Non-Candida albicans Candida yeasts of the oral cavity

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Candida species are prevalent in the oral cavity, in particular among elderly patients with reduced salivary flow and/or dental prostheses, and in immunosuppressed patients. The most frequently encountered species are Candida albicans. Non-Candida albicans Candida (NCAC) strains, however, are isolated in increasing numbers in medically compromised patients. These strains may cause systemic infections and are often resistant to commonly used antifungal agents such as fluconazole. Candida species may be capable of metabolizing ethanol to carcinogenic acetaldehyde and can thus progress oral and upper gastrointestinal tract cancer. Consequently, more focus should be placed on diagnosis and treatment of oral Candida infections, also on other Candida species than C. albicans. This review outlines the current knowledge about the NCAC yeasts with emphasis on oral medicine.

Keywords Candida, oral cavity

1. Introduction

Yeasts are opportunistic pathogens and cause disease in hosts who are compromised by underlying local or systemic pathological processes [1]. Oral candidiasis is a sign of impaired local or systemic defense mechanisms. Reduced saliva secretion, deficiencies of humoral or cell-mediated immunity, local mucosal diseases and the use of wide-spectrum antibiotics are predisposing factors [2]. Candida is part of the oral normal flora in most people. In the newborn, colonization usually occurs from the mother’s vaginal flora or other exogenous sources and it appears that most people are colonized with a distinct strain of Candida; if infection occurs, the infecting strain is then the same strain as the colonizer [3].

Carriage rate for Candida is hard to give since it depends on the age and health of the population studied [4], but a range from 17% to 75% has been reported [5]. For example, in a comprehensive study of 75-year olds in Japan, Candida was detected in 67% of samples from the dorsum of the tongue and the prevalence was significantly associated with the presence of any dental prostheses, missing teeth, the number of retained roots and the percentage of periodontal pockets showing bleeding on probing. Dental prostheses particularly affected the number of Candida strains identified and the density of colonies in this study. In addition, the prevalence of multi-species carriage was linked with the presence of prostheses [6].

Systemic candidiasis in hospitalized and institutionalized patients has increased over the last decades [7, 8]. This is due to the increasing number of immunocompromised patients, immunosuppressive therapies and the elderly as well as the increased use of wide-spectrum antibiotics and indwelling intravascular devices [9]. Candida is the fourth most common cause of hospital-rated bloodstream infections in the U.S. [10, 11] but the mortality rate exceeds that of bacteremia [7]. Oral candidiasis is the most common human fungal infection [12]. Candida albicans is the most commonly isolated fungal
pathogen in the oral cavity, but the number of isolated Candida species other than Candida albicans is increasing [7,13,14]. These species are often resistant to commonly usedazole antifungal agents.

2. Candida species

Yeasts which are part of the genus Candida consist of 150-200 species [15]. They are imperfect unicellular dimorphic fungi which multiply mainly by budding similar cells from their surface and form hyphae and/or pseudohyphae [1]. They were earlier assigned to the family deuteromycetes, indicating a lack of sexual reproduction. However, several pathogenic and non-pathogenic Candida species have been identified to have a sexual stage [16]. Table 1 presents the principal Candida species according to current nomenclature. Figure 1 shows the morphology of some oral Candida species as seen in the scanning electron microscope.

Candida albicans is the most common species isolated from the oral cavity in both healthy and diseased (in 60-80% of the cases) [2,17]. Other species responsible for oral infections have also been identified including C. glabrata, C. krusei, C. parapsilosis, C. dubliniensis, C. tropicalis, C. kefyr and C. guilliermondii [4,14,15,17]. Also species such as C. inconspicua, C. lusitaniae, C. norvegensis and C. rugosa have been isolated occasionally from patients [1]. Yeasts not belonging to the genus Candida such as Rhodotorula glutinis and Saccharomyces cerevisiae are sometimes found in the oral cavity but these are not known to cause oral infections [18]. However, colonization of Candida in the oral cavity does not indicate infection in the absence of clinical lesions or other symptoms. All the candidal species cause the same kind of mucositis but there are differences in the invasiveness and antifungal susceptibilities among species [2]. The role of these other species also referred to as non-albicans species have become increasingly important, especially in high-risk patients.

Table 1 Principal Candida species.

<table>
<thead>
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<th>Candida albicans</th>
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<tr>
<td>Candida dubliniensis</td>
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<td>Candida famata</td>
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<td>Candida glabrata</td>
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<tr>
<td>Candida guilliermondii</td>
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<td>Candida inconspicua</td>
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<td>Candida kefyr</td>
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<td>Candida krusei</td>
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<td>Candida lusitaniae</td>
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<tr>
<td>Candida norvegensis</td>
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<tr>
<td>Candida parapsilosis</td>
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<tr>
<td>Candida rugosa</td>
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<td>Candida tropicalis</td>
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3. Pathogenic non-Candida albicans Candida (NCAC) species

The NCAC species are a heterogeneous group of organisms and different from each other and from C. albicans [19]. Earlier, it was considered that C. albicans was the only species causing infection and C. parapsilosis, C. tropicalis and C. guilliermondii were considered only as occasional pathogens [19]. The development of new medical therapies, treatments for cancer, the increase in invasive medical procedures, the emergence of human immunodeficiency virus (HIV) and AIDS, and the wide-spread use of broad-spectrum antibiotics, however, lead to the increasing recovery of many other NCAC species causing mucosal infections [19]. The NCAC species are thought to cause candidiasis of less virulence explained by the fact that they lack, totally or partially, some virulence factors that the most virulent species C. albicans has. These are, for example, the ability to form hyphae and the ability to perform
phenotypic switching. They may also have a lower adherence capability to buccal epithelial and vascular endothelial surfaces and lower secretion of proteinases [19].

3.1 Candida dubliniensis

*C. dubliniensis* was first described in 1995. It is a species associated with oral lesions in HIV-infected individuals and it is phenotypically and genotypically closely related to *C. albicans* [20, 21]. In vitro phenotypic studies have shown that *C. dubliniensis* has a few characteristics that distinguish it from *C. albicans* [22]. Both produce germ tubes and chlamydospores. Unlike *C. albicans* *C. dubliniensis* isolates grow poorly at 42°C [21]. Despite the similarities with *C. albicans*, *C. dubliniensis* is not a common constituent of the oral microflora and only about 3.5% of healthy individuals carry *C. dubliniensis* in the oral cavity [23]. A prevalence of 15-30% of *C. dubliniensis* in the oral cavities of HIV-infected and
AIDS patients has been reported [23]. It is not a common cause of bloodstream infection and the incidence in systemic infections is low. The reason for this seems to be the lower virulence of \textit{C. dubliniensis} compared to the virulence of \textit{C. albicans}. It has been suggested that the reason for the comparatively low virulence is its lower capacity to form hyphae compared to \textit{C. albicans} [24]. \textit{C. dubliniensis} is, however, the only \textit{Candida} species in addition to \textit{C. albicans} that forms true hyphae. Decreased susceptibility or resistance has been reported in isolates recovered from HIV-patients receiving fluconazole therapy [23]. \textit{C. dubliniensis} has been isolated from a wide range of geographical locations, including Europe, North and South America and Australia [25].

3.2 \textit{Candida glabrata}

Earlier \textit{C. glabrata} was considered a pathogen that causes infection only when detected with \textit{C. albicans}. However there have been several reports on oropharyngeal \textit{Candida} (OPC) infections due only to \textit{C. glabrata} [26,27] and it is now emerging as an important pathogen in both mucosal and bloodstream infections [17]. It is commonly isolated from the oral cavities of HIV-infected individuals [19]. \textit{C. glabrata} is the second-most common agent of candidemia in the United States since the early 1990s [28]. It is considered that \textit{C. glabrata} associated OPC infections in HIV- and cancer patients are more severe and more difficult to treat [17, 27]. This is mainly due to the ability of \textit{C. glabrata} to quickly develop resistance to fluconazole. Cross resistance to the newer azoles has also been found to exist [28]. Resistance can be both innate and acquired. \textit{C. glabrata} infections are difficult to treat and are associated with systemic infections having a high mortality rate [29]. \textit{C. glabrata} exhibits a lower oral keratinocyte-adherence capacity compared to \textit{C. albicans} [17]. The virulence factors and host-parasite interactions of \textit{C. glabrata} are not known [29].

3.3 \textit{Candida guilliermondii}

\textit{C. guilliermondii} has been associated with poor clinical outcomes and hematologic malignancies [30]. It may be found on human skin and as part of the genitourinary and gastrointestinal tract flora. It has been documented to cause infection in patients undergoing surgical procedures, endocarditis in intravenous drug users and fungemia in immunocompromised patients [31]. \textit{C. guilliermondii} has also been isolated in urinary tract infections [3]. It may develop resistance to amphotericin B [32].

3.4 \textit{Candida krusei}

\textit{C. krusei} causes infection mainly in critically ill patients and is most often isolated in hematology patients with severe neutropenia. It is an uncommon pathogen causing candidemia. Isolates have been reported to be resistant to both fluconazole and itraconazole [33,34], and there have also been some reports on resistant strains to amphotericin B [35]. The widespread use of fluconazole to prevent fungal infections in HIV-infected patients has lead to a significant increase in \textit{C. krusei} infections [36].

3.5 \textit{Candida lusitaniae}

The first descriptions of \textit{C. lusitaniae} in 1959 were of a common isolate inhabiting the gastrointestinal tract, and the first reports on cases of human infection caused by \textit{C. lusitaniae} were in 1979 [37]. It is a rare pathogen and few studies have been performed on it. It is less pathogenic than \textit{C. tropicalis} and \textit{C. parapsilosis} and causes infection mainly in immunocompressed hosts with prolonged administration of broad-spectrum antibiotics, prolonged hospitalization, cytotoxic or corticosteroid therapy, or granulocytopenia [38]. It is also found to cause infections in low birth neonatals [39]. \textit{C. lusitaniae} may develop resistance to amphotericin B, but the data are contradictory [35].

3.6 \textit{Candida parapsilosis}

\textit{C. parapsilosis} particularly affects critically ill neonates and surgical intensive care unit patients [11].

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Prematurity and low birth weight have been recognized as risk factors [40]. Intravenous drug users have been reported to have fungemia or endocarditis caused by *C. paralopsilosis* and it is also connected to bone and joint infections [19]. There have been reports on the increase in hematogenous *C. parapsilosis* infections [41]. The affinity of *C. parapsilosis* for medical devices such as intravascular catheters and prosthetic devices has been recognized. This has been explained by the findings on *C. palapsilosis* isolates from blood culture producing an extracellular polysaccharide, or slime, which may aid adherence and biofilm formation on plastic surfaces [19]. It is commonly recovered from human skin and is quite often recovered from the hands of health care workers. *C. parapsilosis* is susceptible to azoles and polyenes. Tolerance to amphotericin B has, however, been reported [32]. Sarvikivi et al. [40] reported of the emergence of fluconazole resistance in *C. parapsilosis* strains in a neonatal intensive care unit. Fluconazole prophylaxis was used in low doses and this lead to resistant strains over a 10-year period.

### 3.7 Candida tropicalis

*C. tropicalis* is the most virulent of the NCAC species. This may be due to its ability to adhere to epithelial cells *in vitro* and its ability to secrete moderate levels of proteinase [19]. It is usually isolated from the oral cavity and skin. It may also cause infections of the esophagus. The latter cases, however, have been shown to correlate with systemic diseases, in other words, poor general health makes the patient liable for candidemia caused by this strain [3].

### 4. Candida biofilms

Fungal biofilms and their role in infection and drug resistance have received increasing amounts of interest in the past years. There is already quite a lot of information about bacterial biofilms but studies and understanding of fungal biofilms are not as thoroughly investigated [42]. Biofilms are known to form on surfaces of catheters, prosthetic heart valves and joint replacements and may be detected from chronic infections such as cystic fibrosis [43]. In the oral cavity yeast biofilms may form on acrylic dentures and dental implants.

Biofilms are structured microbial communities that are tightly attached to a surface and which are embedded within a matrix of extracellular polymers [43,44]. Studies on *Candida* biofilms have revealed that the formation of the biofilm begins with the attachment of the cells to each other. This is followed by the formation of germ tube and extracellular matrix. The third phase is the formation of hyphae and pseudohyphae by the yeast cells [43,44]. The mature biofilm has a three dimensional structure which may be several hundred microns deep [44]. It is gel-like, highly hydrated and the micro-organisms in it are largely immobilized [45]. *C. dubliniensis* biofilms have similar 3-D structures as *C. albicans* [43]. The architecture of *C. parapsilosis* biofilm seems to be different to that of *C. albicans*. It consists of patches of mushroom-shaped biofilm communities rather than biphasic arrangement of discrete layers [11].

Biofilms have reduced susceptibility to the host immune system, disinfectants, and drugs [42,43,44]. All of the commonly used antifungal agents have been reported to have a decreased activity against candidal biofilms [43]. The mechanism of resistance in the biofilms is not fully understood. There have been many suggestions including restricted penetration of drugs through the matrix, phenotypic changes in the cells, and activation of resistance genes [43]. The resistance increases during stages of biofilm maturation [42].

### 5. Antifungal resistance among NCAC species

The most commonly used antifungal agents are azoles (fluconazole, itraconazole, and ketaconazole) and polyenes (amphotericin B). Some *Candida* species have intrinsic resistance and some develop resistance to azoles. The widespread use of fluconazole and itraconazole as therapeutic or prophylactic doses has
Increased recently [19] and is most often associated with the HIV infected with oropharyngeal candidiasis [46]. This has lead to the increase of reports of resistance [47]. C. krusei, C. inconspicua and C. norvegenes is are by nature resistant to fluconazole and C. glabrata possesses the ability to rapidly develop resistance to fluconazole [19]. It is believed that prolonged or repeated exposure to low-dose fluconazole may be associated with resistant isolates of C. albicans and to the selection of resistant non- Candida albicans species in the patient [8]. Antifungal drugs should be used as high doses only for the treatment of oral candidiasis, not for prophylaxis [13]. In a recent study by Bagg et al. [48] of the 270 Candida isolates from patients receiving treatment for advanced cancer 25% were not susceptible to fluconazole at standard doses and 66% of the C. glabrata isolates were fluconazole-resistant [48]. However, in a study by Kuriyama et al. [49] from a total of 618 clinical Candida isolates from patients with different oral diseases almost all were susceptible to fluconazole. Only 6.8% of the C. glabrata strains and none of the C. krusei, C. paralopsilosis and C. tropicalis strains were resistant to fluconazole. Itroconazole resistance was found in 23.7% of the C. glabrata 3.14% of the C. krusei, 7.7% of the C. tropicalis and 1% of the C. albicans strains.

Amphotericin B is the most commonly used polyene antifungal. It has been in use since the 1950s [19]. It has a broad spectrum of activity. There have only been few reports on resistant C. albicans isolates. Recently there have been reports on resistant C. glabrata and C. krusei isolates [19]. Resistant isolates have also been found in C. tropicalis, C. parapsilosis, and C. lusitaniae. C. glabrata is considered as intermediate or susceptible dependent upon dose [35]. Voriconazole is a wide-spectrum azole which is susceptible to most of the isolated strains [14] but reduced susceptibility to this antifungal has also been reported [48].

As discussed above, it has been suggested that Candida strains form biofilms on bioprosthetic surfaces and during this biofilm maturation they become highly resistant to antifungals [50]. There have, however, been many studies which have demonstrated that the matrix does not form a major barrier to drug diffusion [45].

Oral candidiasis is a superficial fungal infection and should be treated locally. Therefore the importance of antifungal resistance in oral candidiasis is more limited than in deep infections which may be fatal [46].

6. Oral candidiasis

Oral candidiasis is mainly caused by the yeasts in the normal flora of the oral cavity. Candida is part of the normal flora in the majority and is in the normal state kept under control by means of specific and non-specific defense mechanisms and by the competition of the microbes in the normal flora. Oral candidiasis is often found in the elderly, the patients wearing dentures and the HIV- and AIDS patients. It is usually caused by C. albicans, C. tropicalis, C. krusei or C. dubliniensis. All the different Candida species cause the same kind of mucositis but there are significant differences in the invasiveness and antifungal susceptibility [2]. Oral yeast carriage does not mean infection. In the case of infection there must be mucositis with clinical symptoms.

Clinical forms of oral candidiasis include erythematous candidiasis, pseudomembranous candidiasis, median rhomboid glossitis, angular cheilitis and candidal leukoplakia [25]. The main local predisposing factors are decreased saliva flow, smoking, mucosal lesions, decreased blood circulation in the mucosa due to for example radiation therapy. Systemic predisposing factors are diabetes mellitus, acquired or inborn immunodeficiency, malignancies, oral cancer and malnutrition.

6.1 Pathogenesis

The ability of Candida to adhere to the mucosa and dentures plays an important role in the pathogenesis of oral yeast infections [51]. Adherence is achieved by specific and nonspecific mechanisms. However the mechanisms of are still not fully understood [52]. Local defence mechanisms have a key role in preventing yeast colonization in the oral cavity. These include the physical local barrier of the epithelia, antimicrobial peptides, secretory immunoglobulin A, and salivary factors such as flow rate and specific
molecules (lysozyme, histatin and lactoferrin) [51]. Secreted aspartic proteinase (SAP), phospholipases and lipases are extracellular enzymes that facilitate adherence and/or tissue penetration. SAPs efficiently degrade extracellular matrix and host surface proteins (laminin, fibronectin, and mucin) [52]. C. albicans, C. dubliniensis, C. tropicalis and C. parapsilosis are known to possess SAP genes.

6.2 Histopathology

The histological profile of C. albicans infections shows yeasts and pseudohyphae. C. glabrata, however, appears to produce only yeast forms [32]. Histopathologic response is in most cases characterized as inflammatory or as an abscess [32]. There are a limited number of studies on the histopathology of NCAC.

6.3 Oral NCAC-infections

Oral candidiasis caused by NCAC-species is increasing. A clinician should suspect NCAC if treatment with commonly used antifungals fails. Table 2 gives the patient groups at risk for oral candidiasis. Some of these are discussed below in more detail.

Table 2. Examples risk patients for oral candidiasis.

<table>
<thead>
<tr>
<th>Patients with dental prostheses</th>
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<tr>
<td>Patients with reduced salivary flow rate</td>
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<td>Patients with oral mucosal diseases</td>
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<tr>
<td>Asthmatic patients on corticosteroid therapy</td>
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<tr>
<td>Diabetic patients</td>
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<tr>
<td>Patients with rheumatic diseases</td>
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<tr>
<td>HIV infected and AIDS patients</td>
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<tr>
<td>Patients with malignant disease</td>
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<tr>
<td>Patients receiving immunosuppressive drugs</td>
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<tr>
<td>Patients receiving radiotherapy to the head and neck</td>
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<tr>
<td>The elderly</td>
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</table>

6.3.1 Oral NCAC candidiasis in HIV-infected patients

It has been reported that more than 90% of HIV-infected individuals develop oral candidiasis during some point of their disease and it is the most common fungal infection among these patients [5]. Oral candidiasis is considered to be an indirect marker of the deficiencies in cell-mediated immunity and a prognostic indicator for the development of AIDS [5,33]. C. albicans is isolated from around 80% of the HIV-infected and the levels of oral Candida are significantly higher than among the healthy [5]. C. dubliniensis is a frequent species isolated from the oral cavities of HIV-infected and AIDS patients [23]. Fluconazole is frequently used as prophylaxis among patients with AIDS [53]. This has been thought to lead to the selection of NCAC species and development of resistant isolates. In a study by Cartledge et al. [34] 10% of 921 clinical isolates from HIV-infected patients with oral candidiasis were NCAC-species. Almost half of the NCAC isolates were identified as C. glabrata, followed by C. krusei (20%). All the C. glabrata and C. krusei isolates were resistant to fluconazole and ketoconazole. Of the C. glabrata isolates 22% were cross-resistant but all the C. krusei isolates were susceptible to itraconazole. Also other groups have reported on resistant strains to both itraconazole and fluconazole in strains from HIV-infected patients [33,54].

6.3.2 Oral NCAC in patients with diabetes mellitus

It is believed that patients with diabetes mellitus are prone to fungal infections. Candidal carriage among this patient population has been reported to be 64% [55] to 77% [25]. In a study by Manfredi et al. [56]
there seemed to be no significant difference in the yeast colonization or NCAC prevalence between diabetes (type I or II) and the non-diabetic patients. In a study by Willis et al. [25] of 414 insulin-using diabetes mellitus patients *C. albicans* was the most common species isolated (63.2%) followed by *C. dubliniensis* (18.2%) and *C. glabrata* (3.4%). These numbers were however not compared with that of non-diabetic patients or diabetic patients not using insulin.

### 6.3.3 Oral NCAC in patients with advanced cancer

Oral yeast carriage is common in patients with advanced cancer. Davies et al. [13] studied 120 patients with advanced cancer (40% of these were carcinoma of the breast, 16.5% carcinoma of the bronchus, 15% carcinoma of the prostate, 6% carcinoma of the large bowel and one had carcinoma of the tongue. Thirty percent of the patients had evidence of oral candidiasis. *C. albicans* was the predominant species (46%), followed by *C. glabrata* (18%), *C. dubliniensis* (6%), and *C. tropicalis* (4%). Also isolates of *C. krusei, C. fomata, C. guilliermondii, C. parapsilosis* and few species other than *Candida* were identified. Of all the patients with *Candida* 23 were colonized with more than one species.

### 6.3.4 Oral NCAC in patients with carcinoma of the head and neck

Oral candidiasis is a common infection in patients receiving radiation for head and neck cancer [14]. Colonization up to 93% and infection up to 29% have been reported among these patients [57]. The oral cavity goes through radical anatomical and physiological changes during the treatment of oral cancer. Radiation causes severe hyposalivation due to the destruction of salivary glandular tissue. Clinical diagnosis of oral infections may be difficult after radiation due to reduced inflammatory responses in the immunocompromised host [58]. It is believed that radiation-induced xerostomia favors intraoral colonization of *Candida* species by histological changes leading to oral mucositis and changes in the saliva and salivary flow [59].

*C. albicans* is the most frequent cause of oral candidiasis (in 60-80% of the cases) also in patients receiving radiotherapy for head and neck cancer [2,14] but the role of NCAC-species [57] and especially *C. glabrata* as an infection causing pathogen in this patient group is increasing [27]. There seems to be a shift from *C. albicans* towards NCAC species during the radiation therapy [60].

Oral candidiasis has been suggested to be carcinogenic [61]. Evidence for the carcinogenic potential of certain strains of *C. albicans* has been demonstrated in rats [62]. Production of nitrosobenzylmethylamine has been proposed to have a key role in the carcinogenicity of these *Candida* strains [63]. In a study by Tillonen et al. [64] *C. albicans*, but not NCAC species, was found to be capable of producing acetaldehyde from ethanol *in vitro*. Acetaldehyde is a potential carcinogen behind ethanol-related oral cancers.

An interesting group are patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED, APS-I). The prevalence of oral candidiasis in APECED patients is exceptionally high. Of all the diagnosed APECED patients in Finland [92] six developed squamous cell carcinoma but no other malignancies. Almost all of the patients were infected by *C. albicans* [61].

### 6.3.5 NCAC in oral mucosal lesions

*Candida* is commonly cultured from oral mucosal lesions. *Candida* has been reported to cause infection in 37% to 50% of oral lichen planus (OLP) cases [65]. The treatment of OLP with steroids may lead to secondary yeast infection and may complicate the treatment of OLP. *C. albicans, C. glabrata* and *C. tropicalis* have been isolated from OLP lesions treated with topical steroids [65].

Oral leukoplakia is defined as a white patch or plaque that cannot be rubbed off or characterized clinically or pathologically as any other disease [66]. Candidal hyphae are found in about 10% of all leukoplakias [67].

The reports concerning the role of *Candida* as an etiological factor in the oral mucosal lesions are sparse and there have been no recent thorough studies on this matter, especially the role of NCAC species. The earliest reports date back to the 80s [68,69]. There have been reports on the positive
association of yeast infection with moderate and severe epithelial dysplasia, median rhomboid glossitis and squamous papillomas [70]. \textit{C. albicans} is usually the most predominant species isolated from oral mucosal lesions but also other species have been reported [71]. It has been suggested that \textit{C. albicans} and particularly some of its biotypes show a high potential of adaptation to the changes associated with the development of oral leukoplakia and lichen planus [71]. \textit{C. albicans} has often been demonstrated as a secondary infection in oral erythroplakia (OE). It is, however, still unknown what the possible role of \textit{Candida} is in the development of OE [72].

6.3.6 NCAC infections in the elderly
The elderly often harbor yeasts in the oral cavity and oral candidiasis is a frequent disease in this group. In a group of 191 elderly referred to hospital because of weakened general condition, yeast count in saliva was positive in more than 80% [73]. They are a risk group to yeast infections due to chronic diseases, medication, poor oral hygiene and reduced salivary flow [74]. Concomitant use of several drugs including antimicrobial agents causes selection pressure in the commensal flora and may lead to yeast overgrowth. Acrylic dentures act as reservoirs of micro-organisms and increase the colonization of oral \textit{Candida} [75]. The use of dentures has been proposed as the most important predisposing factor [76]. According to reports the incidence of NCAC species among this group, and particularly among the institutionalized elderly, is increasing [76,77]. Grimoud et al. [77] reported that among 110 hospitalized elderly \textit{C. glabrata} accounted for 24% of the isolated yeasts when in comparison the percentage had been 1.4% in a study by Kuch et al., in the 1980s [77].

7. Identification of \textit{Candida}
There are differences among the \textit{Candida} species in the susceptibility to the different antifungal agents available. Therefore identification of the species behind an infection is needed to ensure proper medication. CHROMagar [78] is a medium that is widely used to identify \textit{C. albicans}, \textit{C. krusei}, and \textit{C. tropicalis}. The medium contains chromogenic substrates which react with enzymes secreted by the target micro-organisms to yeald colonies of varying colours [79]. \textit{C. albicans} forms green colonies, \textit{C. tropicalis} steel blue colonies, and \textit{C. krusei} fuzzy, rose coloured colonies.

8. Conclusion and future development
Oral candidiasis is prevalent in particular in the elderly patients with dental prostheses and in systemically diseased and immunocompromised patients. NCAC species compromises patients and have been identified in increasing numbers in patient samples. These species pose a threat in the future due to commonly used antifungal drugs.

The pathogenesis of NCAC species is still incompletely understood. Environmental sources such as water, hospital surfaces, and skin and nails of nursing staff have been found to be sources of infections [80]. This is a matter that calls for further study especially as a source of hospital outbreaks.

New virulence factors and the mechanisms of virulence in the NCAC species is not fully understood. Gliotoxin, for example, is a secondary fungal metabolite with immunosuppressive effects. It has been suggested that gliotoxin is secreted by \textit{Candida} and acts as a virulence factor in \textit{C. albicans}. The data, however, is contradictory [81].

Quorum-sensing is a cell signaling mechanism which is thought to be significant in biofilm formation. \textit{Candida albicans} has been shown to exhibit quorum-sensing and the quorum-sensing molecules in \textit{C. albicans} have been identified as tyrosol and farnesol. Tyrosol and farnesol have been shown to act as quorum-sensing molecules in biofilms [82]. Farnesol has been found to have no affect on the growth rate of \textit{C. albicans} and \textit{C. dubliniensis} but inhibits the hyphae and pseudohyphae formation in \textit{C. dubliniensis} [83]. There are relatively few studies on quorum-sensing in NCAC and the response of NCAC species and their hyphal growth and biofilms to tyrosol and farnesol. Also new insights into the morphogenesis of NCAC species are needed.
There are some studies on the interactions between NCAC and the oral epithelium [84] but particularly the cytokine inducing and cell damaging potential of NCAC is still unclear.

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