Antimycotic Agents in Oral Candidosis: An Overview: 2. Treatment of Oral Candidosis

ARJUNA N.B. ELLEPOLA AND LAKSHMAN P. SAMARANAYAKE

Abstract: As both humans and fungi are eukaryotic organisms, antifungal agents affect their cellular metabolism. Thus, a relatively few antifungals with minimal toxicity and side-effects are available compared with a plethora of antibacterials. These agents currently prescribed in dentistry belong to two major groups, the polyenes (nystatin and amphotericin B) and the azoles (imidazoles and triazoles). A newly recognized phenomenon known as the post-antifungal effect implies that antifungals, even at sub-therapeutic concentrations, may suppress the virulent attributes of yeasts, especially intra-orally where topical drug levels fluctuate dramatically during dosing intervals.

***Dent Update* 2000; 27: 165-174**

Clinical Relevance: As fungal resistance to polyenes is virtually non-existent, these should be the first line drugs used in the management of oral candidoses. The newly introduced triazoles should be used under special situations (such as in HIV-infected patients) when other drugs fail, as emergence of triazole-resistant *Candida* species is becoming an increasingly common global problem.

Oral candidosis may usually be managed by topical delivery of antifungal agents. If this fails, treatment should include systemic medications. In patients with recalcitrant infection, topical as well as systemic medications should be used: this may allow a lower dose and reduced duration of systemic therapy, which carries a risk of toxicity because fungal cell metabolism is similar to that of mammalian cells.[1] Most importantly, antifungal agents, however potent, may be rendered ineffective in the long term if the underlying predisposing factors (Table 1) are not attended to in the first instance. Thus, it should be remembered that antifungal agents are only an adjunct to the overall management of oral candidosis.

The antifungal agents available for treatment of candidosis fall into three main categories:

- the polyenes (nystatin and amphotericin B);
- the azoles (miconazole, clotrimazole, ketoconazole, itraconazole and fluconazole);
- the DNA analogue 5-fluorocytosine (systemic use only; not used in dentistry).

The principal antifungals used against oral mycoses belong to the polyenes and the azoles,[2] as summarized in Table 2.

***Arjuna N.B. Ellepola**, BDS (Hon.), PhD, Lecturer, Department of Oral Medicine & Periodontology, Faculty of Dental Sciences, University of Peradeniya, Sri Lanka and Faculty of Dentistry, The Prince Philip Dental Hospital, University of Hong Kong, and **Lakshman P. Samaranayake**, BDS, DDS, FRCPath, FHKCPath, CBiol, MIBiol, FHKAM (Dental Surgery), FHKAM (Pathology), Chair Professor of Oral Microbiology, Faculty of Dentistry, The Prince Philip Dental Hospital, University of Hong Kong.*

POLYENE ANTIFUNGAL AGENTS

Two polyenes (amphotericin B and nystatin) are commonly used for the treatment of oral candidosis. Although fungal resistance to these agents is rare,[3] significant resistance in yeasts, including *Candida albicans*, has been reported in isolates from patients with prolonged neutropenia.[4]

Amphotericin B

Mode of Action

This agent acts by inhibiting fungal growth through an interaction with ergosterol (the principal sterol in fungal membranes), which results in the loss of membrane selective permeability and intracellular components, in turn causing impairment of barrier functions, leakage of cellular components and cell death. Depending on the concentration employed, amphotericin B will exert either a fungistatic or a fungicidal effect. At low concentrations, leakage of cell constituents is restricted to small molecules and ions (sodium and potassium) and the damage is reparable. At high concentrations, larger molecules are transported through the membrane, producing irreversible loss of constituents of cells, and their subsequent disruption. As the mammalian cell membrane also contains sterols, this drug has a certain degree of host toxicity. However, the polyenes bind more effectively to ergosterol than to other mammalian sterols such as cholesterol.[4–6]

The spectrum of activity of amphotericin B includes most fungi that cause disease in humans, including *Candida* species. Amphotericin B is poorly absorbed from the intestinal tract and is usually administered intravenously or topically.

Physiological	Old age, infancy, pregnancy
Local trauma	Mucosal irritation, poor denture hygiene
Antibiotics	Particularly broad-spectrum antibiotics
Corticosteroids	Steroid inhalers, systemic steroids
Malnutrition	High-carbohydrate diet, iron, folate and vitamin B_{12} deficiencies
Endocrine disorders	Hypoendocrine states (e.g. hypothyroidism, Addison's disease), diabetes mellitus
Malignancies	Including blood disorders (e.g. acute leukaemia, agranulocytosis)
Immune defects	AIDS, thymic aplasia
Xerostomia	Due to irradiation, drug therapy, Sjögren's syndrome, cytotoxic drug therapy

Table 1. *Factors that predispose the host to oral candidosis.*

Although they are not very popular, topical amphotericin B oral preparations (lozenges, mouthwashes, creams, ointments) are available for treatment of oral candidosis. Topical therapy may be useful in its own right in primary oral candidosis but could be used as an adjunct to parenteral therapy in secondary candidosis, which manifests both systemically and on mucosal surfaces.

Adverse Effects

The most common and most serious adverse effect of systemic amphotericin B is nephrotoxicity (Table 2). Hypokalaemia and mild anaemia are also common. Other rare adverse effects include acute hypersensitivity reactions, including anaphylaxis, fever and headache. Vomiting, anorexia, backache, seizures and thrombophlebitis at the site of injection have also been reported.[4,5]

Drug Interactions

Amphotericin B may potentiate nephrotoxicity of other agents such as aminoglycosides and cyclosporin; concomitant administration of glucocorticoids may exacerbate electrolyte disturbances, especially hypokalaemia. Mechlorethamine and other anticancer agents may potentiate the nephrotoxic and hypotensive effects of amphotericin B.[6]

Preparations

The currently available preparations for oral delivery of amphotericin B include ointment, suspensions, creams and lozenges. Inhibitory concentrations of amphotericin B can be detected in saliva up to 2 hours after a single lozenge.[2]

The oral dose for adults is 100–200 mg every 6 hours. Lozenges (Fungilin 10 mg) can be given every 8 hours, to a maximum of 80 mg/day. Eight-hourly doses of 1 ml of oral suspension (Fungilin 100 mg/ml) retained in the mouth (after food), especially in contact with the lesion, are also recommended. Intravenous infusions can be administered with care to adults and children at 0.25 mg/kg/day.[4]

Nystatin

Nystatin has a mode of action identical to that of amphotericin B.[3] Blocking of ergosterol biosynthesis alters the permeability of the fungal cell membrane, resulting in leakage of cell constituents and death. Nystatin is probably the most popular agent for treating superficial infections of *C. albicans*. It has both fungicidal and fungistatic activity, depending on the concentration administered. Owing to its systemic toxicity, nystatin should be used topically, although it may be administered orally for the treatment of mucocutaneous infections caused by *C. albicans*.

Preparations

Nystatin is available in the form of creams, tablets, suspensions, oral rinses, gels and pastilles.

The ointment contains perfumes and other agents and is not suitable for intra-oral use, but has been used for treatment of angular cheilitis.

Nystatin tablets (500 000 IU) are commonly used for treatment of oral candidosis and so are the vaginal pessaries (100 000 IU). The latter are highly efficacious when used orally as long as the patient is persuaded to take them. The bitter taste of the tablets results in poor patient compliance.[7]

The suspension can be used for young children or poorly compliant patients, although its rapid clearance from the oral cavity results in concentrations falling to sub-therapeutic levels fairly quickly. The oral rinse is similarly relatively ineffective, because of the short contact time with the oral mucosa. However, it contains sugar and increases the risk of dental caries.[7]

In contrast, the pastilles and lozenges can be sucked slowly and hence have a longer duration of action. Further, the sweetened formulations of pastilles and lozenges results in better patient compliance and, due to prolonged retention, pastilles can be expected to be a better fungicidal agent than the suspension. Nystatin pastilles are ideal for the treatment of *Candida*-associated denture stomatitis and could be used to prevent outbreaks or recurrence of oral candidosis in HIV-infected patients. However, as they are also sweetened with sucrose, their use increases the risk of developing dental caries: long-term use may be contraindicated in dentate, caries-prone individuals.

A slow-release form of the drug provides rapid clinical and mycological improvement in patients with oral candidosis. This slow-release form, to be kept in the mouth and not swallowed, is sugar free and offers a prolonged contact time. It is more effective than the pastilles; the effects lasting for up to a week after treatment.[8] Nystatin has also been incorporated into a controlled drug delivery system and marketed as a mucosal oral therapeutic system (MOTS). In a study of HIV-infected patients with oral candidosis, the MOTS was more effective in lesion resolution than the oral nystatin pastilles.[2] Although the MOTS appear to be a significant step forward in the oral delivery of nystatin, further studies are warranted before it can be licensed for general use.

A number of topical preparations of nystatin can be used in the treatment of

Drug	Form	Dosage	Comments
Amphotericin B	Lozenge, 10 mg	Slowly dissolved in mouth 3–4 times per day after meals for 2 weeks minimum	Negligible absorption from gastrointestinal tract. Given intravenously for deep mycoses which may cause thrombophlebitis, anorexia, nausea, vomiting, fever, headache, weight loss, anaemia, hypokalaemia, nephrotoxicity, hypotension, arrhythmias, etc.
	Oral suspension, 100 mg/ml	Placed in the mouth after eating and retained near lesions 4 times a day for 2 weeks	
Nystatin	Cream	Apply to affected area 3–4 times per day	Negligible absorption from gastrointestinal tract. Nausea and vomiting at high doses.
	Pastille, 100 000 units	Dissolve one pastille in mouth slowly after meals 4 times a day, usually for 7 days	
	Oral suspension, 100 000 units	Apply after meals 4 times a day, usually for 7 days. Continue for several days after post-clinical healing	
Clotrimazole	Cream	Apply to the affected area 2–3 times daily for 3–4 weeks	Mild local effects. Also has anti-staphylococcal activity.
	Lozenge, 10 mg	Dissolve in mouth 5 times a day	
Miconazole	Oral gel	Apply to the affected area 3–4 times daily	Occasional mild local reactions. Also has antibacterial activity. Theoretically the best antifungal to treat angular cheilitis. Interacts with anticoagulants (warfarin), terfenadine, cisapride and astemizole. Avoid in pregnancy and porphyria.
	Cream	Apply twice daily and continue for 10–14 days after lesion has healed	
Ketoconazole	Tablets, 200–400 mg	Once or twice daily with food for 2 weeks	May cause nausea, vomiting, rashes, pruritus and liver damage. Interacts with anti-coagulants, terfenadine, cisapride and astemizole. Contraindicated in pregnancy and liver disease.
Fluconazole	Capsules, 50–100 mg	Once daily for 2–3 weeks	Interacts with anticoagulants, terfenadine, cisapride and astemizole. Contraindicated in pregnancy, liver and renal disease. May cause nausea, diarrhoea, headache, rash, liver dysfunction.
Itraconazole	Capsules, 100 mg	Taken once daily immediately after meals for 2 weeks	Interacts with terfenadine, cisapride and astemizole. Contraindicated in pregnancy and liver disease. May cause nausea, neuropathy, rash.

Table 2. *Examples of antifungal agents used in the treatment of oral candidoses (from various sources).*

oral candidosis. These include:

- dissolved vaginal pessaries (100 000 IU; one three times a day);
- dissolved pastille (100 000 IU; one pastille four times a day);
- ointment/cream to be applied to commissures three times a day;
- oral suspension (100,000 units/ml; four times a day, continued for several days after healing).

AZOLE ANTIFUNGAL AGENTS

These agents are classified into two groups:

- the imidazoles: clotrimazole, econazole, fenticonazole, isoconazole, ketoconazole, miconazole, sulconazole and tioconazole; and
- the triazoles: fluconazole and itraconazole.

The azoles are becoming increasingly popular in the management of oral candidosis. Indeed, fluconazole is the drug of choice in the treatment of oropharyngeal candidosis in HIV infection.

The azoles act by inhibiting the cytochrome p-450 enzymes that are involved in the synthesis of fungal cell membranes. The principal target is 14α-demethylase, which converts 14α-methylsterols to ergosterol in the cell membrane. The azoles cause alteration of the fungal cell membrane by blocking the 14α-demethylation step in the synthesis of ergosterol (depletion of ergosterol and accumulation of 14α-methylsterols); the membrane thus becomes permeable to intracellular constituents and a number of membrane-associated functions are disrupted. The imidazoles in addition interfere with fungal oxidative enzymes to cause lethal accumulation of hydrogen peroxide. The selective toxicity of the azoles is due to their differential affinity for mammalian

and fungal cytochrome p-450.[4–6] The triazoles are more specific for fungal cytochrome p-450 than mammalian, which means they have lower toxicity and fewer adverse effects than the imidazoles.[6]

Clotrimazole, econazole, fenticonazole, isoconazole, miconazole, sulconazole and tioconazole are all used for local treatment to varying extents. Miconazole can be also given by mouth for oral and intestinal infections. Ketoconazole, fluconazole and itraconazole are used for both local and systemic candidoses.

Clotrimazole

Clotrimazole has a broad spectrum of activity, anti-candidal as well as anti-staphylococcal, and is primarily fungistatic (Table 2). It is mainly used in the management of superficial infections in the oral cavity, skin and vagina caused by *Candida*. It is particularly effective in managing oropharyngeal candidosis, especially in immunocompromised individuals, such as HIV-infected patients and transplant recipients. As a cream it is particularly useful in the treatment of angular cheilitis due to its dual action on both yeasts and staphylococci.[2,7]

Adverse Reactions

When applied topically clotrimazole is well tolerated. Adverse reactions are minor and rare, and include local skin irritation, vomiting and nausea. Abdominal cramps, increased urination and elevated liver SGOT levels have also been reported.[5]

Preparations

Clotrimazole is available as a 1% cream, which can be applied to commissures three times a day. Other forms (lozenges, vaginal creams and vaginal tablets) are also available for topical use.[6] The most common method of delivery of clotrimazole in oral candidosis is the use of a lozenge, available in 10 mg units which must be dissolved in the mouth five times a day. Slow dissolution in the mouth is thought to result in binding of clotrimazole to the oral mucosa, from which it is gradually released to maintain at least fungistatic concentrations for several hours. Patient compliance is said to be enhanced by the more pleasant taste of clotrimazole compared with the bitter flavour of certain nystatin preparations. This is due to the prescription of nystatin tablets and pessaries, which are specifically not formulated for oral use.[2]

Miconazole

Miconazole, like clotrimazole, has a broad spectrum of activity against fungi, including *C. albicans*. It is also effective against some Gram-positive bacteria such as staphylococci and hence useful in the management of angular cheilitis where concurrent bacterial and fungal infection may be present. Miconazole can be given topically, intravenously or intrathecally.

Miconazole is effective in all types of oral candidosis including chronic mucocutaneous candidosis. However, the systemic use of miconazole has been largely superseded by the availability of other less toxic drugs such as ketoconazole and fluconazole.

Adverse Effects

Adverse effects of topical use of miconazole are uncommon. Burning and skin maceration can occur following cutaneous use. Itching, burning, urticaria, headache and cramps have been associated with the use of vaginal preparations. The most common effect after intravenous use is thrombophlebitis. Nausea may develop in some cases. Rarely, anaphylaxis and cardiotoxicity can occur.

Oral anticoagulants such as warfarin are widely prescribed in the management of deep vein thrombosis, pulmonary embolism, and those with prosthetic heart valves. Drugs of the azole group are known to enhance the anticoagulant effect of warfarin when given systemically, and it has recently been reported that the concurrent use of warfarin and miconazole oral gel for the treatment of oral candidosis resulted in potentially life-threatening derangement of warfarin anticoagulation.[9]

a

b

Figure 1 (a, b). *Miconazole lacquer used in the treatment of* Candida*-associated denture stomatitis. The commercial pack.*

Preparations

Tablets, oral gel (Daktarin 24 mg/ml), intravenous injections, topical and vaginal preparations are available. Cream is a very effective mode of treatment for angular cheilitis lesions caused by *Candida* and *Staphylococcus aureus* (Table 2). Also, the drug can be administered empirically when a microbial report is not available or when it is not possible to identify the exact nature of the infective agent.[2]

Miconazole has been formulated into a lacquer, which is effective in the treatment of *Candida*-associated denture stomatitis (Dumicoat 50 mg/g; Figure 1). Application of the contents of one bottle to the upper surface of the upper denture after thorough cleansing and drying, repeated twice at intervals of one week, is recommended. Studies have shown that a single application of miconazole lacquer over the fitting surface of a denture, as a slow delivery agent, is capable of considerably reducing the numbers of *Candida* on the denture surfaces for a substantial period of time.[10]

Ketoconazole

Ketoconazole is effective against a wide spectrum of fungi and yeasts, including

Candida spp. and, unlike other imidazoles, it is readily absorbed after oral administration. It has been used in the management of cutaneous, oral, oesophageal and vaginal candidal infections for a number of years.[6] Ketoconazole has no place in the treatment of primary oral candidoses; its main indication is for secondary oral candidoses such as in chronic mucocutaneous candidosis.[2] However, triazoles such as fluconazole are increasingly being used for this purpose.

Mucosal candidoses of the mouth and oesophagus respond well to ketoconazole, although there is little evidence to suggest that it is better than nystatin in treating infections in granulocytopenic patients.[5] On the contrary, ketoconazole shows better results than nystatin in reducing oropharyngeal candidal colonization in mice depleted of CD4+ lymphocytes.

Adverse Effects

The most common adverse reactions to ketoconazole are gastrointestinal intolerance with nausea and vomiting. Hepatotoxicity is not uncommon but is generally asymptomatic with reversible elevation of serum transaminase (Table 2). Care must be taken during usage as fatal hepatotoxicity and nephrotoxicity have been reported: liver function tests should be performed throughout any prolonged ketoconazole therapy and treatment should be discontinued in patients with progressively increasing transaminase levels.[11]

Ketoconazole blocks steroid synthesis in host cells, with subclinical adrenocorticosteroid deficiency. Depression of testosterone biosynthesis can manifest as painful gynaecomastia, loss of libido and sometimes loss of hair.[4] It is also a potential teratogen. Because of the possible effects on the liver and steroid metabolism, it should not be used as a first-line treatment for mucosal or cutaneous infections.

Drug Interactions

Many drugs interact with ketoconazole. For instance, it is capable of decreasing the hepatic metabolism of non-sedative antihistamines such as terfenadine and astemizole, which can lead to increased levels of these drugs and their metabolites, with resultant arrhythmias, tachycardia and (rarely) death. Similarly, ketoconazole can suppress the metabolism of cyclosporin, leading to elevated concentrations and accompanying profound immunosuppression and renal dysfunction, which may be life-threatening. Absorption of ketoconazole may be reduced by antacids and H_2-receptor blockers such as cimetidine and ranitidine. Rifampin, a potent inducer of hepatic metabolizing enzymes, can decrease serum ketoconazole concentrations.[6]

Preparations

Tablets, suspensions and creams are available; 2% cream may be applied to commissures three times a day in chronic hyperplastic candidosis. Depending on the infection the standard systemic dosage is 200–400 mg daily.[7]

Fluconazole

Fluconazole is water soluble and does not require a low gastric pH for absorption; it is poorly bound to plasma protein and is eliminated by renal excretion. An important aspect of fluconazole is that it reaches high concentrations in the normal and inflamed central nervous system.[5]

Fluconazole has a broad spectrum of antifungal activity. It is active against most strains of *C. albicans* but is less active against non-*albicans* species, particularly *C. krusei* and *C. glabrata*, which are intrinsically resistant to the drug.[3] *In-vitro* sensitivity to fluconazole is highly dependent on the test conditions and it is not unusual to obtain very high MIC values *in vitro* for strains that are responsive to the drug *in vivo*. Further, although fluconazole is remarkably more effective than ketoconazole in the treatment of candidal infections, its growth-inhibitory activity against *C. albicans in vitro* is considerably less than that of ketoconazole. Interestingly, fluconazole (400 mg daily) has been proved effective against oropharyngeal and oesophageal candidosis in a patient with endocrinopathy syndrome, even though the infecting *C. albicans* was resistant to azole antifungals *in vitro*.[12]

Fluconazole is given either orally or intravenously and is well absorbed after oral administration. What distinguishes fluconazole from many other azoles is this excellent absorption from the gastrointestinal tract, and its very long serum half-life of 27–37 hours. It also differs from other azole antifungals in being weakly protein bound in serum, which explains its excellent penetration into most body sites. Unlike other azoles, fluconazole is not metabolized in humans, and is excreted largely through the kidney approximately 80% unchanged.[4,5] It follows therefore, that the effect of fluconazole on hepatic function is negligible compared with other azoles, which are metabolized mostly in the liver.

The high systemic absorption of fluconazole has been useful in treating oral candidosis in HIV-infected patients and it is now considered the drug of choice for candidoses in HIV disease. Weekly fluconazole (200 mg) appears a safe and effective way of preventing oropharyngeal candidosis, and this regimen has a useful role in the management of HIV-infected patients who are at risk for recurrent mucosal candidosis.[13] Further, when HIV-infected patients with oropharyngeal candidosis were randomly assigned to receive 14 days of therapy with liquid suspension of fluconazole (100 mg, daily) or liquid nystatin (50 000 IU, four times daily), it was found that the systemic fluconazole therapy was more effective than the topical nystatin therapy in treating oral candidosis and provided a longer disease-free interval before relapse.[14] Fluconazole and clotrimazole were equally effective in treating thrush in HIV-infected individuals, but mycological cure occurred more often with fluconazole. Administration of fluconazole in capsule form has proved effective in the prophylaxis and treatment of mucosal candidosis in immunocompromised patients, and a topical effect could be obtained in oropharyngeal candidosis with a fluconazole suspension, possibly due to

its oral delivery via crevicular exudate and saliva. It has been shown that, after a single dose, 100 mg fluconazole achieved higher salivary concentrations than did 400 mg ketoconazole. This may explain why fluconazole has a higher clinical efficacy in the treatment of oropharyngeal candidosis than ketoconazole.

Fluconazole is effective in resolving palatal candidosis at a dose nine times lower than ketoconazole. It has been successfully used in the management of candidal leukoplakia, cheilo candidosis and oral candidosis in bone marrow recipients, in malignant disease and in acute leukaemia. In patients with *Candida*-induced denture stomatitis, fluconazole is especially effective when administered along with an oral antiseptic such as chlorhexidine.

Adverse Effects

Fluconazole is well tolerated and adverse effects such as nausea, headache, gastrointestinal discomfort and abdominal discomfort are usually mild and subjective (Table 2). It may cause elevation of liver enzymes and an allergic rash. Jaundice and liver dysfunction have been seen in some patients treated with fluconazole in HIV-related oral candidal infection. It is prudent to avoid fluconazole in pregnancy as it may cause embryotoxicity.

Drug Interactions

Although the drug interactions are fewer than those of ketoconazole, fluconazole nevertheless has significant interactions with several medications. The structural analogy of these two azoles indicates that non-sedating antihistamines such as terfenadine and astemizole should not be administered with fluconazole. By decreasing the hepatic metabolism of several agents, fluconazole can bring about high serum concentrations of these agents if administered concurrently. For instance, decreased clearance of cyclosporin may result in significant immunosuppression, leukopenia and renal dysfunction; similar interactions with phenytoin, warfarin and hypoglycaemics can produce toxic phenytoin concentrations in serum, prolonged prothrombin times and hypoglycaemia, respectively.[6]

Preparations

Fluconazole is available in capsule and intravenous formulations. For adults, the oral and intravenous dosage for treating oropharyngeal candidosis is 50 mg daily for 7–14 days: 50 mg daily for 14–30 days is recommended for oesophageal candidosis[4] (Table 2).

Itraconazole

Itraconazole is a water insoluble and lipophilic drug, and requires a lower pH for ionization than ketoconazole; it is highly protein bound and excreted in bile. It is well absorbed after oral administration and has a wide spectrum of activity, including *Candida* spp. It is effective in various superficial mycoses including oral candidosis due to *C. albicans*, *C. krusei* and *C. glabrata.* As the last two are intrinsically resistant to fluconazole, itraconazole is ideal for the management of fluconazole-resistant *Candida*.[15]

Adverse Effects

Generally, itraconazole is well tolerated although gastrointestinal disturbances, headache and dizziness have been reported. Transient asymptomatic transaminase elevations and hypokalaemia have also been reported.

Drug Interactions

Cyclosporin clearance is reduced by itraconazole, and serum concentrations of the former should be monitored to prevent potentially major complications. Similarly, simultaneous use of itraconazole and terfenadine or astemizole should be avoided. Itraconazole has been reported to decrease digoxin clearance, and serum digoxin concentrations should be measured during concurrent therapy.[6]

Preparations

Itraconazole is available in capsule and oral solution forms. The adult oral dose in oropharyngeal candidosis is 100 mg daily for 15 days[4] (Table 2). Compliance with the oral solution may be better than for the capsule formulation because patients with severe oropharyngeal candidosis will find it easier to swallow.

DISADVANTAGES OF USING AZOLES

- All the azoles are fungistatic, not fungicidal. This is therefore an important consideration when treating chronic infections in immunocompromised patients, such as those with AIDS, and when treating infections at critical sites (e.g. candidal meningitis).
- None of the azoles is entirely benign and they are all expensive.
- Hepatotoxicity may be common to all of them, and the potential for endocrine toxicity exists, particularly at higher doses.[6]

Resistance

The emergence of resistance to the triazoles, particularly to fluconazole, is disturbing. It is now a serious clinical problem in patients with HIV disease.[3] Candidal resistance to fluconazole is also seen in intravenous drug users and in those with systemic candidosis, such as patients with chronic mucocutaneous candidosis. There is also evidence of transfer of resistance between fluconazole-resistant *C. albicans* and non-*albicans* isolates to ketoconazole, miconazole and itraconazole. Fluconazole resistance appears to result from mutation.

Three main resistance patterns of fluconazole have been identified.

1. A progressive increase in the MIC over weeks or months, and infection with the same *Candida* strain.
2. A sudden or rapid failure of therapy, with the emergence of a new resistant strain.
3. Acquisition of a new and resistant organism from a sexual partner.

Fluconazole resistance may also appear in patients who have received no fluconazole therapy. It has been suggested that transfer of fluconazole-

resistant *Candida* between patients is due to sexual activity.

Previous fluconazole use and severe immune defects are risk factors for fluconazole resistance. There is also evidence that intermittent or low-dose fluconazole therapy is more likely to result in emergence of resistance than continuous or high-dose therapy.

Azole resistance can also arise because of changes in the candidal target enzyme 14α sterol demethylase, reduced fungal membrane permeability to azoles, or increased efflux of azoles from the organisms.[3]

INCORPORATION OF ANTIFUNGAL AGENTS INTO DENTURE MATERIALS

The recalcitrant nature of *Candida*-associated denture stomatitis has prompted attempts to incorporate antifungals such as nystatin into dental materials, and there has been some degree of success. For instance, nystatin has been incorporated into denture liners; miconazole and ketoconazole are effective in suppressing candidal growth when combined with tissue conditioners.

When the feasibility of a sustained-release delivery system for the treatment of denture stomatitis was studied *in vitro*, using four antifungals (chlorhexidine gluconate, clotrimazole, fluconazole and nystatin) incorporated into a tissue conditioner, it was found that all drugs were released from the tissue conditioner matrix with simultaneous inhibition of candidal growth.[16]

These reports indicate the *in vitro* inhibitory effect of antifungals on candidal growth, the nutrient-rich environment, and the cleansing effect of the oral cavity, is likely to minimize the beneficial action *in vivo*. Further, the dose of the agents used in these *in vitro* studies appear to be high, costly and impracticable in clinical situations. In addition, the possible emergence of resistant organisms due to the constant presence of the drugs in the oral environment cannot be ruled out.

However, despite these caveats, slow-release agents and the related improvements in technology may be harnessed in future for incorporating antifungals into dental materials.

Organismal factors	Drug factors	Environmental factors
● Phenotypic and genotypic characteristics of the organism	● Mode of action	● Type of growth medium
● Inoculum size	● Exposure time	● pH of the growth medium
● Growth phase of the organism at the time of exposure	● Concentration	● Incubation temperature
	● Combined use of antimicrobials	● Mechanical shaking of the culture

Table 3. *Factors that affect the post-antifungal effect of an antimycotic agent.*

OTHER AGENTS USED IN ORAL CANDIDOSIS

A vast array of new antifungal agents – amorolfine, natifine, terbinafine, tolaftate, rilopirox, cilofungin, pradimycin, voriconazole and benanomicin A – are either being marketed or undergoing extensive clinical trials.

Chlorhexidine has been used as an adjunct in the management of oral candidoses since its introduction in the 1970s. For instance, 0.2% chlorhexidine gluconate has been successfully employed as a mouth-rinse in the treatment of *Candida*-associated denture stomatitis and in pseudomembranous candidosis, while 2% suspension is used as an overnight denture disinfectant.

Chlorhexidine gluconate has a bimodal action on *Candida*:

- It is fungicidal even at very low concentrations.
- It is capable of significantly suppressing candidal adhesion to both inorganic and organic substrates.

Many studies have clearly demonstrated this second property, particularly in suppressing candidal adhesion to denture acrylic surfaces. Further, exposure of buccal epithelial cells to chlorhexidine gluconate significantly reduces the adhesion of *Candida* to buccal cells.

Its multifaceted anti-candidal action has prompted many clinicians to propose chlorhexidine mouthrinse as an appropriate alternative to conventional antifungals in the management of oral candidosis.[17] However, chlorhexidine should not be used simultaneously with nystatin as they interact, forming chlorhexidine–nystatin complexes and rendering both agents ineffective.[18]

POST-ANTIFUNGAL EFFECT

Suppression of yeast growth that persists following limited exposure to antifungal agents has been termed the post-antifungal effect (PAFE).[19] It must be emphasized that the PAFE arises due to exposure of yeasts to antifungals for a short duration, rather than a continuous exposure for a longer period of time.

Suppression of microbial growth is an inevitable accompaniment during the PAFE period. However, what is more interesting and intriguing is the associated weakening of microbial virulence, which may influence the host–parasite relationship. In clinical terms, the main significance of the PAFE is the impact that it may have on the dosage regimens of the antimycotics.[19] For instance, agents with longer PAFE could be administered at longer intervals and vice versa, without loss of efficacy and with lower frequency of adverse effects. The duration of the PAFE and even the presence or absence of the PAFE is influenced by a number of factors (summarized in Table 3).

There is scant information on the PAFE in *Candida*. Recent reports suggest that significant PAFE were produced by limited exposure of *Candida* to nystatin and amphotericin B although little (if any) PAFE has been observed with the imidazoles and fluconazole.[20,21]

It has been shown that in bacteria the post-antibiotic effect is not restricted to suppression of bacterial growth: accompanying effects include changes in cell morphology, inhibition of enzyme and toxin production, loss of adhesive properties and reduction of cell surface hydrophobicity and increased susceptibility to host humoral and cellular immunity. Many of these effects are probably overlapping and closely linked. Despite these observations, the impact of the PAFE on cellular attributes of *Candida* have not yet been extensively investigated. However, it has been demonstrated that brief exposure to the polyenes (nystatin and amphotericin B) and ketoconazole perturbs germ tube formation in *C. albicans*, although fluconazole exerted no such effect during the PAFE period.[22] Further, all these drugs were also able to inhibit adhesion of *Candida* to denture acrylic surfaces significantly during the PAFE period.[23] Similar suppression of candidal adhesion to buccal epithelial cells were elicited by these antimycotics during this period.[24]

Cell surface hydrophobicity is a complementary factor involved in yeast adhesion to host surfaces and is considered an important pathogenic attribute of *Candida*. Recent studies have disclosed that the polyenes and ketoconazole are capable of effectively minimizing the relative cell surface hydrophobicity of oral *C. albicans* isolates during the PAFE period, but limited exposure to fluconazole had no such effect.[25]

CONCLUSION

A major challenge in the management of patients with oral candidosis, especially immunocompromised patients, is to make a sensible selection from a number of antimycotics currently available. The mechanism of action of the drug should be considered when selecting an antimycotic – this is vital when treating patients who are chronically immunocompromised, such as those with HIV infection, for whom azoles (especially fluconazole) should be the drug of choice. The polyenes should be routinely used in empirical therapy of primary oral candidoses as inappropriate use of the more useful azoles as the first-choice drug may result in emergence of resistant strains, thus rendering the drug worthless. Most antifungals cause hepatotoxicity, and the potential for endocrine toxicity exists, particularly at high doses. Another consideration is the cost.

By prescribing these agents according to their pharmacodynamic properties, it is possible to achieve maximal antifungal activity while simultaneously minimizing patient exposure. Clearly, an ideal antimycotic for treating oral candidoses is not yet available. But certain agents are better than others with respect to efficacy, tolerability, patient compliance and cost effectiveness. Most importantly, antifungal agents, however potent they are, may be rendered ineffective in the long term if the underlying predisposing factors are not attended to in the first instance.

REFERENCES

1. Epstein JB. Antifungal therapy in oropharyngeal mycotic infections. *Oral Surg Oral Med Oral Pathol* 1990; **69:** 32–41.
2. Samaranayake LP, Ferguson MM. Delivery of antifungal agents to the oral cavity. *Adv Drug Del Rev* 1994; **13:** 161–179.
3. White TC, Marr KA, Bowden RA. Clinical, cellular and molecular factors that contribute to antifungal drug resistance. *Clin Microbiol Rev* 1998; **11:** 382–402.
4. Lambert H, O'Grady FW. Antifungal agents. In: Lambert H, O'Grady FW, eds. *Antibiotics and Chemotherapy*. London: Churchill Livingstone, 1997: pp.27-37.
5. Finch RG, Snyder IS. Antifungal drugs. In: Craig CR, Stitzel RE, eds. *Modern Pharmacology*. Boston: Little Brown, 1994; pp.647–656.
6. Lesse AJ. Antifungal agents. In: Smith CM, Reynard A, eds. *Essentials of Pharmacology*. Philadelphia: Saunders, 1995; pp.404–411.
7. Greenspan D. Treatment of oropharyngeal candidosis in HIV-positive patients. *J Am Acad Dermatol* 1994; **31:** S51-S55.
8. Greenspan D, Dodd CL, MacPhail LA, Encarnacian MJ, Greenspan JS. *MOTS-nystatin for Treatment of Oral Candidiasis in HIV Infection*. Boston: American Association for Dental Research, 1992.
9. Pemberton MN, Sloan P, Ariyaratnam S, Thakker NS, Thornhill MH. Derangement of warfarin anti-coagulation by miconazole oral gel. *Br Dent J* 1998; **184:** 68–69.
10. Dias AP, Samaranayake LP, Lee MT. Miconazole lacquer in the treatment of denture stomatitis: clinical and microbiological findings in Chinese patients. *Clin Oral Invest* 1997; **1:** 47–52.
11. Samaranayake LP, MacFarlane TW, eds. *Oral Candidosis*. Oxford: Wright, 1990.
12. Field EA, Millns B, Pearce PK, Martin MV, Parkinson T, Hitchcock CA. Fluconazole therapy of oropharyngeal candidiasis in a patient with multiple endocrine failure does not correlate with *C. albicans* susceptibility to fluconazole *in vitro*. *J Med Vet Mycol* 1996; **34:** 205–208.
13. Schuman P, Capps L, Peng G *et al*. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection. A randomized, double-blind, placebo-controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. *Ann Intern Med* 1997; **126:** 689–696.
14. Pons V, Greenspan D, Lozada-Nur F *et al*. Oropharyngeal candidiasis in patients with AIDS: randomized comparison of fluconazole versus nystatin oral suspensions. *Clin Infect Dis* 1997; **24:** 1204–1207.
15. Laguna F, Rodriguez-Tudela JL, Martinez-Suarez RP *et al*. Patterns of fluconazole susceptibility in isolates from human immunodeficiency virus-infected patients with oropharyngeal candidiasis due to *Candida albicans*. *Clin Infect Dis* 1997; **24:** 124–130.
16. Schneid TR. An *in vitro* analysis of a sustained release system for the treatment of denture stomatitis. *Spec Care Dent* 1992; **12:** 245–250.
17. Giuliana G, Pizzo G, Milici ME *et al*. *In vitro* antifungal properties of mouth rinses containing antimicrobial agents. *J Periodontol* 1997; **68:** 729–733.
18. Barkvoll P, Attramadal A. Effect of nystatin and chlorhexidine gluconate on *C. albicans*. *Oral Surg Oral Med Oral Pathol* 1989; **67:** 279–281.
19. Craig. WA, Gudmundsson S. The postantibiotic effect. In: Lorian V, ed. *Antibiotics in Laboratory Medicine*. Baltimore: Williams &Wilkins, 1996; pp.296–329.
20. Ellepola ANB, Samaranayake LP. The post antifungal effect (PAFE) of antimycotics on oral *Candida albicans* isolates and its impact on candidal adhesion. *Oral Dis* 1998; **4:** 260–267.
21. Ellepola ANB, Samaranayake LP. The *in vitro* post-antifungal effect of nystatin on *Candida* species of oral origin. *J Oral Pathol Med* 1999; **28:** 112–116.
22. Ellepola ANB, Samaranayake LP. The effect of limited exposure to antifungal agents on the germ tube formation of oral *Candida albicans*. *J Oral Pathol Med* 1998; **27:** 213–219.
23. Ellepola ANB, Samaranayake LP. Adhesion of oral *Candida albicans* isolates to denture acrylic following limited exposure to antifungal agents. *Arch Oral Biol* 1998; **43:** 999–1007.
24. Ellepola ANB, Samaranayake LP. Adhesion of oral *Candida albicans* to human buccal epithelial cells following limited exposure to antifungal agents. *J Oral Pathol Med* 1998; **27:** 325–332.
25. Ellepola ANB, Samaranayake LP. The effect of limited exposure to antimycotics on the relative cell-surface hydrophobicity and the adhesion of oral *Candida albicans* to buccal epithelial cells. *Arch Oral Biol* 1998; **43:** 879–887.