MINI REVIEW

Commensal Oral *Candida* in Asian Cohorts

Lakshman Samaranayake

Faculty of Dentistry, The University of Hong Kong, Prince Philip Dental Hospital, Hong Kong, China

Abstract

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The oral carriage rate of *Candida* in healthy humans ranges from 40% to 60%. However for a prolonged period, the oral candidal prevalence in humans was documented essentially using data from studies in the West as their prevalence in inhabitants in different regions of the world, including Asia was not known. Yet, recent reports from a number of studies indicate the quality, quantity and prevalence of oral yeasts differ between Asia and other regions for reason that are still unclear. This mini review on such data from Asian studies on oral carriage of *Candida* provides another intriguing facet of the behavior of this ubiquitous yeast.

Keywords *Candida*, commensal oral *Candida*, oral candidal prevalence, Asian cohorts

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Introduction

Candida is an ubiquitous fungus. Its prevalence in healthy human oral cavities, according to Western studies, ranges from 40% to 60%. However, when appropriate conditions such as local or systemic deficiencies in the host defenses supervene they multiply creating multiple pathologies. In the oral cavity these can be divided into a triad of entities now known as erythematous, pseudomembranous and hyperplasic variants. Despite its importance as a sentinel opportunistic infection in diseases, such as the human immunodeficiency virus (HIV), little is known about the major etiological agent of oral candidiasis (*syn*=candidosis) — *Candida albicans* (*C.albicans*), or other *Candida* species, especially in Asian cohorts (Samaranayake and MacFralane, 1990). Thus, for a prolonged period oral candidal prevalence in humans was documented essentially using data from studies conducted in the West and their prevalence in inhabitants in different regions of the world was not known.

In one of the earliest studies from Asia, Sedgley and Samaranayake (1994) found using saline oral rinse samples, in 300 community-dwelling Hong Kong Chinese attending an outpatient dental clinic, the oral prevalence of yeasts to be 24%, with *C. albicans* forming 77% of all yeasts isolated. However, subjects taking medication or wearing dentures had a significantly higher oral yeast prevalence of 36.8% and 44.7%, respectively, as well as those who were over 50 years of age. Comparisons of these and previous Western studies suggested that the oral prevalence of yeasts in health to be notably lower in this Southern Chinese population.

In another, 4-year longitudinal study in 116 Chinese primary school children in Hong Kong Sedgley *et al*. (1997) noted the oral prevalence of yeasts for each consecutive year to be 7.7%, 12.0%, 14.4% and 15.5%, respectively, with a weighted mean of 12.5%. *C.albicans* comprised 84% of all yeasts isolated. Repeated isolation of *Candida* species from individual children over the 4-year study period was rare, suggesting that candidal carriage of these organisms is transient and perhaps lower than from the Western populations.

These intriguing data on yeast carriage in healthy

mouths which differed from the traditional norms have led a few workers to explore this area further. These findings from Hong Kong, Thailand, and Cambodia in HIV-infected individuals, leprosy patients and betel chewers provide us with a fascinating glimpse of the clinical epidemiology of an ubiquitous fungus which we know so little about. In this mini review the data from Asian studies on oral carriage of *Candida* in a number of Asian cohorts are provided.

HIV infected individuals and oral yeast carriage

Almost all patients with HIV infection develop oral candidiasis at some point during the progression of the infection to acquired immunodeficiency syndrome (AIDS). In the early stages of HIV infection, the development of oral candidiasis is highly predictive of worsening immunodeficiency. Hence many have attemptted to sequentially follow the different communities or clades or families of *Candida* residing inside the mouth and how they behave when the host progresses from symptomless HIV infection to full blown AIDS. These early studies attempting to characterize *C. albicans* into different subtypes or clades used rather primitive biotyping methods that are currently superseded by various genotyping techniques.

In a landmark study, oral *C.albicans* isolates from HIV-infected individuals from Hong Kong, Australia, Germany and England were characterized using such a biotyping system. A total of 33 isolates from Hong Kong, 37 from Australia, 30 from Germany, and 17 from England were characterized using a biotyping system based upon enzyme profiles, carbohydrate assimilation patterns, and boric acid resistance of the yeasts (Tsang *et al.*, 1995). A total of 44 biotypes were identified, and *A1R* and *A1S* were the two major biotypes, accounting for 17.9% and 11.1% of all isolates, respectively. A few biotypes were unique to individual countries. These workers, therefore, concluded that many different sub-strains of *C.albicans* persist in HIV-infected patients, most of which are globally prevalent.

A similar study was conducted in Cambodia by the same group of workers to determine the prevalence of *Candida* species in HIV-infected Cambodians with oral candidiasis and either unexposed (group Ⅰ) or exposed to antimycotics (group Ⅱ), together with a healthy control population (group Ⅲ). In 161 HIV patients with oral candidiasis (group Ⅰ: 121 pts; group Ⅱ: 40 pts) and in 81 controls (group Ⅲ) swab samples of tongue and palate were obtained (Schmidt-Westhausen *et al.*, 2004). Oral candidiasis was detected in 100% and 70% of groups Ⅰ and Ⅱ, respectively. *Candida* species were isolated from 91% and 100% of groups Ⅰ and Ⅱ, respectively, and from 79% of controls. *C.albicans* was the most common, with non-*albicans* species such as *Candida tropicalis* (*C.tropicalis*) and *Candida krusei* (*C.krusei*) being notable isolates. The data further indicated that variants of oral candidal infections in HIV disease are similar to those seen in the pre-HAART era and, a very high isolation rate of *C.krusei* in all three groups.

Candida krusei and leprosy patients

Although *C.albicans* is the most common human yeast pathogen, other *Candida* species such as *C.krusei* are now recognized as emerging agents, especially in patients with HIV disease. *C.krusei* is intrinsically resistant to the widely used triazole antifungal fluconazole and poses therapeutic problems, especially in systemic candidiasis.

Reichart *et al*. (2002) pursued the thread of high isolation rates of *C.krusei* in HIV-infected patients in Cambodia and further extended their studies into a relatively neglected patient cohort in Thailand. Thus, in a surveillance study of leprosy patients (with arrested or burnt-out disease) in a leprosarium in northern Thailand, they found the oral carriage of *C.krusei* (36%) significantly ($P< 0.05$) higher than that in a healthy control group (10%). Among the *Candida*-positive patients, 16 of 35 (46%) carried *C.krusei* and, surprisingly, *C.albicans* was the second most common isolate (12 of 35 patients; 34%). The corresponding figures for the control group were 2 of 13 (15%) and 6 of 13 (46%), respectively.

Studies of the antifungal resistance of the *C. krusei* isolates from patients indicated that all except one of the isolates were resistant to fluco-

nazole, two isolates were resistant to ketoconazole, and all isolates were sensitive to amphotericin B. Evaluation of their genetic profiles by randomly amplified polymorphic DNA analysis with three different primers and subsequent analysis of the gel profiles by computerized cluster-derived dendrograms revealed that the *C.krusei* isolates from patients belonged to 10 disparate clusters, despite the origin from a single locale. These nascent findings indicated an alarmingly high prevalence of a *Candida* species resistant to a widely used antifungal in a part of the globe where HIV disease is endemic.

These seminal data provided a tantalizing glimpse of the oral mycotic flora in an, as yet, undescribed patient population. Most importantly, the findings revealed the high prevalence of *C.krusei* in the cohort and the intriguingly divergent genomic profiles of these strains. In biological terms, the prolific diversity of such a relatively innocuous opportunistic pathogen, which usually resides in ripe exotic fruits, is surprising and warrants further study.

The authors further surmised that in view of the predominance of a triazole-resistant *C.krusei* strain in this population and the high prevalence and incidence of HIV infection in northern Thailand, which in turn predisposes individuals to candidiasis, similar prevalence studies should be pursued with other regional population groups. If such data indicate a predominance of this yeast in the general populace, this may have implications for the protocols guiding the management of HIV-related candidiasis, in which fluconazole is the drug of choice.

Betel quid chewing and Candida

Betel quid chewing (BQC), a very popular habit in many Asian countries has been studied and well documented by Reichart and Philipsen (1996) in their unique tome. Hence, it is not surprising that they investigated the effect of BQC on the oral carriage of *Candida* and attendant mucosal pathology. In an as of yet unrepeated sentinel study they investigated the effect of BQC, on the oral carriage of *Candida* species in 48 Cambodian women with BQC habit and 13 control subjects without the habit. In addition, the lesions of the oral mucosa likely to be associated with BQC habit were assessed (Reichart *et al*., 2002). In individuals with a median duration of BQC of 10 years they noted, betel chewer's mucosa (85.4%), oral leukoplakia (8.3%), leukoedema (37.5%) and oral lichen planus (4.2%). Oral candidiasis was seen neither in BQ chewers nor in controls. *Candida* species were found in 70.8% of the cases (controls 69.2%). *C.albicans* was isolated from 27.1% of the study cohort, *C.tropicalis* was the second most common isolate. One control case was colonized by *Candida dubliniensis* (*C. dubliniensis*) — the first report of this organism from a Cambodian population. There was no significant difference in the candidal carriage rate or the *Candida* species isolated between the study and the control group. Hence the authors concluded that BQC has no significant impact on oral colonization by *Candida* species.

In an identical study in northern Thailand the same workers obtained oral swabs from the tongue and palate of 50 Padaung women with and 50 control individuals without BQC habit (Reichart *et al*., 2005) (Figure 1). The mean age of BQ chewers was 35.4 years, of non-chewers was 19.2 years. *C.parapsilosis* was the most common *Candida* species isolated both in BQ chewers (46%) and non-chewers (44%) and *C.albicans* in 24% of BQ chewers and 18% of non-chewers. There was no significant difference in carriage of *Candida* species isolated between both groups. 44% of BQ chewers revealed betel chewers mucosa and 10% showed leukoedema (Figure 2).

Figure 1 A Padaung woman from northern Thailand with a characteristic red lip due to the betel quid chewing habit

(Picture courtesy of professor Peter Reicahrt)

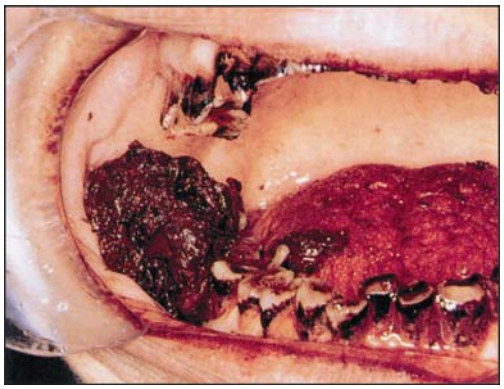

Figure 2 The typical manner in which the "betel quid" comprising mainly betel leaves, areca nut and slaked lime is retained in the buccal sulcus by a BQ chewer, leading to staining of teeth (seen here) and other related mucosal pathologies

(Picture courtesy of professor Peter Reicahrt)

Perhaps the most intriguing finding from a mycologists point of view from the foregoing studies is the very high prevalence of exotic *Candida* species in these special cohorts. Thus, *C.krusei, C.parapsilosis* and not *C.albicans* were the most prevalent in leprosy patients in Cambodia and BQC Padaung Women in Thailand, respectively. Further work needs to be done to demystify the intriguing prevalence of various *Candida* species in these population groups and the pathologies, if any, they cause.

Conclusions

From the foregoing it is clear that little data are available on a dark niche of oral biology that is difficult to pursue due to the geographic isolation and the social stigmata associated with the foregoing population groups. As mentioned, the new data on oral *Candida* in these cohorts, which differ from the accepted norms yet commonly quoted in the literature, are noteworthy. A rich harvest awaits those who strive to continue these and related other work (Reichart *et al*., 1995; Reichart *et al*., 1994).

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Corresponding author: Lakshman Samaranayake

Address: Faculty of Dentistry, The University of Hong Kong, Prince Philip Dental Hospital, 34 Hospital Road, Sai Ying Pun, Hong Kong

Tel: (852) 2859 0342 Fax: (852) 2547 6257 E-mail: lakshman@hku.hk