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Oral Microbiological Evidence among Palliative Patients: An Integrated Systematic Review

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Abstract

Life-limiting diseases such as cancers and its related treatments often compromise normal oral microbial flora and predispose a palliative patient to diverse oral infections. Knowledge on microbial flora in the oral cavity of patients with life-limiting diseases is essential to develop treatment options for clinical practitioners. This review aimed to systematically synthesize the published evidence on the oral microbiology of palliative patients. An integrative review was undertaken with defined search strategy from five databases with manual search through key journals and reference list. Studies included were published during the year 2000–2017 focusing on microbiological evidence associated with oral conditions among palliative patients. *Candida* presence was reported in the oral cavity of terminally ill patients in seven of nine articles, with *Candida albicans* being the predominant species. The majority of the included studies used oral swabs as a technique for isolation of the organism. This review is first to systematically synthesize the published evidence on the oral microbial flora of palliative patients, taking into account the techniques for identification of the microbiota. Larger multicenter studies may help in developing standardized clinical guidelines for the oral care of these patients.

Keywords: Cancer, *Candida*, microbial flora, oral care, terminally ill

INTRODUCTION

The oral cavity of humans is coated with a plethora of microorganisms.^[1] Although most of these are considered as “beneficial flora” and have a useful purpose in the body, any imbalance can create a widespread havoc to general and oral health of the individual.^[2] *Candida* species are normally present as commensals in the oral cavity with 30%–50% of a healthy individual carrying *Candida albicans* (*C. albicans*).^[2] However, conditions such as chemotherapy and radiotherapy can compromise the immunity and self-renewal of epithelial cells leading to disruptions in the barriers that normally defend the host against microbial invasion, thus predisposing a patient to fungal infections.^[3,4] The prevalence of clinical fungal infection increased by 24% among head-and-neck cancer patients pre- and postradiotherapy/chemotherapy.^[5]

Existing evidence on characterizing the oral microbiology of healthy individuals^[6,7] shows that 40% of the palliative patients lose their ability to communicate their oral health needs; therefore, they may suffer with treatable oral infections for a prolonged period of time.^[8] This may contribute to the underreporting of oral infections among palliative patients,

which may result in failure among health professionals to fully appreciate the problem. On the other hand, limited knowledge about oral conditions and related pathologies among palliative patients may continue to remain as a barrier for health-care practitioners to devise oral care interventions for this population.

Therefore, this systematic review aimed to synthesize the published evidence on the oral microbiology of palliative patients, with the following objectives:

- To identify the types of microflora in the oral cavity of palliative patients
- To identify the techniques used to investigate the microbiological presence in the oral cavity of palliative patients.

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METHODS

Data sources

Search strategy was devised by the research team comprising of a dentist (JSD), a palliative nurse (MRV), a medical doctor (DR), and a health-care researcher (ZR). Five electronic databases were used: ScienceDirect, PubMed, Google Scholar, Ovid, and EBSCOhost. Manual search was also conducted through key journals and reference list. We limited our search to articles published from January 2000 to December 2017. The search terms were “oral condition” OR “oral disease” OR “dental disease” OR “mouth disease” OR “mouth condition” OR mucositis OR stomatitis OR candidiasis OR cheilitis OR xerostomia OR “periodontal disease” OR halitosis OR thrush OR “angular cheilitis” OR “denture stomatitis” OR gingivitis OR periodontitis OR “mouth ulcer” OR “aphthous ulcer” AND palliative OR terminally-ill OR “terminally ill” OR “advanced disease” OR “advanced illness” OR dying OR end-of-life OR hospice OR cancer AND treatment OR intervention OR therapy OR management OR “oral care” OR “mouth care” OR “dental management” AND “end-of-life care.”

Study selection

Inclusion criteria specified that studies must be: (1) in full text, (2) in English language – to ensure no bias in translation, (3) research articles only – to ensure the articles retrieved had gone through peer-reviewed process, (4) published between year 2000 and 2017 – to ensure up-to-date research studies of the topic, (5) focused on palliative patients, and (6) analysis on microbiological evidence of oral conditions.

Figure 1 illustrates the PRISMA flow chart of study selection process. The initial combined search identified 25,311 articles from 5 databases and 19 articles from other sources (manual searching and through references). The titles of the articles were reviewed, and duplicates were removed which resulted in 25,263 being excluded as they did not focus on oral conditions among palliative patients. The abstracts of the remaining 67 articles were read to ensure the relevance of the articles to our study. This resulted in 28 articles being excluded. Two reviewers (ZR and DR) then independently read the remaining 39 articles and coded them for inclusion or exclusion. Following the independent review, the two reviewers met to discuss preliminary findings and to reach a consensus on the studies to be included, and thirty studies were excluded. Thus, for the purpose of analysis, there were a total of nine articles.

Data extraction

In the data extraction process, the study details are extracted in Table 1. This was done by two reviewers (ZR and DR). All reviewers discussed each article to reach consensus regarding the study details. The following information was extracted from each included study: author (s), year published, title, purpose, setting, origin of specimens, techniques, and microflora.

Assessment of study quality

The quality of the identified studies was assessed using Joanna Briggs Institute critical appraisal tool (a checklist for analytical

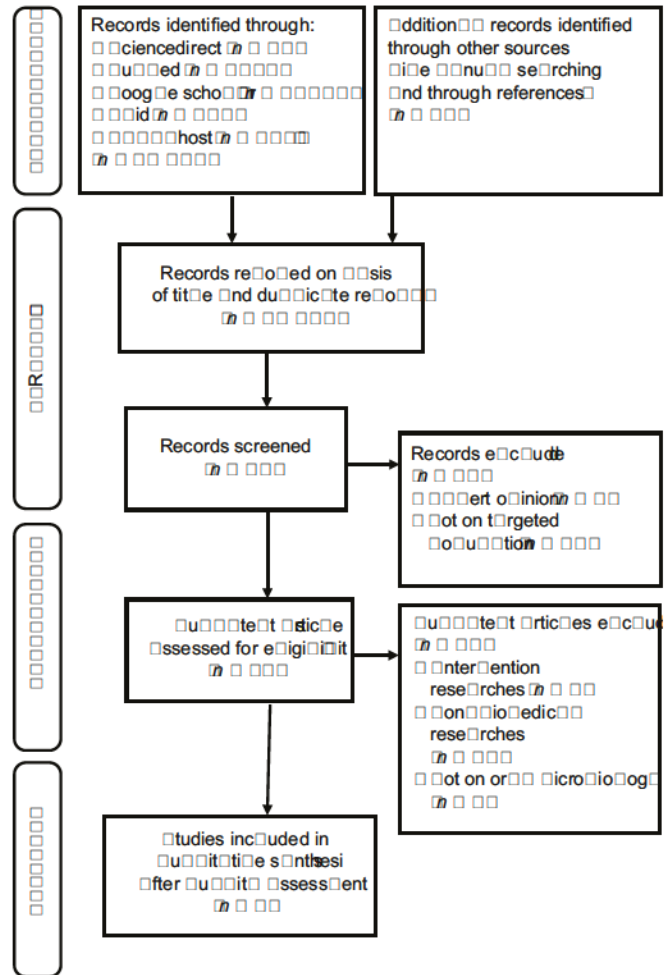


Figure 1: Process of study selection

cross-sectional studies) which consisted of eight questions focusing on the clarity of inclusion criteria, study subjects, setting, validity and reliability of the exposure and outcome measures, issues on confounding factors, and appropriateness of statistical analysis used.^[9] Each question has a choice of “yes,” “no,” “unclear,” or “not applicable” as an answer. Then, an overall appraisal was made whether to include or exclude each study, or to seek further information, with comments. Only the articles that were agreed by all involved researchers were included in this systematic review to inform the findings.

Data analysis

Extracted data from all included studies were analyzed using the Whittemore and Knafelz principles of integrative review with four stages: data reduction, data display, data comparison, and conclusion drawing and verification.^[10] At data reduction stage, all nine primary sources included in the integrative review were divided into a predetermined conceptual classification aligned with the aim of this review which is microbiological presence in the oral cavity of palliative patients and its identification techniques. Each primary source was reduced to a single page (available on request from authors). This helped us to systematically

Table 1: Summary of studies included

Author (s)/year	Title	Purpose	Setting	Origin of specimens	Techniques	Microflora present
Davies et al./2002	Oral yeast carriage in patients with advanced cancer	To investigate oral yeast carriage among patients with advanced cancer	United Kingdom	120 advanced cancer patients	Isolation and identification of yeasts from oral swabs Isolation of yeasts Using Sabouraud dextrose agar and CHROMagar™ Candida Identification of yeasts Using API 20 C AUX yeast identification system, species-specific PCR and 26S rDNA gene sequencing.	Oral yeast carriage present in 79 individuals (65.8%). Identified isolated individual species include: <i>C. albicans</i> , 46% <i>C. glabrata</i> , 18% <i>C. dubliniensis</i> , 5% Others <5%
Davies et al./2008	Oral candidosis in community based patients with advanced cancer	To determine the epidemiology, etiology, clinical features, and microbiological aspects of oral candidosis among community-based patients	United Kingdom	390 advanced cancer patients	Isolation and identification of yeasts from oral swabs Isolation of yeasts Using Sabouraud dextrose agar and CHROMagar™ Candida Identification of yeasts Using API 20 C AUX yeast identification system, species-specific PCR and 26S rDNA gene sequencing	272 individuals (69.7%) had microbiological evidence of oral yeast carriage <i>C. albicans</i> found sole in patients (n=51) is 26 Non- <i>C. albicans</i> in 13 patients Mixed species in 12
Sh/2011	Oral candidiasis amongst cancer patients at Qods hospitals in Sanandaj	To determine the occurrence of oral candidiasis among cancer patients at Qods hospitals in Sanandaj.	Iran	60 cancer patients	Isolation and identification of yeasts from oral swabs Isolation of yeasts Using Sabouraud dextrose agar and CHROMagar	19 <i>Candida</i> species were isolated; <i>C. albicans</i> outnumbered other species and accounted for 73.7% episodes of trash
Jayachandran et al./2016)	Oral candidiasis among cancer patients attending a tertiary care hospital in Chennai, South India: An evaluation of clinicomycological association and antifungal susceptibility pattern	To determine the species of <i>Candida</i> isolated from oral cavity of patients with malignancy	India	180 cancer patients on chemotherapy and/or radiotherapy	Two oral swabs taken over the lesions, for direct Gram staining to look for the presence of Gram-positive yeast cell and pseudohyphae, and for inoculating the specimen into Sabouraud dextrose agar	<i>C. albicans</i> was the predominant species isolated (94) (58%), followed by <i>C. tropicalis</i> (34) (20.9%)
Safdar et al./2001	Prospective study of <i>Candida</i> species in patients at a comprehensive cancer center	To prospectively evaluated the species stratification associated with heavy colonization and systemic infection in patients at Memorial Sloan Kettering Cancer Center in New York	United States of America	223 patients with cancer and AIDS	A germ tube test was performed for presumptive identification of <i>C. albicans</i> . Organisms that failed to form a germ tube were further tested by the auxanographic plate method Five to ten colonies were obtained from the primary culture and transported on Trypticase agar slants	<i>C. albicans</i> was the predominant species accounting for 235/349 <i>Candida</i> isolates (67.3%) Among 114 non-albicans <i>Candida</i> spp. <i>C. glabrata</i> (45.6%) <i>C. tropicalis</i> (18.4%) <i>C. parapsilosis</i> (16.6%) <i>C. krusei</i> (9.6%)
Suhail Lone et al./2014	Oral <i>Candida</i> colonization and infection in cancer patients and their antifungal susceptibility in a tertiary care hospital	To investigate the epidemiology of oral yeast colonization and infection among cancer patients	India	150 cancer patients and 150 healthy controls	Oral swabs (from tongue, buccal mucosa, and labial sulcus) taken from all the participants for yeast culture by directly inoculating on HiCrome <i>Candida</i> differential agar	Among the cancer group, total colonization was prevalent in 50% and oral candidiasis in 30% of all cancer patients <i>C. albicans</i> was the most common species (74.39%) causing colonization and candidiasis with 100% susceptibility to the two azoles

Contd...

Table 1: Contd...

Author (s)/year	Title	Purpose	Setting	Origin of specimens	Techniques	Microflora present
Alt-Epping et al./2012	Symptoms of the oral cavity and their association with local microbiological and clinical findings: A prospective survey in palliative care	To assess the subjective symptom burden and the prevalence of clinical and microbiological oral findings	Germany	101 cancer patients	Oral swab taken from buccal mucosa, the palatal ring, and tongue for culture, followed by a mouth wash for quantitative HSV DNA testing, using PCR technique	Yeasts were found in mouth swabs of 70 patients, and HSV DNA was detected in 19 patients Presence of <i>Candida</i> species was 88% among the study participants
Davies et al./2006	Oral candidosis in patients with advanced cancer	To determine the epidemiology, etiology, clinical features, and microbiological aspects of oral candidosis in a cohort of patients receiving specialist palliative care	United Kingdom	120 advanced cancer patients	Isolation and identification of yeasts from oral rinses and oral swabs Isolation Using Sabouraud dextrose agar and CHROMagar <i>Candida</i> Identification Using API 20 C AUX yeast identification system, PCR (nested), and DNA sequencing	79 individuals (66%) had microbiological evidence of oral yeast carriage 36 individuals (30%) had combined clinical and microbiological evidence of oral candidosis <i>C. albicans</i> was the predominant organism isolated from the oral swabs of patients with oral candidosis
Astvad et al., 2015	OPC in palliative care patients in Denmark	To evaluate the clinical and microbiological incidence of yeast carriage/OPC	Denmark	54 terminally ill patients	Paired samples from the buccal mucosa and the surface of the tongue were taken. The sampling included one sterile cotton swab smeared on a glass slide, fixated with methanol, followed by a sterile charcoal swab in Stuart Transport Medium	Yeast carriage rate was 83%. <i>C. albicans</i> accounted for half of the isolates cultured

C. albicans: *Candida albicans*, *C. glabrata*: *Candida glabrata*, *C. dubliniensis*: *Candida dubliniensis*, HSV: Herpes simplex virus, OPC: Oropharyngeal candidiasis, PCR: Polymerase chain reaction

compare primary sources on specific issues, variables, and sample characteristics. It also allowed us to organize data into a manageable framework.

At Stage 2 – data display, the single-page data from the nine included studies are then extracted and displayed in Table 1. This helped us to visualize the patterns and relationships between and within primary data sources.

At Stage 3 – data comparison, we used constant comparison as a method of an iterative process of examining data to identify themes that had similar patterns and relations.

Finally, at Stage 4 – conclusion and verification, we verified patterns using primary data and identified any similarities, differences, and any spurious findings. These were dealt with in order to ensure that valuable information was not lost. Five meetings were held in order to identify and reach a consensus on the final themes.

RESULTS

Characteristics of study

Overall, nine articles were found eligible and included in this review. The included study settings involved patients of advanced cancer conditions or palliative patients from

five European, three Asian, and one American country. The total number of each study participants ranged from 54 to 390. The microbiological evidence of oral conditions among palliative patients of the nine eligible studies is summarized in Table 1.

Common oral microorganisms present in palliative patients

Of nine studies, seven specifically reported *Candida* presence in the oral cavity of palliative patients.^[3,11-16] Two studies reported the presence of yeast carriage.^[17,18] *C. albicans* was the predominant species with at least 50% of the total mycological infection reported in seven of nine studies [Table 1]. Other species of *Candida* reported were *Candida glabrata*, *Candida dubliniensis*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*.

Predisposing factors for oral microbial pathology among palliative patient

Two studies reported dentures, xerostomia, and oral hygiene as predisposing factors for oral microbial pathology among palliative patients.^[11,17] Another study reported antibiotic and corticosteroid usage as predisposing factors for *Candida* species infections.^[15] Another prospective study considered clinical findings and laboratory findings to develop appropriate treatment strategies.^[18]

Association between oral symptoms and oral microbial flora

Only three studies reported a significant association between the presence of oral symptoms and the oral microbial flora, Jayachandran *et al.* found a significant association between dry mouth symptom and presence of *Candida* species.^[3] Davies reported that oral yeast carriage and denture wearing were significantly associated ($P < 0.006$). Similarly, there was an association between oral yeast carriage and low salivary flow rate ($P < 0.009$).^[11] Finally, a significant association was reported between prior treatment with triazole and isolation of fluconazole-resistant *C. albicans* ($P < 0.005$), but this relationship was not observed in *C. glabrata* isolates ($P = 0.4$).^[13] The other six studies reported only the mean and percentage of various *Candida* species.

Techniques used for identification of microbiological presence

Of the nine studies, eight studies used oral swabs to identify the microbiological presence except one,^[13] where a germ tube test was used for presumptive identification of *C. albicans*. In five studies, Sabouraud dextrose agar and/or CHROMagar were used for isolation of microbes,^[3,11,12,15,17] one study used Trypticase agar slants,^[13] another study used HiCrome *Candida* differential agar,^[14] and two studies did not specify the type of agar used.^[16,18]

Two studies adapted antifungal susceptibility test that used minimum inhibition concentration of various antifungal agents such as azoles, nystatin, and amphotericin against different isolates of *Candida* species.^[12,16]

Another two studies performed Clinical and Laboratory Standards Institute-guided microbroth dilution method to detect antifungal susceptibility.^[3,14] Another study used the National Committee for Clinical Laboratory Standards guidelines to identify antifungal susceptibility.^[13]

DISCUSSION

Our systematic review found *Candida* as the most common microflora in the oral cavity of palliative patients, with *C. albicans* being the predominant species. This finding is worrying because although *C. albicans* is often present as commensal in the oral cavity, their transition as an opportunistic pathogen is made possible when the host defense is compromised,^[19] for example, patients undergoing chemotherapy and/or radiotherapy targeting carcinomas and sarcomas.^[19] This is evident as oral candidiasis is common in head-and-neck cancer patients,^[19] with 70%–75% *Candida* carriage in patients taking chemotherapy and/or radiotherapy.^[20] A study reported that chemotherapy and/or radiotherapy causes mucositis and changes in saliva consistency. Xerostomia or thick saliva makes the oral environment conducive for fungal colonization.^[21]

Oral candidiasis is also a common side effect of cancer treatments which harm the body's mucous membranes and further weaken the immune system, making it more difficult for the body to fight off the *Candida* infection.^[16,22] Studies

have suggested the use of antifungal medications during cancer treatment to prevent an infection.^[16,22] In palliative conditions, diverse form of antifungal medications, such as mouthwashes, gels, ointments, capsules, or given as an infusion, and can help to have an effect on a limited local region (topical), on the entire body (systemic) or with a combined effect. However, no evidence is available whether these antifungal medications can help reduce other oral candidiasis symptoms such as pain or difficulty swallowing.

There are various techniques available for the isolation of *Candida* within the oral cavity such as the use of smear, an imprint culture, collection of whole saliva, concentrated oral rinse, and mucosal biopsy,^[23] and the majority of our included studies only used oral swabs for isolation. It is a relatively simple method of detecting growth of microflora, site specific, and can obtain semi-quantitative estimation of *Candida*, and this technique is difficult to standardize.^[23] Since *Candida* is the resident microflora within the oral cavity, a more reliable and appropriate isolation methods are required to ascertain its presence along with their quantity.

CONCLUSION

To our knowledge, this study is the first systematic review taking into account the techniques to identify the oral microflora among palliative patients. It is hoped that the information generated from this review will lead to a better understanding of oral conditions among palliative patients in order to direct the treatment options and enhance the quality of care for these terminally ill patients. Future studies with multicenter approach may help to develop standardized clinical guidelines for oral care of palliative patients.

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Conflicts of interest

There are no conflicts of interest.

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