treatment failure has been reported in clinical *A. fumigatus* isolates (Denning *et al*., 1997; Manavathu *et al*., 2000), and the inherently low susceptibility to amphotericin B and the older established triazoles of fungi such as *Fusarium* spp., *Scedosporium* spp., and the *Zygomycota* is considered to be the principal reason for high mortality rates when these moulds cause disseminated disease (Groll and Walsh, 2001).

3.2. Antifungal resistance cannot be transmitted by extrachromosomal DNA

However, there is a most important difference between resistance development and transmission among fungi as compared with bacteria; fungi do not, to our knowledge, have any mechanism comparable to bacteria for the transfer of genes encoding resistance from one isolate to another. Antifungal resistance

is not encoded in extrachromosomal DNA, and transformation of fungi with DNA is far less easy than with bacteria, even under optimized laboratory conditions.

Current experimental studies with *C. albicans* show that, contrary to long-held opinions, the fungus probably can undergo mating, but does so naturally at a remarkably low frequency (Soll *et al*., 2003). The same seems likely to apply to *A. fumigatus* (Poggeler, 2002). This inability to transmit antifungal resistance implies that development of clinically relevant resistance, at least to amphotericin B and triazoles where experience with their usage now extends to 20–30 years, is likely to be encountered almost exclusively among patients undergoing active treatment with these agents. How else can it be explained that the fluconazole resistance that developed so readily with oropharyngeal *Candida* infections in HIV-positive patients during the 1990s is now so much reduced in the most recent surveys (Barchiesi *et al*., 2002; Martins *et al*., 1998; Tacconelli *et al*., 2002)? The low prevalence or absence of resistance among patients who have received no prior azole treatment is demonstrated clearly in a large survey of South African patients infected with HIV (Blignaut *et al*., 2002). The lesson of the pre-HAART HIV era is that, among HIV-positive patients under the pressure of azole therapy, resistance to the agents can develop rapidly among many isolates of *C. albicans* (21% is the highest recorded point prevalence; Martins *et al*., 1997) and prevalences of *C. dubliniensis* and *C. glabrata* rise unequivocally (Dupont *et al*., 2000). However, transmission of resistant strains to untreated individuals seems not to occur on any significant scale.

The rapid azole resistance development seen among *Candida* isolates in the HIV-positive patient cohort has not been observed consistently in any other clinical setting, although reports from some institutions attest to obvious increases in prevalence of *C. glabrata* concurrent with the introduction of routine fluconazole prophylaxis (Abi-Said *et al*., 1997; Price *et al*., 1994). These reports are balanced by publications showing the *opposite* change in other institutions (Baran *et al*., 2001; Kunova *et al*., 1997) and by emergence of *C. glabrata* temporally associated with amphotericin B, not azole prophylaxis (Michel-Nguyen *et al*., 2000). Warnings of an epidemic of azole resistance among *Candida* isolates are not supported by large surveys showing very low rates of such resistance among recent isolates from blood (Pfaller *et al*., 1999b, 2003a) nor by reports indicating no change in levels of resistant isolates in a number of settings, including community-acquired mycoses such as vaginal *Candida* infections (Asmundsdottir *et al*., 2002; Chen *et al*., 2003; Marrazzo, 2003; Walker *et al*., 2000).

Among fungi other than *Candida* spp., no publications so far suggest the emergence of antifungal resistant isolates on a large scale, although resistance to agents such as itraconazole undoubtedly *can* develop during treatment, as

already mentioned. A survey of 170 isolates of *A. fumigatus* found only three resistant to itraconazole (Verweij *et al*., 2002).

3.3. Antifungal resistance: conclusion

The most considered response that can be given to questions about the danger of emergence of antifungal-resistant fungi is that the phenomenon definitely occurs and that it has been seen to occur rapidly in oral *Candida* isolates in HIV-infected patients. However, in other clinical settings, the emergence of resistant fungi seems not to be an inevitable corollary of antifungal usage, and recorded changes in incidence and/or prevalence of causative fungal species have been associated with alterations in the type of patient at risk of mycosis and the methods of their management (Husain *et al*., 2003; Kovacicova *et al*., 2001; Krcmery and Barnes, 2002; Nucci and Colombo, 2002; Singh *et al*., 2002; Torres *et al*., 2003), and by no means exclusively with alterations in antifungal treatments. Prudence to avoid unnecessary use of antifungal agents is reasonable; anxiety about the large-scale emergence of resistant strains is not.

4. RATIONAL USE OF ANTIFUNGAL AGENTS

4.1. Antifungal agents available for prophylaxis and treatment of invasive mycoses

A further factor diminishing concerns about resistance developing when antifungal agents are used is the increased antifungal coverage offered by the current armoury of antifungal drugs. The number of antifungal agents and of antifungal classes have grown remarkably in recent years (Odds *et al*., 2003). This section provides a very brief review of the agents available. Table 1 lists the main properties of systemic antifungal agents approved for clinical use or soon likely to be approved.

Amphotericin B, a polyene, kills susceptible fungal species by directly damaging their cell membranes. The selective toxicity of amphotericin B for fungal, as opposed to mammalian membranes, is low, and nephrotoxicity is the major hazard associated with use of the drug. The risk of nephrotoxicity has been considerably reduced by the availability of lipid-associated amphotericin B formulations. The cost of the lipid complex and colloidal suspension formulations is higher than that of conventional (deoxycholate-complexed) amphotericin B, and that of liposomal amphotericin B is considerably higher, but

Table 1. Systemic antifungal agents

Antifungal class	Agent	Mode of action	Antifungal spectrum	Comments
Polyenes	Amphotericin B	Damages fungal membranes by binding to ergosterol	Most fungal types but weak vs *Aspergillus flavus, Fusarium* spp., *Scedosporium* spp., *Zygomycota*	IV administration only; nephrotoxicity greatly reduced in lipid-associated formulations
Pyrimidine analogue	Flucytosine	Interferes with DNA synthesis after intracellular conversion to 5-fluorouracil	*Candida* spp., *Cryptococcus neoformans*	Toxic to bone marrow when blood levels high; resistant strains fairly common among susceptible species
Triazoles	Fluconazole	Inhibits 14α-sterol demethylase and alters sterol-dependent membrane fluidity	*Candida* spp., *Cryptococcus neoformans*, some filamentous fungi but not *Aspergillus* or *Fusarium* spp.	A safe and effective agent, limited by gaps in its spectrum and by poor activity vs *C. krusei* and some isolates of *C. glabrata*
	Itraconazole	See fluconazole	Many fungal types but not *Fusarium* spp., *Scedosporium* spp., or *Zygomycota*	Poor and variable oral bioavailability from capsules; oral solution has good bioavailability but poor palatability; IV formulation contains high cyclodextrin concentration; many interactions with drugs metabolised by hepatic P450 enzymes

	Voriconazole	See fluconazole	Many fungal types including some isolates of *Fusarium* spp., *Scedosporium* spp., and *Zygomycota*	Side effects include high incidence of visual disturbances; many interactions with drugs metabolised by hepatic P450 enzymes
	Ravuconazole	See fluconazole	Many fungal types including some isolates of *Fusarium* spp., *Scedosporium* spp., and *Zygomycota*	Agent in clinical development at the time of writing; clinical details not yet known
	Posaconazole	See fluconazole	Many fungal types including some isolates of *Fusarium* spp., *Scedosporium* spp., and *Zygomycota*	Agent in clinical development at the time of writing; clinical details not yet known
Echinocandins	Caspofungin	Inhibits synthesis of β-1:3-D-glucan in fungal cell walls	Most *Candida* and *Aspergillus* spp., some other filamentous fungi; not *Cryptococcus neoformans*	IV only. Very low toxicity and drug–drug interaction potential
	Anidulafungin	Inhibits synthesis of β-1:3-D-glucan in fungal cell walls	Most *Candida* and *Aspergillus* spp., some other filamentous fungi; not *Cryptococcus neoformans*	Agent in clinical development at the time of writing; clinical details not yet known
	Micafungin	Inhibits synthesis of β-1:3-D-glucan in fungal cell walls	Most *Candida* and *Aspergillus* spp., some other filamentous fungi; not *Cryptococcus neoformans*	Agent in clinical development at the time of writing; clinical details not yet known

many practitioners regard the higher cost of these formulations as justifiable in view of their considerably improved safety profiles.

Flucytosine inhibits growth of fungi that can actively import the compound and convert it to 5-fluorouracil, which restricts its use principally to *Candida* and *Cryptococcus* infections. The prevalence of yeast isolates resistant to flucytosine was probably overstated in the past, when susceptibility testing was not standardized (Sanglard and Odds, 2002). The current use of flucytosine is mainly as adjunct therapy in combination with other antifungal agents.

Fluconazole is well established as a safe and effective drug that has now been used for many years for the prophylaxis and treatment of fungal infections, particularly *Candida* infections. The agent is essentially inactive against *Aspergillus* spp. and has become regarded increasingly as a drug principally of use for treating yeast (*Candida* and *Cryptococcus*) infections. It has the shortest list of the drug–drug interactions that typify the triazole antifungal family (the fungal cytochrome P450 target is structurally similar to mammalian P450 enzymes) and is the least likely of the class to generate transient changes in serum levels of hepatic enzymes.

Itraconazole has a broad spectrum of antifungal activity that should make it a useful agent for treating many types of invasive mycosis. However, in its capsule formulation, its bioavailability is poor in some patients. Its formulation as an oral solution offers reliable bioavailability but its poor palatability often leads to patient noncompliance and both the oral solution and intravenous solution depend on high hydroxylpropyl-β-cyclodextrin concentrations to dissolve the itraconazole and this substance is a cause of diarrhoea and occasional renal effects. Itraconazole has a long list of drug–drug interactions associated with its use.

Voriconazole has an antifungal activity spectrum and potency similar to, but even better than that of itraconazole. It has proved itself to be first-line therapy for invasive aspergillosis (Herbrecht *et al*., 2002). Its associated drug–drug interactions are similar to those of itraconazole and approximately 30% of patients given voriconazole orally or IV experience visual disturbances of short duration.

Caspofungin, the first of the echinocandin antifungal family to be registered for clinical use, is available only for intravenous administration. Its antifungal spectrum excludes *Cryptococcus neoformans* but otherwise covers the main pathogenic *Candida* and *Aspergillus* species. The agent has an excellent safety profile and few to no drug–drug interactions. Micafungin has been licensed in Japan for treatment of several types of *Aspergillus* and *Candida* infection. Its antifungal spectrum and IV-only formulation are very similar to those of caspofungin. Anidulafungin, the third echinocandin likely to be close to regulatory approval, so far seems also to have a similar profile to the other agents in the class.

4.2. Recommending uses of antifungal agents: the limitations

The existence of a diverse range of classes and formulations of antifungal drugs (Table 1) should offer many possibilities for their use in the prevention and treatment of invasive mycoses. In practice, any recommendation is limited by the officially licensed indications for each individual agent (which often vary from country to country) and by the extent to which recommendations can be supported by evidence from well-designed prospective, randomized clinical trials. What follows will include suggestions for antifungal usage that are offered as future possibilities and are not (yet) supported either by licensed drug indications or by evidence-based medicine. Such suggestions are offered in good faith and arise from the consideration that licensing and evidence-based medicine commonly lag substantially behind the available opportunities for therapeutic management.

Agents undergoing major clinical trials but not yet licensed in the United States or Europe have not been included among the recommendations that follow. It is likely highly that posaconazole and ravuconazole will have many properties in common with the licensed triazoles, itraconazole and voriconazole, and that anidulafungin and micafungin will closely match caspofungin. However, their place in clinical practice will depend on the details of their formulations and their adverse event and drug interaction profiles, so it is too early to guess their final place in the antifungal armoury.

Since 2000, several publications have provided guidelines from working parties and other consensus groups for antifungal prophylaxis and treatment in several categories of patients (Bohme *et al*., 2001; Denning *et al*., 2003; Dykewicz, 2001; Hughes *et al*., 2002; K. Marr and Boeckh, 2001; Quilitz *et al*., 2001; Rex *et al*., 2000; Saag *et al*., 2000; Stevens *et al*., 2000). These recommendations show impressive similarities in their choices of agent and other suggestions for management and should be consulted for the excellence of the detail they provide. The discussion that follows takes account of these publications, but ventures further, as already stated, by suggesting some new approaches for management that are not yet supported by data from appropriate clinical trials.

Two principles are common to most of the published guidelines, as follows:

1. Fluconazole represents a reasonable antifungal choice where the infection under treatment is known or likely to be caused by *C. albicans* or other fluconazole-susceptible *Candida* sp. For infections caused by *C. krusei* or fluconazole-resistant strains of a *Candida* species, a systemic antifungal agent with activity against the infecting yeast is the preferred choice.

2. Amphotericin B is a broad-spectrum, systemically active antifungal agent for use against infections by most fungal types, but a lipid-associated formulation should be used in patients who have impaired renal function, or develop signs of nephrotoxicity under treatment.

This advice, though entirely reasonable, was published before any data were published for the novel systemically active agents. It should, therefore, be supplemented by the general suggestion:

3. New triazoles (itraconazole and voriconazole) and the echinocandin caspofungin all have defined and licensed places in the treatment of aspergillosis and other invasive fungal infections; in some patients they may offer demonstrable benefits over the better-known fluconazole and amphotericin B, and the possibility that they are more appropriate choices needs to be considered in every case where diagnostic evidence suggests a strong possibility of serious fungal disease.

4.3. Rational prophylaxis against fungal disease

Prevention of fungal disease is an obviously desirable goal for patients at high risk of invasive infection. Each individual patient has to be assessed for the appropriateness of antifungal prophylaxis: the level of risk of mycosis, the extent of immunocompromising factors such as neutrophil count, the ability of the patient to take oral medication, and the other drugs being used to manage the patient are just a few of the detailed factors that need to be considered in deciding whether to use antifungal prophylaxis and, if so, which drug to choose.

Patients at risk of invasive fungal disease fall into one of two very broad categories: (1) patients with neutropenia and (2) patients with normal leukocyte counts but who are at risk because of other forms of debilitation (e.g., low birth weight, abdominal or transplant surgery, chronic granulomatous disease, burns, etc.). Strategies for preventing fungal infections in neutropenia have been worked out over very many years. Many of the clinical trials were subjected to a meta-analysis by Bow and colleagues (Bow *et al*., 2002), which concluded that prophylaxis of neutropenic patients with azoles or intravenous amphotericin B formulations reduced morbidity and mortality due to fungal infection, but it had no effect on the incidence of aspergillosis and was of much greater benefit in patients with prolonged neutropenia or undergoing stem-cell transplantation than in other neutropenic patients undergoing chemotherapy.

This meta-analysis sets the stage for a rational approach to antifungal prophylaxis in neutropenia. It is logical that the need for preventive anti-infective

therapy increases with the level of risk of the infection. Giving prophylaxis to a patient who has previously suffered an invasive mycosis and who is again made neutropenic by subsequent chemotherapy carries the special name "pre-emptive" therapy. So the decision about *whether* to attempt prophylaxis in a neutropenic patient should be taken on the basis of level of risk. Criteria for assessment of risk of invasive fungal disease in neutropenia have been detailed by others and the recommendation is, therefore, relatively simple: Patients at high risk definitely require prophylactic antifungals, patients at intermediate risk may benefit from antifungal prophylaxis, and patients at low risk do not require prophylaxis.

The choice of agent for prophylaxis in neutropenia is controversial, since many potentially suitable antifungal drugs do not have prophylaxis as a licensed indication. Fluconazole *is* licensed and has been used prophylactically for many years. However, there are trial data to prove that a triazole such as itraconazole, which includes *Aspergillus* spp. in its spectrum, is superior to fluconazole, which does not, when given as prophylaxis to very high-risk patient groups such as allogeneic stem-cell transplant recipients (Boogaerts *et al*., 2001). The eventual rational choice for prophylaxis in such special subsets of patient is therefore likely to be an agent with proven activity against both *Candida* and *Aspergillus* spp., which will include itraconazole and voriconazole (both can be given orally and IV), caspofungin, and amphotericin B (both IV only).

For patients without neutropenia, the decision to undertake prophylactic antifungal therapy and the choice of agent are more controversial than with neutropenic patients. Few intensive therapy units (ITUs) and even fewer surgical wards would ever consider routine antifungal prophylaxis for all their patients. However, there is respectable evidence to show that—as with neutropenic patients—the subsets of patients at highest risk of invasive mycosis *do* benefit from a prophylactic approach. Fluconazole was shown to prevent *Candida* peritonitis in patients who had undergone invasive intra-abdominal surgery (Eggimann *et al*., 1999) and to reduce the incidence of invasive mycoses in critically ill post-surgical patients of all types (Pelz *et al*., 2001). Itraconazole and fluconazole gave results judged as equivalent in preventing invasive mycoses in liver transplant recipients (Winston and Busuttil, 2002). Both nystatin and fluconazole were shown to be effective antifungal prophylaxis when given to very low birth weight neonates receiving intensive care (Kaufman *et al*., 2001; Kicklighter *et al*., 2001; Sims *et al*., 1988).

On the basis of these studies, a conclusion can be drawn that, given adequate and carefully drawn up guidelines to define the sets of non-neutropenic patients at highest risk of invasive fungal disease in any given clinical setting, a prophylactic antifungal regime may be instituted with benefit. The choice of agent will depend on whether a *Candida* or a mould infection is more likely in a high-risk patient.

4.4. Empirical antifungal therapy in neutropenic patients

By definition, empirical therapy does not fit the description of "rational" therapy (although it would be entirely irrational to *exclude* a persistently febrile neutropenic patient from antifungal treatment!). In clinical trials with antifungal agents, the usual criterion for treatment is fever in a neutropenic patient that persists for 5 days or more despite antibacterial chemotherapy. The clinical trials lean solely on fever as a primary criterion both for admission to the study and for efficacy. Though rigorously scientific, this approach fails to resemble the most common situation in "febrile neutropenia" where, by 5 days after onset of fever, the attending physicians usually have clues as to the nature of any possible fungal infection. This means that agents such as fluconazole can be avoided when the diagnostic evidence, albeit feeble, points to a possible invasive aspergillosis.

Trial data in "empiric" antifungal therapy can be criticized on many fronts and recently have been in a forceful manner (Bennett *et al*., 2003). The limitations of study designs may have *under*estimated, rather than optimized the performance of the many agents that have been tested clinically. At present, amphotericin B (in various formulations), fluconazole, itraconazole, and voriconazole have all shown efficacy in published trials (though all are not licensed for empirical therapy in, e.g., the United States) and—to judge from meeting abstracts—caspofungin will also demonstrate efficacy as empirical therapy.

In the present author's opinion, the problems with empiric antifungal therapy can be overstated; they result from the well-known difficulties of establishing sound diagnoses of invasive infections due to *Candida* and *Aspergillus* species. It seems unthinkable that agents with efficacy proven against mycoses with a well-established diagnosis should suddenly become impotent against the same mycosis in the absence of diagnostic information. The problem, then, lies with the expectation that any prolonged fever that does not respond to antibacterial therapy in a neutropenic patient must be the result of a fungal infection. In the everyday clinical arena, a best judgement can be and has to be made as to whether a patient's fever might be attributable to a mycosis and, if the possibility is high, the best course is to institute antifungal therapy as rapidly as possible, not to wait for an academically defined period of non-responsiveness to antibacterial agents. Perhaps, in time, people with the appropriate clinical expertise and experience will be able to draw up an algorithm for more rational management of "fever in neutropenia" that will facilitate decisions whether or not to institute antifungal therapy.

4.5. Rational therapy of diagnosed invasive mycosis

Published guidelines for the management of proven candidaemia and other forms of *Candida* infection (Rex *et al*., 2000) and of proven invasive aspergillosis of all types (Stevens *et al*., 2000) indicate that the well-established systemically active antifungal agents all have a role to play in appropriate circumstances.

For candidaemia, amphotericin B, liposomal amphotericin B, fluconazole, and caspofungin (but *not* yet voriconazole or itraconazole) are all licensed therapies in the United States. Choice of agent should be determined according to the circumstances of the patient. For invasive aspergillosis, voriconazole and amphotericin B are now regarded as the agents of first choice, with caspofungin and itraconazole available should alternative therapies be required.

From published case reports and small series, voriconazole is developing a reputation as a useful agent for treatment of *Scedosporium* infections (Girmenia *et al*., 1998; Munoz *et al*., 2000; Walsh *et al*., 2002) and the drug may prove to be useful in other infections caused by uncommon mould species. The newest triazoles, posaconazole and ravuconazole, may also prove ultimately to have a role in such infections, and the potential value of the echinocandin class for uncommon fungal diseases remains to be evaluated. Susceptibility testing *in vitro* is likely to be of more value in determining the choice of agents for unusual mycoses than for the more common *Candida* and *Aspergillus* infections.

4.6. Antifungal combinations and therapy changes

The combination of high-dose oral fluconazole with IV amphotericin B is no less effective than amphotericin B alone for treatment of candidaemia in non-neutropenic patients and may be slightly more efficacious (Rex *et al*., 2003). However, the main stimulus for the use of combinations of antifungals is therapeutic failure of single agents in life-threatening situations such as invasive aspergillosis and diseases caused by unusual fungi. Prospective clinical trials of antifungal combinations in unusual mycoses will be extremely hard to design and implement; all the evidence so far available comes from anecdotal and open studies, much of it so far presented only in meetings abstracts and lectures. Clear evidence that combinations reduce mortality rates when a mycosis has been well diagnosed is hard to find. It is too early to pronounce on the potential future value for antifungal combinations.

When treatment of an invasive mycosis appears to be failing, a commonly raised question is whether to change antifungal treatment and, if so, to what. A patient treated with fluconazole can be usefully switched to one of the broader spectrum triazoles (voriconazole, itraconazole, etc.), but to switch from one

broad-spectrum triazole to another would require strong evidence *in vitro* of superior antifungal potency at achievable blood levels of the second azole. Outwith straightforward pharmacological considerations (formulation, route of administration, potential for toxicity, or drug interactions in a given patient), there is no particular reason not to switch from one appropriate antifungal class to another. The advent of the echinocandins into clinical use expands the possibilities for class switching in treatment failure, and may in time generate a database that can offer predictive clues to optimize treatment switches.

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