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SPECIAL ARTICLE

A systematic review of oral fungal infections in patients receiving cancer therapy

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Abstract
Purpose The aims of this systematic review were to determine, in patients receiving cancer therapy, the prevalence of clinical oral fungal infection and fungal colonization, to determine the impact on quality of life and cost of care, and to review current management strategies for oral fungal infections.

Methods Thirty-nine articles that met the inclusion/exclusion criteria were independently reviewed by two calibrated reviewers, each using a standard form. Information was extracted on a number of variables, including study design, study population, sample size, interventions, blinding, outcome measures, methods, results, and conclusions for each article. Areas of discrepancy between the two reviews were

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resolved by consensus. Studies were weighted as to the quality of the study design, and recommendations were based on the relative strength of each paper. Statistical analyses were performed to determine the weighted prevalence of clinical oral fungal infection and fungal colonization.

Results For all cancer treatments, the weighted prevalence of clinical oral fungal infection was found to be 7.5% pre-treatment, 39.1% during treatment, and 32.6% after the end of cancer therapy. Head and neck radiotherapy and chemotherapy were each independently associated with a significantly increased risk for oral fungal infection. For all cancer treatments, the prevalence of oral colonization with fungal organisms was 48.2% before treatment, 72.2% during treatment, and 70.1% after treatment. The prophylactic use of fluconazole during cancer therapy resulted in a prevalence of clinical fungal infection of 1.9%. No information specific to oral fungal infections was found on quality of life or cost of care.

Conclusions There is an increased risk of clinically significant oral fungal infection during cancer therapy. Systemic antifungals are effective in the prevention of clinical oral fungal infection in patients receiving cancer therapy. Currently available topical antifungal agents are less efficacious, suggesting a need for better topical agents.

Keywords Oral candidiasis · Oropharyngeal candidiasis · Fungal infection · Fungal colonization · Antifungal agents

Introduction

Certain fungal organisms, notably *Candida albicans*, are commensal inhabitants of the oral cavity in a large proportion of individuals. Under normal conditions, these fungal organisms co-exist with the other microorganisms of the normal oral flora and do not cause disease. However, changes in the oral and/or systemic environment can result in an overgrowth of these fungal species, leading to clinical oral fungal infection. These changes include immunosuppression (induced by drugs or disease), imbalance in the oral flora (e.g., secondary to antibiotic therapy), hyposalivation (induced by drugs, disease or radiation therapy), and local tissue damage (e.g., mucositis secondary to chemotherapy and/or radiation therapy). Cancer patients receiving chemotherapy and/or radiation therapy are prone to all of the aforementioned predisposing factors and are therefore considered to be at higher risk for oral fungal infection than the general population [1, 2].

Oral candidiasis accounts for the vast majority of oral fungal infections, and can have a number of clinical presentations, including:

- Pseudomembranous candidiasis (thrush): presents as white curd-like pseudomembranes, which can be removed with some pressure, leaving behind an erythematous mucosa.
- Chronic hyperplastic candidiasis: presents as a hyperkeratotic white patch, with or without hyperplasia of epithelial tissue, which cannot be removed by scraping.
- Erythematous candidiasis: presents as intensely red inflamed areas of the oral mucosa, often under a denture or following antibiotic therapy.
- Angular cheilitis: presents as erythema, fissuring, and crusting of the commissures (angles) of the lips.

The most common forms of intraoral candidiasis reported in oncology patients are pseudomembranous and erythematous candidiasis, while hyperplastic candidiasis is rarely reported [3–5]. Oral candidiasis can be asymptomatic or associated with a number of symptoms. Erythematous candidiasis is often associated with a burning sensation of the mouth [6]. Involvement of the dorsal tongue may lead to a diffuse loss of filiform papillae, leading to a "bald" and red appearance, often accompanied by discomfort and taste changes. Pseudomembranous candidiasis may be accompanied by burning pain, taste changes when eating, and a foul taste when not eating [7]. Angular cheilitis is often uncomfortable and may cause pain when opening the mouth wide. Thus, the symptoms of oral candidiasis can have a significant impact on quality of life and can impair nutritional intake. In an oncology population, where compliance with treatment and maintenance of nutritional intake are vital, oral candidiasis can therefore affect systemic outcomes of cancer therapy. In addition, immunosuppressed cancer patients are at higher risk for oral candidiasis to spread to the oropharyngeal regions and subsequently to the systemic circulation. Systemic dissemination is also possible through the lesions of cancer therapy-induced oral mucositis and can be fatal [8]. Since oral candidiasis can be easily treated, particularly in the early stages, the early recognition and treatment of oral candidiasis is very important in oncology patients. However, there is limited information on the prevalence of oral fungal infection in this population and its impact on quality of life and cost of care.

The National Institutes of Health (NIH) Consensus Development Conference on the Oral Complications of Cancer Therapies held in 1989 highlighted the importance of recognition and management of oral infections, including oral candidiasis, in patients receiving cancer therapy [9]. The consensus statement mentioned the risk of systemic candidiasis in neutropenic patients and addressed topical and systemic management strategies [9].

There have been significant advances in the treatment of cancer in the last two decades. Newer and more effective chemotherapy regimens have been developed. Similarly, newer modalities of radiation therapy, including Intensity Modulated Radiation Therapy, allow for more precise targeting of radiation while minimizing radiation to adjacent

structures such as the salivary glands. Newer anti-fungal agents and prophylactic strategies have also been developed. Thus, the prevalence, impact, and management of oral fungal complications of cancer therapy are likely to have changed. The aims of this systematic review, therefore, were:

- To determine the prevalence of clinical oral fungal infection and fungal colonization in patients receiving cancer therapy.
- To determine the impact of oral fungal infections on quality of life and cost of care in patients receiving cancer therapy.
- To review current management strategies for prevention of oral fungal infections in patients receiving cancer therapy.

Methods

A research librarian conducted literature searches for studies published between January 1989 and December 2007 using PubMed, EMBASE, and The Cochrane Library. The search was specific to human studies reporting oral fungal infections as a side-effect of cancer therapy. The publication types included in this review were: randomized and non-randomized clinical trials, cohort studies, before and after studies, and case-control studies. The following publication types were excluded: non-systematic reviews, studies without original data on oral complications, studies that did not report data on oral fungal infection/colonization rates for specific cancer treatments received by subjects, case reports, opinion papers, and studies not published in English.

Each eligible article was evaluated independently by two reviewers, who then entered the data on a customized data abstraction form for reviewing oral fungal infections. Information on a number of variables including study design, study population, sample size, interventions, blinding, outcome measures, methods, results, and conclusions was abstracted from each article. The review of literature and development of recommendations were based on a standardized manual, common to all the systematic reviews of oral complications of cancer therapy. The quality of selected articles was assessed and scored with respect to sources of bias, representativeness, scale validity, and sample size. These parameters were utilized to determine the weighted prevalence of fungal infection or colonization. Further details of this process are described in the methodology paper by Brennan et al. [10].

Results

Sixty-five articles were initially identified based on the literature search. Following review, it was determined that thirty-nine articles met the inclusion/exclusion criteria described above. Of these, 24 studies [4, 5, 11–32] tested a specific antifungal intervention and 15 [3, 33–46] were not testing an antifungal intervention. Studies reporting clinical oral fungal infection used clinical examination, with or without supporting cultures, to make the diagnosis. Studies reporting fungal colonization used fungal cultures. There were no studies that provided data on quality of life or cost of care related to oral fungal infection during cancer therapy. Cancer diagnoses represented included head and neck cancer, Hodgkin's and non-Hodgkin's lymphoma, acute and chronic lymphocytic leukemia, acute myelogenous leukemia, multiple myeloma, and cancers of the lung, ovaries, breast, and prostate. Some studies included mixed cancer populations.

Observational studies: prevalence of clinical oral fungal infection

For all cancer treatments, the weighted prevalence of clinical oral fungal infection (all oral candidiasis) was 7.5% pre-treatment, 39.1% during treatment, and 32.6% after the end of cancer therapy. When examined by type of cancer therapy, the prevalence of oral candidiasis during head and neck radiation therapy (37.4%) was similar to that during chemotherapy (38%) (Table 1).

Observational studies: prevalence of fungal colonization

For all cancer treatments, the weighted prevalence of oral colonization with fungal organisms was 48.2% before treatment, 72.2% during treatment, and 70.1% after treatment. The prevalence of oral fungal colonization during chemotherapy (72.8%) was similar to that during radiation therapy (74.5%) (Table 2). Five studies [33, 37, 40, 41, 43] specifically assessed the prevalence of *Candida albicans* colonization during cancer therapy and collectively provided a mean weighted prevalence of 46.2%. Some of these studies also reported prevalence of colonization with other candida species during cancer therapy; with mean weighted prevalence rates of 16.6% for *Candida tropicalis*, 5.5% for *Candida glabrata*, and 3% for *Candida krusei* (Table 3).

Interventional studies: effectiveness of therapies to prevent clinical oral fungal infection

Twenty-four studies reported the effectiveness of antifungal agents in preventing clinical oral fungal infection in patients receiving cancer therapy, with some studies testing more than one agent (Table 4). Twelve studies [4, 5, 12, 19, 20, 23–25, 27, 29, 31, 32] had placebo or no treatment arms and collectively contributed to a weighted prevalence of

Table 1 Weighted prevalence of clinical oral fungal infection by cancer therapy

Cancer therapy	Number of studies [references]	Total number of subjects	Prevalence pre-treatment: mean (SE) [95% CI]	Prevalence during treatment mean (SE) [95% CI]	Prevalence post-treatment mean (SE) [95% CI]
All treatments	Eleven [3, 33–36, 38–40, 44–46]	478	7.5%	39.1% (0.08) [21.0–57.2]	32.6% (0.09) [0–100]
CT only	Five [34, 38, 39, 45, 46]	212	NA	38.0% (0.13) [1.2–74.7]	NA
RT only	Six [3, 33, 35, 36, 40, 44]	260	7.5%	37.4% (0.16) [0–88.4]	32.6% (0.09) [0–100]
CT + RT	One [36]	6	NA	66.7%[a]	NA

CT chemotherapy, *RT* radiation therapy, *SE* standard error, *CI* confidence interval, *NA* not available due to lack of eligible papers providing this data

[a] There is no SE or CI listed because these data were derived from only one eligible paper

clinical oral fungal infection (all oral candidiasis) of 20.3% in the placebo groups. Four of these studies examined subjects with head and neck cancer (weighted mean prevalence of 38.4%), with the remaining eight studying other tumor populations (weighted mean prevalence of 14.1%). In contrast, 17 studies [4, 5, 11, 13–16, 19–23, 26–29, 32] using fluconazole provided a weighted prevalence of 1.9% in the fluconazole group (Table 4). These 17 studies included four in patients with head and neck cancer (weighted prevalence of 2.2%) and 13 studies in other tumor populations (weighted prevalence of 1.8%). Data from three studies indicated a weighted mean prevalence of 2.3% for patients receiving amphotericin B [21, 22, 28] and four studies together indicated a weighted mean prevalence of 1.5% for itraconazole [11, 12, 25, 31]. Two studies in neutropenic cancer patients examined the use of a prophylactic antifungal regimen consisting of clotrimazole troches every 12 h and a mouthwash containing nystatin, Benadryl, and cepacol every 6 h, which resulted in a weighted prevalence of 14.6% for clinical oral fungal infection [15, 16]. One study examined the use of nystatin suspension as prophylaxis in patients receiving induction chemotherapy for leukemia and reported an oropharyngeal candidiasis prevalence of 6% in this group [13]. One study examining the use of amifostine during head and neck radiation therapy reported the occurrence of clinical oral candidiasis in 11 of 38 subjects (28.9%) in the amifostine group as compared to 9 of 16 subjects (56.2%) in the placebo group (p=0.07) [24].

Interventional studies: effectiveness of therapies to reduce oral fungal colonization rates

The weighted prevalence of oral fungal colonization in patients receiving fluconazole (determined from four studies [19, 20, 28, 29]) was 20% (Table 5). Three of these studies had placebo arms and provided a mean weighted colonization rate of 51.3% for the patients on placebo. One study tested the effects of mouth rinses containing nystatin, chlorhexidine, nystatin and chlorhexidine, and saline on fungal colonization. The colonization rates in the four groups ranged from 21% to 28% with no significant difference between any of the groups, including the saline group [18].

Discussion

The current systematic review confirms the increased risk of oral fungal infections in patients receiving cancer therapy, with supporting data on oral fungal colonization and infection in the various treatment groups. Head and

Table 2 Weighted prevalence of oral fungal colonization by cancer therapy

Cancer therapy	Number of studies [references]	Total number of subjects	Prevalence pre-treatment: mean (SE) [95% CI]	Prevalence during treatment mean (SE) [95% CI]	Prevalence post-treatment mean (SE) [95% CI]
All treatments	Seven [33, 34, 37, 39, 41–43]	267	48.2% (0.09) [22.3–74.1]	72.2% (0.05) [59.5–84.8]	70.1% (0.01) [57.8–82.3]
CT only	Four [34, 39, 41, 42]	157	47.3% (0.16) [0–100]	72.8% (0.09) [0–100]	69.3%
RT only	Three [33, 37, 43]	110	50.0% (0.07) [0–100]	74.5% (0.09) [34.1–100]	71.4%
CT + RT	Zero	0	NA	NA	NA

CT chemotherapy, *RT* radiation therapy, *SE* standard error, *CI* confidence interval, *NA* not available

Table 3 Weighted prevalence of colonization by candida species

Candida species	Number of studies [references]	Total number of subjects	Prevalence: mean (SE) [95% CI]
Candida albicans	Five [33, 37, 40, 41, 43]	174	46.2% (0.13) [9.8–82.5]
Candida tropicalis	Three [33, 40, 43]	122	16.6% (0.07) [0–48.4]
Candida glabrata	Three [33, 41, 43]	120	5.5% (0.02) [0–12.8]
Candida krusei	Three [33, 41, 43]	120	3.0% (0.02) [0–9.8]

SE standard error, *CI* confidence interval

neck radiotherapy and chemotherapy were each independently associated with a significantly increased risk for oral fungal infection. For patients receiving radiation therapy to the head and neck, the prevalence of clinical oral fungal infection in the observational studies (37.4%) was similar to that for the placebo/no treatment groups of interventional studies examining this population (38.4%), thus confirming the high risk in this relatively homogenous population. This increased risk is likely due to the salivary hypofunction resulting from radiation therapy, as supported by a study suggesting that use of the salivary gland function preserving agent, amifostine, during radiation therapy may reduce the risk for clinical oral candidiasis [24]. On the other hand, for patients receiving chemotherapy for other (primarily hematologic) cancers, the prevalence of clinical oral fungal infection in the observational studies (38%) was higher than that in the placebo/no treatment group in the interventional studies (14.1%). This difference may be attributable to a wide range of chemotherapy regimens utilized in the studies evaluated and selection bias based on more stringent exclusion criteria for interventional studies, which may limit the generalizability of prevalence data from such studies. Patients receiving chemotherapy are often immunosupressed, which increases the risk for infections, including oral candidiasis. Local tissue damage due to cancer therapy-induced oral mucositis and a consequently reduced ability to maintain oral hygiene may also increase the risk for oral candidiasis in both chemotherapy and head and neck radiation therapy populations. Patients receiving high-dose myelosuppressive chemotherapy in advance of stem cell transplants are now routinely given antifungal prophylaxis, and therefore, this group did not influence the clinical infection prevalence rates for chemotherapy patients.

Oral colonization with fungal organisms is also increased during cancer therapy. Although *Candida albicans* continues to be the most common species involved, other species, such as *Candida tropicalis* and *Candida glabrata*, are also present in a clinically significant proportion of patients. This is important because non-albicans *Candida* species, especially *Candida tropicalis*, are more likely to spread into the systemic circulation. The presence of *Candida tropicalis* in mucosal surveillance cultures has been reported to have a high predictive value for invasive fungal infection in neutropenic patients [47]. By comparison, *Candida albicans* in mucosal cultures is a poor predictor of subsequent systemic dissemination. The different implications of oral colonization vs infection underscore the need for treating clinicians to be alert for signs of clinical oral fungal infection in patients receiving cancer therapy.

In general, topical agents are considered preferable to systemic agents due to lower risk of side-effects and drug interactions. The Infectious Diseases Society of America

Table 4 Weighted prevalence of clinical oral fungal infection during cancer therapy by preventive treatment regimen

Treatment	Number of studies [references]	Total number of subjects	Weighted prevalence	Standard error	95% Confidence interval
Fluconazole	Seventeen [4, 5, 11, 13–16, 19–23, 26–29, 32]	1,642	1.9%	0.006	0.1–3.1
Amphotericin	Three [21, 22, 28]	454	2.3%	0.01	0–7.0
Itraconazole	Four [11, 12, 25, 31]	452	1.5%	0.17	0–5.2
Amifostine	One [24]	38	28.9%	NA	NA
Clotrimazole and nystatin	Two [15, 16]	96	14.6%	NA	NA
Nystatin alone	One [13]	53	6%	NA	NA
Placebo/ No treatment	Twelve [4, 5, 12, 19, 20, 23–25, 27, 29, 31, 32]	989	20.3%	0.54	8.4–32.1

NA not available

Table 5 Weighted prevalence of fungal colonization during cancer therapy by preventive treatment regimen

Treatment	Number of studies (reference)	Total number of subjects	Weighted prevalence	Standard error	95% Confidence interval
Fluconazole	Four [19, 20, 28, 29]	272	20.0%	0.06	0–40.2
Placebo	Three [19, 20, 29]	244	51.3%	0.84	15.1–87.5

(IDSA) guidelines recommend the use of clotrimazole troches or nystatin suspension/pastilles as first-line therapy for the management of mild oropharyngeal candidiasis [48]. However, studies reviewed for the 1989 conference [49] and for this review together present an inconsistent picture of the efficacy of topical agents in patients receiving cancer therapy (level of evidence II, recommendation grade C). Troches/pastilles require saliva to dissolve, and hyposalivation is a frequent problem in this population, especially in patients receiving head and neck radiation therapy. In addition, troches/pastilles can be traumatic to patients who have significant oral mucositis secondary to cancer therapy. Most formulations of troches/pastilles also contain sugar, which is not desirable from a caries prevention standpoint, especially in patients with hyposalivation. Advantages of nystatin rinse include its affordability and ease of use. Disadvantages include the short contact time with the oral tissues and occasional complaints about its taste.

Studies on the efficacy of systemic agents for antifungal prophylaxis provided a more consistent result. The largest number of studies used fluconazole, which was found to be very effective in the prevention of clinical oral fungal infection and in reducing oral fungal colonization in patients receiving cancer therapy (level of evidence I, recommendation grade A). This is consistent with the IDSA guidelines, which recommend the use of systemic fluconazole as first-line therapy for the management of moderate−severe oropharyngeal candidiasis [48]. For fluconazole-refractory disease, the IDSA guidelines recommend itraconazole or posaconazole, with voriconazole and amphotericin B reserved for refractory cases. We reviewed a limited number of studies using amphotericin B and itraconazole for oropharyngeal candidiasis in oncology patients, which indicated good efficacy for these agents. Additional systemic agents available include the lipid formulations of amphotericin B, and the echinocandins (caspofungin, anidulafungin, and micafungin). Use of systemic agents may be limited by their side effects, especially for amphotericin B. In addition, these agents are best used for short courses and their use for prophylaxis in certain oncology settings (e.g., patients receiving head and neck radiation therapy over 6−7 weeks) can be problematic. The emergence of resistant species is one important concern with such prophylactic use.

We were unable to find any eligible papers addressing the cost-effectiveness of prophylaxis specifically against oral fungal infection. However, prophylaxis against systemic fungal infections can also be expected to be effective against oral fungal infections. In patients receiving chemotherapy for acute myelogenous leukemia, prophylaxis of all patients with fluconazole was more expensive than using IV amphotericin B in febrile patients or IV micafungin after diagnosis of invasive fungal infection. However, fluconazole prophylaxis was associated with higher survival rates, at an additional cost of US $625−652 per year of life survived [50]. In neutropenic patients being treated for hematological malignancies, itraconazole prophylaxis was found to be clinically more effective and also more cost-effective than fluconazole prophylaxis or no prophylaxis [51]. Some studies have demonstrated that, due to its higher efficacy, posaconazole may be more cost-effective than fluconazole or itraconazole for prophylaxis against invasive fungal infections [52–54]. Finally, in patients undergoing hematopoetic stem cell transplant, prophylaxis with IV micafungin was associated with lower total costs than oral fluconazole prophylaxis, despite the significantly higher drug and administration costs of micafungin [55, 56]. Thus, the literature supports the clinical efficacy and cost-effectiveness of prophylaxis against invasive fungal infections, in neutropenic cancer patients. Cornely et al. have pointed out that, although superficial fungal infections (such as oral candidiasis) are usually responsive to local and/or systemic agents, there may be value in prophylaxis since colonization of two independent sites is a known risk factor for invasive candidiasis in patients with underlying hematologic disease [57]. However, it is worth noting that, in highly immunosupressed populations, antifungal prophylaxis is typically aimed at invasive fungal infections and can be expected to be effective against oral fungal infection; thus, specific antifungal prophylaxis against oral fungal infection is not needed in such circumstances.

Considering the high prevalence of clinical oral fungal infection in patients receiving cancer therapy, identification of more effective topical antifungal agents to avoid the potential side-effects of systemic agents would be beneficial. Studies are also needed to provide data regarding the impact of oral fungal infection on quality of life and cost of care in the oncology population.

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