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REVIEW ARTICLE

Antimicrobials as a contributory factor in oral candidosis – a brief overview

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The advent of the human immunodeficiency virus infection and the increasing prevalence of compromised individuals in the community due to modern therapeutic advances have resulted in a resurgence of opportunistic infections, including oral candidosis, which is by far the most common oral fungal infection in man. Broad-spectrum antibiotics used in the treatment of a wide range of disease conditions have also been attributed as a predisposing factor of oral candidosis. In this mini review we discuss the research findings on the relationship between antibiotics and oral candidosis and possible mechanisms of pathogenicity following such therapy.
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Introduction

Oral candidosis in the form of thrush has been well known since the time of Hippocrates (Samaranayake, 1990). The disease has assumed a renewed importance with the introduction of broad-spectrum antibiotics and immunosuppressants and lately with the advent of acquired immune deficiency syndrome (AIDS) (Arendorf *et al*, 1998). Oral candidosis is one of the earliest manifestations of AIDS (Klein *et al*, 1984) and more than 90% of HIV-infected individuals develop oral candidosis which is by far the most frequent oral manifestation in these patients (Arendorf *et al*, 1998). Furthermore, since the first clinical definition of AIDS, the CDC/WHO have recognized oral candidosis as one of the major opportunistic infections and an indicator of the disease (Ellepola and Samaranayake, 2000a). Oral candidosis manifests in a variety of clinical guises ranging from pseudomembranous (thrush), erythematous, linear gingival erythema associated with HIV infection to *Candida*-associated denture stomatitis and median rhomboid glossitis and angular stomatitis, possibly of multifactorial origin (Ellepola and Samaranayake, 2000a).

Candida is a normal oral commensal (Samaranayake, 1990) and the majority of us carry *Candida* species in the oral cavity. Nevertheless, only a few develop oral candidosis in one form or the other. The translation of this endogenous commensal to the disease-causing 'parasite' may be associated with factors other than the pathogenic attributes of the organism itself, which is rather unique compared with most of the other infectious diseases, where the virulence of the organism is considered to be the key factor in the pathogenesis. Hence *Candida* species are strictly opportunistic. It could be stated with little doubt that neither the superficial nor the systemic forms of *Candida* infections could be initiated in the absence of underlying pathology.

Broad-spectrum antibiotic therapy is considered as one of the most common iatrogenic factors which initiate oral candidosis (Epstein and Polsky, 1998). Hence Lehner (1966), in his early classification of oral candidosis, categorized 'antibiotic sensitive tongue' or 'antibiotic sore tongue' consequent to broad-spectrum antibiotic therapy. The latter is characterized by a raw, erythematous dorsum of the tongue which may or may not be painful. This condition now falls under the category of erythematous candidosis as per the new classification of Samaranayake (1991). Although there is scant evidence as to the cause and effect relationship between antibiotics, *Candida* and acute atropic candidosis, there is little or no doubt that broad-spectrum antibiotics contribute to *Candida* overgrowth rather than narrow-spectrum antibiotics. The most common broad-spectrum drug associated with oral candidosis is tetracycline (Samaranayake, 1990). However, other drugs such as metronidazole, ampicillin, etc., have been occasionally attributed as agents that cause oral candidosis (Simjee *et al*, 1985; Carr *et al*, 1998).

Tetracyclines are bacteriostatic antibiotics that inhibit protein synthesis. They have a wide spectrum of action

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against gram-positive and gram-negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasma, and against some protozoa. It is used in the treatment of acne, exacerbation of chronic bronchitis, and treatment of chronic periodontitis. Tetracyclines enter microorganisms in part by passive diffusion or active transport and inside the cell, they bind reversibly to the 30s subunit of bacterial ribosome and prevent the addition of amino acids to the growing peptide, thus inhibiting protein synthesis (Seymour and Heasman, 1995).

Metronidazole is also a bacteriostatic drug which enters and converts into active form by reducing its nitro group in anaerobic microorganisms, thus preventing nucleic acid formation (Schmadel and McEvoy, 1990). It is effective against anaerobes such as Bacteroides (Diniz *et al*, 2003) and is usually used in the treatment of diarrhoea (Vasa and Glatt, 2003), anaerobic, and protozan infections (Diniz *et al*, 2003).

This brief review is an attempt to discuss the research findings on the relationship between antibiotics and oral candidosis.

Research findings

The most common broad-spectrum antibiotic associated with oral candidosis is tetracycline and a number of investigations have been conducted to assess this relationship (Table 1). Studies have been conducted in a longitudinal prospective manner, which demonstrated a higher oral carriage of the order of twofold, although only one such study reached statistical significance ($P < 0.001$) (McVay and Sprunt, 1951). *Candida* carriage was assessed by the swabbing technique in all the investigations mentioned in Table 1. Hence studies using the more accurate concentrated oral rinses or imprint sampling methods should be considered (Samaranayake *et al*, 1986). McKendrick *et al* (1967) were the only group who studied antibiotic-treated and antibiotic-untreated patients of equal clinical status, over a period of 6 months using a sampling method similar to the oral rinse technique mentioned above. However, they could not demonstrate a significant difference in the oral carriage of *Candida* in tetracycline- and placebo-treated chronic bronchitis. Large-scale surveys by Walker *et al* (1979) and Caldwell and Cluff (1974) who studied superficial fungal infections in a total of 21 842 hospital patients treated with a variety of antibiotics have found that the highest prevalence of superficial candidosis was in patients treated with aminoglycosides and the lowest was in those on penicillin and tetracycline.

Minocycline, a long-acting tetracycline, is widely used in the management of acne vulgaris. There is considerable clinical evidence to suggest that minocycline enhances the development of oral candidosis infection. For instance, minocyclines are accountable for oral candidosis in about 13.6% of patients on these drugs for acne (Goulden *et al*, 1996). The tetracycline family of antibiotic drugs has been shown to be effective in the treatment of immunobullous disorders such as pemphigus vulgaris, pemphigus foliaceous and bullous pemphogoid. A recent study revealed that about 22% of patients on such therapy developed oral candidosis because of minocycline therapy (Ozog *et al*, 2000).

It is now known that the effect of metronidazole on vaginal yeast carriage is significantly greater than that of tetracycline (Odds, 1988) and it remains to be determined whether metronidazole, now commonly prescribed for oral infections, has a similar effect on the oral yeast flora. In a study performed by Simjee *et al* (1985), out of 48 patients who were treated for amoebic liver disease with metronidazole and tinidazole, the only side effect reported was oral candidosis which developed in two patients in each drug group. A study of 30 patients who received cancer chemotherapy in protected environment units showed that yeasts were recovered from 80% of patients after antibiotics compared with the 17% before treatment. Of the 19 yeasts cultured 16 were *Candida albicans* (Johnston and Bodey, 1972).

Animal studies

The relationship between antibiotics (especially tetracyclin) and oral candidosis in animal models has been studied by a few workers. Animals such as Sprague–Dawley rats and mice have been used for these experiments and some examples of which follows. Allen *et al* (1985a,b) used two groups of Sprague–Dawley rats to investigate the mucosal candidosis consequent to tetracyclin treatment. Candidosis was induced in rats by intraoral inoculation following treatment with tetracycline solution and double distilled water. After 20 weeks, inspection of tongues showed similar lesions on both

Table 1 Effect of tetracycline therapy on oral carriage of *Candida* species

		% *Candida* carriers			
Study population	*No. individuals*	*Pretreatment*	*Post-treatment*	*Increase (fold)*	*Reference*
Healthy adults	12	0	23[a]	–	Meads *et al* (1951)
Hospital patients	30	20	70	3.5*	McVay and Sprunt (1951)
Chest patients	24	21	25	1.2**	Tewari and Flecher (1966)
Hospital patients	50	16	30	1.9**	Shastry *et al* (1969)
Outpatients	122	15	16	1.1**	Mohapatra *et al* (1969)
Hospital patients	34	15	38	2.6**	Mistry and Apte (1971)

[a]Based on multiple cultures from same subjects over study period. Modified from Odds (1988).
*$P < 0.001$; **not significant.

groups, which were confirmed histologically. No significant difference in the number of lesions in both groups was noted (Allen *et al*, 1985a,b). The aforementioned studies reconfirmed the studies of Clark (1971), Russell and Jones (1973) and Russell *et al* (1976) who were able to produce minimal effects. A murine model for oropharyngeal candidosis using tetracycline hydrochloride and cortisone had been described by Kamai *et al* (2001). Tetracycline had no effect on the number of *C. albicans* while cortisone acetate induced a high level of infection (Kamai *et al*, 2001). In contrast to previous reports, continuous oral inoculation (34 weeks) of *C. albicans* was done in SPF rats after initial tetracycline medication. Fifty percent of animals harbored *C. albicans* in the mouth, and 25% of them demonstrated pseudomycelial penetration of the mucosa. More than 90% of the candidal foci were found in non-keratinized areas while only the dorsal surface of the tongue showed foci of infection (Fisker *et al*, 1982a). In a similar study, tetracycline was given to mice in drinking water, a day prior to inoculation with *C. albicans* and evaluated after 3 days. Tetracycline treatment of mice resulted in oral candidosis with a large number of viable *Candida* compared with untreated controls (Takakura *et al*, 2003). Studies have also shown that orally administered tetracycline in rats enhanced candidal colonization and invasive infection (Jones *et al*, 1976; Fisker *et al*, 1982b; Hassan *et al*, 1985).

Pathogenesis

There is little detailed evidence that in the healthy state, the commensal oral microflora play an important role in preventing the overgrowth of *Candida*. Much of the evidence is indirect and there is uncertainty about the mechanism involved. The commensal microflora could regulate yeast numbers by inhibiting the adherence of yeasts to oral surfaces (Samaranayake, 1990). However, other mechanisms include competition between oral bacteria and yeasts for the availability of nutrients. Evidence that the former mechanisms exist and function *in vivo* tends to be indirect, and is based on the commonly accepted view that the inhibitory activity of certain antibiotics (especially tetracycline) on the commensal flora permits yeast overgrowth and subsequent acute candidosis. However, caution must be exercised in readily accepting this rather simplistic theory. Further support for the idea that bacteria present in mixed saliva compete successfully with yeasts for available nutrients and thereby suppress yeast growth or adhesion is provided by Wu and Samaranayake (1999), who reported that yeast growth occurred when glucose was added *in vitro* to mixed saliva, creating a nutrient-excess condition. Studies, using an agar disk screening method developed by MacFarlane and Makrides (1982) have shown that many strains of *Streptococcus salivarius*, *Streptococcus sanguis* and *Lactobacillus casei* supressed the growth of *C. albicans*. A similar result was reported by Krasner *et al* (1956) using a variety of lactobacillus species isolated from the mouth of humans. The latter data support the currently popular 'probiotic therapy' in the management of yeast infections in the gut and other regions of the body.

The persistence of *Candida* on mucosal surfaces requires fungal adherence to epithelial cells. A close correlation was found between adhesion of *Candida* species and their ability to cause infection (Ray *et al*, 1984; Klotz and Penn, 1987; Segal *et al*, 1988). Evidence that the commensal bacterial flora may prevent the colonization and overgrowth of *Candida* in the oral cavity by inhibiting yeast adherence to oral surfaces was first reported by Liljemark and Gibbons (1973). They speculated that the oral colonization of gnotobiotic mice by either *S. salivarius* or *Streptococcus mitior* suppressed subsequent attempts at oral colonization with *C. albicans*. Similar results have been obtained *in vitro* by pretreating acrylic and HeLa cell monolayers with whole bacterial cells and culture supernatants of various streptococcal species (*S. salivarius*, *Streptococcus mutans*, *S. sanguis*, *S. mitior*) and *L. casei* prior to performing adherence assays (Samaranayake *et al*, 1980; Makrides and MacFarlane, 1982; Samaranayake and MacFarlane, 1982). The study by Velichko and Karaev (1987) on tetracycline with respect to its effect on *Candida* adhesion to epitheliocytes of oral mucosa showed that administration of 0.1% solution of the antibiotic to the mice for 4 days increased the candidal adhesive number and adhesive index by up to 175 and 250% respectively.

There is also evidence that lipoteichoic acid from *L. casei* and *S. salivarius* perhaps complexed with surface fibrils, following its denudation from the bacterial cell surfaces, may be involved in the inhibition of yeast adherence to buccal epithelial cells (BEC). Other studies have also shown that both gram-positive and gram-negative aerobes and anaerobes such as *S. salivarius*, *Escherichia coli* and *Porphyromonas gingivalis* significantly suppressed adhesion of *C. albicans* to BEC (Nair and Samaranayake, 1996a). The effect of bacteria on the adhesion of *Candida* to BEC was investigated with a modified membrane filter system. Candidal adhesion was significantly reduced on preexposure to *S. sanguis* and *P. gingivalis* (Nair and Samaranayake, 1996a) and the adhesion of yeasts to acrylic surfaces is modulated both by the quantity and quality of preexisting bacterial flora on acrylic surfaces (Nair and Samaranayake, 1996b).

Whilst the foregoing indicate that a number of mechanisms that pertain to specific groups of bacteria may prevent yeast colonization of epithelial surfaces, there are data to suggest that yeast colonization may be indirectly promoted through coaggregation and agglutination mechanisms between bacteria and yeasts. Accordingly, Verran and Motteram (1987) reported that the presence of *S. sanguis* and *S. salivarius* on non-acrylic plastic surfaces enhanced the subsequent adherence of *C. albicans*. The *in vivo* coaggregation described by Bagg and Silverwood (1986) between *C. albicans* and various oral bacteria including *S. sanguis*, *S. salivarius*, *S. mutans*, *Fusobacterium nucleatum*, and *Actinomyces viscosus* also suggested that oral bacteria may indirectly promote the adherence of yeasts to host tissue. Holmes

et al (1995) also reported that coaggregation of *Candida* with a variety of streptococcal species may promote oral colonization by yeast cells. Therefore, it is possible that the commensal oral flora can both facilitate and inhibit the adherence to, and colonization of, oral surfaces by *Candida* species, and a fine balance exists in the oral population dynamics of fungal and bacterial flora.

On the other hand, the reasons for the differences observed in the abovementioned studies could be due to the differences in respective assays or inherent variations in assay procedures and the quantity and quality of bacterial flora used. Future workers in this field should therefore pay heed to the assay technique in order to obtain globally comparable data.

While the foregoing mechanisms may operate within the confines of the oral cavity, the systemic effects of antibiotics on the oral carriage of yeasts could possibly operate via changes in the immune response (Figure 1). There is intriguing evidence that some antibiotics, for example penicillin or tetracycline, may enhance the immune response to *Candida* (Domer and Hector, 1987) whilst others such as erythromycin and co-trimoxazole (Bridges *et al*, 1980) and some aminoglycosides (Ferrari *et al*, 1980) reduce neutrophil candidacidal activity *in vitro*. Yet, the immunomodulating effect of antibiotics *in vivo*, and its effect on oral candidosis in the oral cavity in particular, remains to be determined.

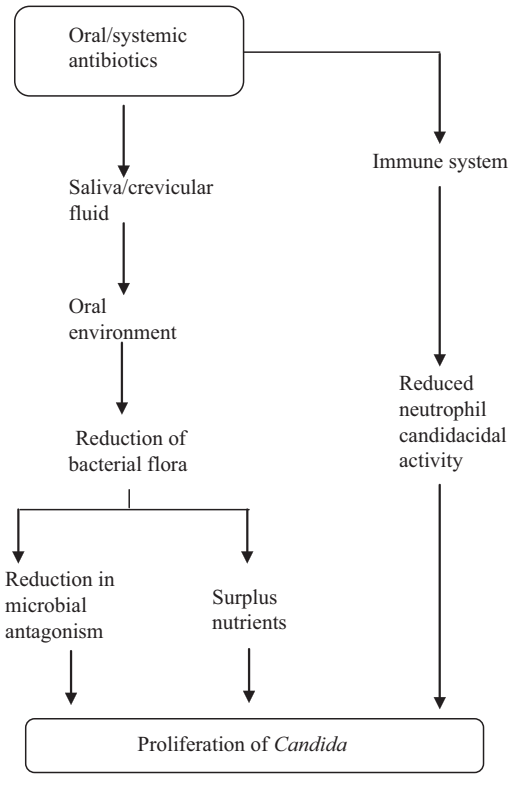

Figure 1 The possible mechanisms by which antibiotic therapy may foster proliferation of *Candida* in the oral cavity [This figure was originally published in *Oral Candidosis*, Samaranayake LP, Host factors and oral candidosis, pp. 66–103, Copyright Elsevier (1990)].

Management

Antifungal agents that are available for the treatment of candidosis fall into three main categories: the polyenes (nystatin and amphotericin B); the ergosterol biosynthesis inhibitors – the azoles (miconazole, clotrimazole, ketoconazole, itraconazole, and fluconazole), allylaminesthiocarbamates, and morpholines; and DNA analog 5-fluorocytosine (White *et al*, 1998), and newer agents such as caspofungins (Pfaller *et al*, 2003). However, the principal antifungals used against oral mycoses belong to the polyenes and the azoles (Ellepola and Samaranayake, 2000b). In addition, chlorhexidine has also been used as an adjunct in the management of oral candidosis (Ellepola and Samaranayake, 2001).

A few studies have investigated the effectiveness of a combination of antifungals with antibiotics. The antifungal activities of four tetracycline analogs in combination with amphotericin B were determined against 20 strains of *C. albicans* (Lew *et al*, 1977). The killing-curve technique indicated that doxycycline had an intermediate degree of synergistic activity, whereas tetracycline had no synergistic activity at clinically relevant concentrations. On the contrary, an *in vitro* study by Raab and Hogl (1980) showed that the antimycotic activity of amphotericin B was significantly higher in the presence of hydroxytetracycline. The study by MacNeill *et al* (1997) showed that tetracycline hydrochloride, even when used at high concentrations *in vitro*, allowed uninhibited growth of *C. albicans* whereas chlorhexidine gluconate inhibited cell growth and replication. Although the results are confusing, the management of oral candidosis by antifungals alone is effective, provided the underlying predisposing factor(s) is under control.

Conclusion and future directions

There is an alarming increase in the misuse of antibiotics in developing countries; especially with the availability of over-the-counter drugs. Hence both clinicians and the public should be aware that misuse of antibiotics leads not only to development of drug resistance in bacteria but also to opportunistic infections such as candidosis.

As far as the oral cavity is concerned there is little doubt that the basic mechanism by which antibiotics enhance candidal growth is by reducing the commensal bacterial population. Yet, the literature is incomplete and further work is required to elucidate fully the underlying mechanisms and processes that are involved in the homeostasis of the oral environment vis-à-vis bacteria and candida.

References

Allen CM, Beck FM, Lurie FA, Pinsky HM (1985a). Influence of tetracycline on number and size of candidal lesions of the dorsal rat tongue. *Prog Clin Biol Res* **181:** 283–285.

Allen CM, Beck FM, Lurie FA, Pinsky HM (1985b). Role of tetracycline in pathogenesis of chronic candidiasis in rat tongues. *Infect Immun* **47:** 480–483.

Arendorf TM, Bredekamp B, Cloete CA, Sauer G (1998). Oral manifestations of HIV infection in 600 South African patients. *J Oral Pathol Med* **27:** 176–179.

Bagg J, Silverwood RW (1986). Coagglutination reactions between *Candida albicans* and oral bacteria. *J Med Microbiol* **22:** 165–169.

Bridges CG, Dasilva GL, Yamamura M, Valdimarsson H (1980). A radiometric assay for the combined measurement of phagocytosis and intracellular killing of *Candida albicans*. *Clin Exp Immunol* **42:** 226–233.

Caldwell JR, Cluff LE (1974). Adverse reactions to antimicrobial agents. *JAMA* **230:** 77–80.

Carr P, Felsenstein D, Friedman RH (1998). Evaluation and management of vaginitis. *J Gen Intern Med* **13:** 335–346.

Clark JD (1971). Influence of antibiotics on certain intestinal bacteria on orally administered *Candida albicans* in germ-free and conventional mice. *Infect Immun* **4:** 731–737.

Diniz CG, Arantes RM, Cara DC *et al* (2003). Enhanced pathogenicity of susceptible strains of the *Bacteroides fragilis* group subjected to low doses of metronidazole. *Microbes Infect* **5:** 19–26.

Domer JE, Hector RF (1987). Enhanced immune responses in mice treated with penicillin-tetracycline or trimethoprim-sulfamethoxazole when colonized intragastrically with *Candida albicans*. *Antimicrob Agents Chemother* **31:** 691–697.

Ellepola AN, Samaranayake LP (2000a). Antimycotic agents in oral candidosis: an overview: 1. Clinical variants. *Dent Update* **27:**111–112, 114–116.

Ellepola AN, Samaranayake LP (2000b). Antimycotic agents in oral candidosis: an overview: 2. Treatment of oral candidosis. *Dent Update* **27:** 165–170, 172–174.

Ellepola AN, Samaranayake LP (2001). Adjunctive use of chlorhexidine in oral candidosis: a review. *Oral Dis* **7:** 11–17.

Epstein JB, Polsky B (1998). Oropharyngeal candidiasis: a review of its clinical spectrum and current therapies. *Clin Ther* **20:** 40–57.

Ferrari FA, Pagani A, Marconin M *et al* (1980). Inhibition of candidacidal activity of human neutrophil leukocytes by aminoglycoside antibiotics. *Antimicrob Agents Chemother* **17:** 87–88.

Fisker AV, Schiott CR, Philipsen HP (1982a). Long term oral candidosis in rats. *Acta Pathol Microbiol Immunol Scand [B]* **90:** 221–227.

Fisker AV, Schiott CR, Philipsen HP (1982b). Short-term oral candidosis in rats, with special reference to the site of infection. *Acta Pathol Microbiol Immunol Scand [B]* **90:** 49–57.

Goulden V, Glass D, Cunliffe WJ (1996). Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* **134:** 693–695.

Hassan OE, Jones JH, Russell C (1985). Experimental oral candidal infection and carriage of oral bacteria in rats subjected to a carbohydrate-rich diet and tetracycline treatment. *J Med Microbiol* **20:** 291–298.

Holmes AR, Cannon RD, Jenkinson HF (1995). Interaction of *Candida albicans* with bacteria and salivary molecules in oral biofilms. *J Ind Microbiol* **15:** 208–213.

Johnston DA, Bodey GP (1972). Oropharyngeal cultures of patients in protected environment units: evaluation of semiquantitative technique during antibiotic prophylaxis. *Appl Microbiol* **23:** 846–851.

Jones JH, Rusell C, Young C, Owen D (1976). Tetracycline and the colonization and infection of the mouths of germ-free and conventionalized rats with *Candida albicans*. *J Antimicrob Chemother* **2:** 247–253.

Kamai Y, Kubota M, Kamai Y *et al* (2001). New model of oropharyngeal candidiasis in mice. *Antimicrob Agents Chemother* **45:** 3195–3197.

Klein RS, Harris CA, Small CB *et al* (1984). Oral candidiasis in high-risk patients as the initial manifestation of the acquired immuno deficiency syndrome. *N Engl J Med* **311:** 354–358.

Klotz SA, Penn RL (1987). Multiple mechanisms may contribute to the adherence of *Candida* yeasts to living cells. *Curr Microbiol* **16:** 119–122.

Krasner RI, Young G, Yudkofsky PL (1956). Interactions of oral strains of *Candida albicans* and lactobacilli. *J Bacteriol* **72:** 525–529.

Lehner T (1966). Classification and clinico-pathological features of *Candida* infections in the mouth. In: Winner H, Hurley R, eds. *Symposium on Candida* infections. Livingstone: Edinburgh, pp. 119–136.

Lew MA, Beckett KM, Levin MJ (1977). Antifungal activity of four tetracycline analogue against *Candida albicans in vitro*: potentiation by amphotericin B. *J Infect Dis* **136:** 263–270.

Liljemark WF, Gibbons RJ (1973). Suppression of *Candida albicans* by human oral streptococci in gnotobiotic mice. *Infect Immun* **8:** 846–849.

MacFarlane TW, Makrides HC (1982). A new screening method for investigating microbial interactions. *J Appl Bacteriol* **52:** 271–274.

MacNeill S, Rindler E, Walker A *et al* (1997). Effects of tetracycline hydrochloride and chlorhexidine gluconate on *Candida albicans*. An in vitro study. *J Clin Periodontol* **24:** 753–760.

Makrides HC, MacFarlane TW (1982). The effect of commensal bacteria on the adherence of *Candida albicans* to epithelial cells. *JOR* **61:** 551–555.

McKendrick AJ, Wilson MI, Main DM (1967). Oral *Candida* and long term tetracycline therapy. *Arch Oral Biol* **12:** 281–290.

McVay LV Jr, Sprunt DH (1951). A study of moniliasis in aureomycin therapy. *Proc Soc Exp Biol Med* **78:** 759–761.

Meads M, Rowe WP, Haslam NM (1951). Alterations in the bacterial flora of the throat during oral therapy with aureomycin. *AMA Arch Intern Med* **87:** 533–540.

Mistry CJ, Apte VJ (1971). Fungal (*Candida albicans*) growth after tetracycline therapy and its management. *J Assoc Physicians India* **19:** 465–468.

Mohapatra LN, Ramachandran K, Shastry JC, Tandon BN (1969). Prophylactic use of amphotericin B for *Candida* infection amongst patients on broad spectrum antibiotic treatment. *Indian J Med Res* **57:** 128–132.

Nair RG, Samaranayake LP (1996a). The effect of oral commensal bacteria on candidal adhesion to human buccal epithelial cells *in vitro*. *J Med Microbiol* **45:** 179–185.

Nair RG, Samaranayake LP (1996b). The effect of oral commensal bacteria on candidal adhesion to denture acrylic surfaces. An *in vitro* study. *APMIS* **104:** 339–349.

Odds FC (1988). *Candida and candidosis; A review and bibliography*, 2nd edn. Bailliere Tindall: London.

Ozog DM, Gogstetter DS, Scott G, Gaspari AA (2000). Minocycline-induced hyperpigmentation in patients with pemphigus and pemphigoid. *Arch Dermatol* **136:** 1133–1138.

Pfaller MA, Messer SA, Boyken L *et al* (2003). Caspofungin activity against clinical isolates of fluconazole-resistant *Candida*. *J Clin Microbiol* **41:** 5729–5731.

Raab W, Hogl F (1980). Interactions between amphotericin B and hydroxytetracycline. *Z Hautkr* **55:** 1162–1171.

Ray TL, Digre KB, Payne CD (1984). Adherence of *Candida* species to human epidermal corneocytes and buccal mucosal cells: correlation with cutaneous pathogenicity. *J Invest Dermatol* **83:** 37–41.

Russell C, Jones JH (1973). Effects of oral inoculation of *Candida albicans* in tetracycline-treated rats. *J Med Microbiol* **6:** 275–279.

Russell C, Jones JH, Gibb AC (1976). The carriage of *Candida albicans* in the mouths of rats treated with tetracycline briefly or for a prolong period. *Mycopathologia* **58:** 125–129.

Samaranayake LP (1990). Host factors and oral candidiasis. In: Samaranayake LP, MacFarlane TW, eds. *Oral candidosis*. Butterworth & Company Ltd: UK, pp. 66–103.

Samaranayake LP1991). Superficial fungal infections. In: Scully C, ed. *Current opinions in dentistry*. Current Science: Philadelphia, PA, pp. 415–422.

Samaranayake LP, MacFarlane TW (1982). Factors affecting the *in vitro* adherence of the fungal oral pathogen *Candida albicans* to epithelial cells of human origin. *Arch Oral Biol* **27:** 869–873.

Samaranayake LP, McCourtie J, MacFarlane TW (1980). Factors affecting the *in vitro* adherence of *Candida albicans* to acrylic surfaces. *Arch Oral Biol* **25:** 611–615.

Samaranayake LP, MacFarlane TW, Lamey P-J, Ferguson MM (1986). A comparison of rinse culture and imprint sampling techniques for the detection of yeasts, coliforms and *Staphylococcus aureus* carriage in the oral cavity. *J Oral Pathol* **15:** 386–388.

Schmadel LK, McEvoy GK (1990). Topical metronidazole: a new therapy for rosacea. *Clin Pharm* **9:** 94–101.

Segal E, Lehrman O, Dayan D (1988). Adherence *in vitro* of various *Candida* species to acrylic surfaces. *Oral Surg Oral Med Oral Pathol* **66:** 670–673.

Seymour RA, Heasman PA (1995). Tetracycline in the management of periodontal diseases. A review. *J Clin Periodontol* **22:** 22–35.

Shastry JC, Ramachandran K, Mohapatra LN, Tandon BN (1969). A study of *Candida* in throat swabs and gastrointestinal tract of the patients on broad spectrum antibiotic or steroid treatment. *Indian J Med Res* **57:** 133–140.

Simjee AE, Gathiram V, Jackson TF, Khan BF (1985). A comparative trial of metronidazole v. tinidazole in the treatment of amoebic liver disease. *S Afr Med J* **68:** 923–924.

Takakura N, Sato Y, Ishibashi H *et al* (2003). A novel murine model of oral candidiasis with local symptoms characteristic of oral thrush. *Microbiol Immunol* **47:** 321–326.

Tewari SN, Flecher R (1966). The efficacy of mysteclin and tetracycline. *Br J Clin Pract* **20:** 639–641.

Vasa CV, Glatt AE (2003). Effectiveness and appropriateness of empiric metronidazole for *Clostridium difficile*-associated diarrhea. *Am J Gastroenterol* **98:** 354–358.

Velichko EV, Karaev ZO (1987). Effect of antibiotics on candidal adhesion to epitheliocytes. *Antibiot Med Biotekhnol* **32:** 360–362.

Verran J, Motteram KL (1987). The effect of adherent oral streptococci on the subsequent adherence of *Candida albicans* to acrylic *in vitro*. *J Dent* **15:** 73–76.

Walker AM, Jick H, Porter J (1979). Drug-related superinfection in hospitalized patients. *JAMA* **242:** 1273–1275.

White TC, Marr KA, Bowden RA (1998). Clinical, cellular and molecular factors that contribute to antifungal drug resistance. *Clin Microbiol Rev* **11:** 382–402.

Wu T, Samaranayake LP (1999). The expression of secreted aspartyl proteinases of *Candida* species in human whole saliva. *J Med Microbiol* **48:** 711–720.