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Oral complications of childhood cancer and its treatment: current best practice

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1. Introduction

As the advances in the treatment of children with cancer continue to improve overall survival, we need to focus our attention on the complications of treatment to reduce their frequency and their impact on disease remission, improve the cure rate and quality of life, and lessen the cost of care. Oral complications are recognised as a common adverse effect of childhood cancer therapy, with risks for septicaemia, nutritional compromise, significant pain and long-term morbidity [1,2].

A review of current published research related to the oral complications of cancer and its treatment, while revealing a generous amount of research in adults, shows a paucity of controlled clinical trials in children. Research in this area has increased our understanding of the aetiology and pathophysiology of oral mucositis. Therapeutic approaches to the oral complications of cancer are, however, largely based on clinical experience, and therefore no approach has emerged as the 'gold standard'. Further research is needed to standardise preventative oral care, and the prophylaxis and treatment of mucositis, bacterial, fungal and viral oral infections, in order to improve the quality of life for patients undergoing treatment for childhood cancer. This article will review recent research applicable to oral mucositis, oral infections, xerostomia and dental abnormalities in paediatric cancer therapy and discuss current best practice in the management of these complications.

2. Mucositis

Oral mucositis is the term used to describe the erythematous inflammatory changes that occur on buccal and labial surfaces, the ventral surface of the tongue, the floor of the mouth and the soft palate of patients receiving stomatotoxic chemotherapy and radiation. [1,2]. Patients describe the initial condition as a burning or tingling sensation making the mouth hypersensitive to foods. Eating, swallowing and talking become difficult as the mucositis progresses [3]. When nutrition is impaired as a result of refusal to eat, healing may be delayed since an overall decrease in cell renewal and migration occurs after caloric starvation and protein deprivation. [4]. Damage and breaks in the epithelial barrier of the oral mucosa allow infection by the resident oral flora to develop and are a significant risk for disseminated infection [1]. There are reports on the pain of oral mucositis, particularly in patients receiving combination therapy as in stem-cell transplants (SCT), and the effectiveness of patient-controlled analgesia (PCA) in the management of this pain [5,6].

Current studies record the incidence of oral mucositis in childhood cancer therapy as 50–54% [7,8]. Children and adolescents appear to have a greater incidence of chemotherapy-induced mucositis than adults, which might be explained by a more rapid epithelial mitotic rate, although the lesions heal more quickly [9,10]. Other factors influencing the frequency and severity of mucositis are simultaneous radiochemotherapy, which affects patients with head-and-neck cancer and those undergoing conditioning for SCT, pretreatment xerostomia and prior oral health [1,2,9,10]. Patients in good dental health who maintain scrupulous oral hygiene during cancer treatment tend to have fewer episodes of mucositis than do patients with poor oral health and maintenance [9,11]. Conversely, pre-existing dental diseases constitute a reservoir of pathogenic and opportunistic organisms that can contribute to local infections in the inflamed oral mucosa [4]. Agents that are DNA-cycle specific, such as bleomycin, cisplatin, fluorouracil and methotrexate, are known to be more stomatotoxic than cell-phase non-specific agents [10,11]. Certain

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chemotherapeutic agents, such as methotrexate and etoposide, may also be secreted in the saliva, leading to increased direct stomatotoxicity [10]. Drug-induced mucositis is dependent on dose and schedule, and can be a dose-limiting toxicity [10].

During conventional curative radiation for head-and-neck cancer, the first signs of mucositis, a white discoloration or erythema, will appear after 10 Gy radiotherapy. The more severe stages of mucositis, pseudomembranes and ulceration, occur after 30 Gy [12].

The intensity of oral mucositis is commonly scored using World Health Organisation or National Cancer Institute oral toxicity scales, which describe the progression of signs/symptoms from mild to moderate to severe and life threatening in grades 1–4 [13,14]. Several clinical and research-orientated oral assessment guides have been developed that evaluate mucositis with more detailed criteria [15,16]. Standardising the precise quantification of oral complications is essential when conducting clinical trials of new treatments [15].

3. New insights into the pathophysiology of mucositis

Sonis's biophysical model describing the pathophysiological concepts of mucositis provides a new framework for both assessment and management. In Sonis's model there are four phases of mucositis: an initial inflammatory/vascular phase, an epithelial phase, an ulcerative/bacteriological phase and a healing phase [9]. Since each phase offers the opportunity for therapeutic interventions, their assessment and potential strategies for their management will be discussed together in the ensuing paragraphs.

In Sonis's model, the inflammatory/vascular phase occurs within 24–36 h of the administration of the stomatotoxic radiation or chemotherapy, when inflammatory cytokines such as interleukin 1 and tumour necrosis factor are released from epithelial tissue [9]. When this inflammatory cascade is released, the vascularity of the tissues is increased and additional concentrations of cytotoxic agents may be deposited in the mucosa [9]. The simple approach of sucking on ice chips during the infusion of chemotherapy can cause local vasoconstriction and may reduce the uptake of agents with a short half-life into mucosal cells [17]. Ice-chip cryotherapy was effective in reducing the severity of mucositis in phase I and II trials with edatrexate and carboplatin [18,19]. Oral cryotherapy is the only measure of proven effectiveness in preventing mucositis mentioned in the current Cochrane Oral Health Review [20].

The epithelial phase occurs 4–5 days after administering the cytotoxic agent, when the reduced cell turnover in the oral basal epithelium and the flood of locally produced cytokines allows further tissue damage, atrophy and ulceration [9]. Treatments in this phase need to be directed at restoring cell growth in the epithelial tissue and reducing cytokine release to prevent further tissue damage. A multitude of drugs have been evaluated in research studies, including sucralfate and oral glutamine, which continue to be tested, and newer agents such as cytokine mouthwashes, which show promise of potential benefit in this epithelial stage. The clinical use of sucralfate, with its cytoprotectant properties and possible epithelial regenerative effect, has produced inconsistent results [4 11,21,22]. Cengiz and colleagues found that sucralfate in a mouthwash in four doses before meals and at bedtime in adult patients receiving head-and-neck radiation significantly decreased the degree of mucositis and oral pain during feeding [21]. Other studies have failed to show this effect [4,11,22]. Systemic use of colony-stimulating factors (G/GMCSF) has been proved to accelerate the recovery of neutrophils after myelosuppressive chemotherapy. Earlier neutrophil recovery may play an important part in decreasing the duration and severity of oral mucositis [23]. However, GCSF may also directly induce the proliferation of endothelial cells and keratinocytes [23]. Clinical studies in adults on the topical application of GM-CSF mouth rinses following the administration of 5-fluorouracil resulted in a shorter duration and quicker resolution of oral mucositis f [23]. Glutamine is the most abundant amino acid in the blood and appears to have a major role in mucosal cellular metabolism as a respiratory fuel for enterocytes in the gut [24]. Anderson and colleagues, in a study conducted mostly in adolescents and children who had previously experienced mucositis after an identical course of chemotherapy, found that glutamine in a swish-and-swallow suspension during and after chemotherapy reduced the duration and severity of mucositis [24].

By 1 week after the administration of a stomatotoxic drug, when the haematological effects are beginning, particularly as the absolute neutrophil count drops, ulcerations become exudative and erosive [9]. This ulcerative phase and the concomitant neutropenia provide an opportunity for bacteria, viruses and yeast to proliferate. The endotoxins produced may further enhance the inflammatory cascade and intensify the oral mucosal damage [9]. Studies on the use of topical antimicrobials and antiseptic rinses that may be useful for treatment in this stage, such as chlorhexidine and lozenges of polymixin B, tobramycin, and amphotericin B, reveal conflicting results with no clear recommendations evident from current research [10,11,22]. In a group of adult patients receiving stomatotoxic chemotherapy, Dodd and colleagues evaluated three mouthwashes commonly used to treat chemotherapy-induced mucositis—salt and soda, chlorhexidine, and 'magic' mouthwash (lidocaine (lignocaine), Benadryl, and Maalox)—and found no significant differences in the time of cessation of signs and symptoms of mucositis.

Given its similar effectiveness, they recommend the least costly salt and soda mouthwash [25].

Pain and nutrition, in addition to risk for infection, need to be carefully assessed in this ulcerative phase. The co-operation of children with mucosal ulcerations in eating and performing oral hygiene usually requires analgesic premedication. Topical anaesthetics such as lidocaine (lignocaine), dyclonine and diphenhydramine in mouth rinses, with or without an antacid suspension, may be useful for localised, non-contiguous mucosal ulcerations and are frequently recommended in paediatrics [26,27]. At our institution, patients are instructed to rinse or swab with equal proportions of viscous lidocaine (lignocaine), diphenhydramine and an aluminium magnesium hydroxide suspension every 4 h and then spit out. Lidocaine (lignocaine) may result in burning with use, and obtund taste and the gag reflex, and it may also have cardiovascular and central nervous effects [26]. These effects warrant close supervision during its use in child patients who may have difficulty in spitting. A topical analgesic with anti-inflammatory action, benzydamine HCl, may reduce radiation-induced mucositis but has not been studied in chemotherapy-induced mucositis [26]. When topical analgesics fail or are not feasible because oral pain prohibits the intake of medications and food, parenteral administration is used. There is a high degree of variability in both the dose and duration of opioid required to achieve adequate analgesia for mucositis pain. PCA can accommodate this variability better than other methods of opioid delivery [6]. Despite adequate pain control, children with mucositis often cannot be enticed to eat and parenteral or enteral feeding may be needed. A study by Pietsch and colleagues found that glutamine-supplemented enteral feedings in children receiving intensive chemotherapy or SCT had minimal complications and significant cost savings when compared to parenteral nutrition [28]. The effect of the free glutamine-containing formula (Vivonex Pediatric; Novartis Nutrition, Minneapolis, MN) chosen in this study was supported by studies showing that certain enteral formulations not only preserve the integrity of the intestine and reduce bacterial translocation but also enhance the immune response [28].

Healing can begin in 2–3 weeks as oral mucosal cells and leucocytes, which have the same renewal rate, recover, if nutrition is not compromised and infection with an opportunistic organism has not occurred.

4. Other oral complications

4.1. Viral infections

Herpes simplex virus (HSV) is the most common viral infection occurring in child patients being treated for oncological diseases [2,29,30]. It occurs most often as a reactivation of the virus in a previously infected individual. HSV infection usually begins as vesicular lesions either peri- or intraorally, which will then progress to crusted lesions. Intraoral lesions may never develop this crusted appearance, but rather may remain ulcerated with a yellowish appearance [31]. In many cases, it is difficult to distinguish between mucositis and oral HSV. In these cases a viral culture is needed to tell the difference. However, patients infected with HSV will often have characteristic oedematous and punched-out lesions along their gingival margins, which can help the practitioner to make a clinical diagnosis [32]. HSV infection can be exquisitely painful and cause such profound oedema of the oral mucosa that the patient presents with pain, distress, drooling and an inability to swallow.

The treatment of patients infected with HSV includes supportive care with fluids, parenterally if they are unable to take fluid orally, and pain management. Antiviral therapy with acyclovir, given orally or intravenously depending on the severity of the infection, remains the standard care in the paediatric population [29,31]. Analogues of acyclovir have been developed, such as famciclovir, valacyclovir, ganciclovir and foscarnet [29,31]. The use of these medications has not been widely studied in paediatrics, and they are not FDA approved for paediatric use. Some practitioners are using them in adolescents. It is recommended that patients with a high risk for reactivation of HSV, such as SCT patients, be placed on prophylactic doses of acyclovir to prevent reactivation [29].

4.2. Fungal infections

Oral fungal infections are very common in children receiving treatment for cancer. Child patients are at a higher risk for oral fungal infections, due to the use of broad-spectrum antibiotics and steroids, and poor oral hygiene and poor nutrition [1,30]. *Candida albicans* is the primary cause of opportunistic fungal infection in patients who are immune compromised [30]. 60% of individuals carry *C. albicans* as part of their normal oral flora [32]. When patients are immunosuppressed, neutropenic and/or on steroids they can have an overgrowth of candida in their mouths. This overgrowth is worsened if xerostomia is present or if they have poor mouth care [32].

Oral fungal infections can present in several ways, most commonly as erythematous or pseudomembranous candidiasis. Erythematous candidiasis is mostly found in adult patients who wear dentures [32]. It is not white, but rather appears as patchy or diffuse areas of erythema, mostly on the palate [30–32]. Pseudomembranous candidiasis presents as patchy or curd-like white lesions, which can be removed but which causes bleeding and erosion beneath them [30–32]. Hyperplastic

candidiasis presents as elevated white plaques that cannot be wiped off and look more like leukoplakia. Lesions do not respond to treatment should be biopsied [30–32].

Children with oral candidal infections generally do not present with any complaints. The lesions are usually found on physical examination. Occasionally patients will complain of nausea if the lesions spread to the oesophagus. The presence of oropharyngeal candidiasis plus symptoms of oesophagitis is predictive of oesophageal candidiasis [33]. Untreated oral candidiasis may progress to systemic disease, which can be fatal [1,31,32,34]. Almost all cases of systemic candidiasis originate from the mouth [2].

Treatment options for oropharyngeal candidiasis include topical azoles (clotrimazole troches), oral azoles (fluconazole, ketoconazole or itraconazole) or oral polyenes (nystatin or amphotericin B suspension) [33]. Nystatin oral suspension and clotrimazole troches continue to be the common treatment choices in childhood oral candidiasis. *C. albicans* is very sensitive to these medications [33]. However, they have similar drawbacks. They require four times-a-day topical oral administrations, which encourages poor compliance in children, and they have a high sucrose content, which predisposes to dental caries, particularly in patients with xerostomia. In a study of a preventative oral protocol in children with acute lymphoblastic leukaemia, nystatin oral suspension was prepared with sorbitol instead of sucrose [35]. Topical treatments are effective in treating initial cases of oral candidal infection, but in patients who have refractory or recurrent infections, orally administered and absorbed azoles may be a better choice [33]. Topical treatment is ineffective in treating patients with oesophageal candidiasis [33].

Fluconazole, with its once-daily administration, is an effective alternative treatment. Rex and colleagues found oral fluconazole as effective as the topical treatments and noted that in some studies it was found to be superior [33]. By using twice the usual daily dose as a loading dose one can more rapidly achieve a steady-state concentration of the drug in the blood [33]. It is suggested that the dose for treating oral candidiasis in children is 6 mg/kg per day on day 1 and then 3 mg/kg per day on days 2–10.

Other antifungal medications used to treat fungal infections are ketoconazole, itraconazole, voriconazole and amphotericin B. These drugs may be used for refractory or recurrent cases of oral candidiasis and for patients with documented or suspected systemic infection. One study in human immunodeficiency virus-infected children showed that itraconazole was effective in treating oropharyngeal candidiasis at doses of 2.5 mg/kg per day and 5 mg/kg per day [33].

The newest drug for the treatment of fungal infections is caspofungin acetate. Its safety and effectiveness in child patients has not been established, although there are controlled clinical studies using it to treat systemic fungal infections in children. In adult studies conducted by Merck Laboratories, the efficacy of caspofungin acetate was similar to that of amphotericin and fluconazole for candidaemia, oesophageal candidiasis and invasive aspergillosis [36]. The incidence of drug-related clinical and laboratory adverse events, including nephrotoxicity, was lower with caspofungin acetate than with amphotericin B [36].

4.3. Xerostomia

Xerostomia, or dry mouth, is a condition that is caused by both chemotherapy and radiation to the head and neck. It is the result of damage to the acini of the salivary gland, which changes the consistency and amount of saliva in the mouth. This change promotes a more acidic pH, creating an environment that is conducive to the formation of dental caries [1,2,37,38]. Patients with xerostomia change from Gram-positive bacteria as their normal oral flora to a Gram-negative and fungal flora [31], which places them at greater risk for a life-threatening opportunistic infection during periods of neutropenia. Dry mouth is distressing because it is not only uncomfortable but also causes changes in taste, and difficulty with chewing, swallowing and speaking. Damage caused by chemotherapy is usually transient and self-limiting, resolving within 48 h [1]. The damage caused by radiation to the head and neck is usually permanent, although some patients will have a return of some salivary function by 4–12 months after therapy [1,37]. The outcome is best in those patients whose radiation field does not directly involve the parotid glands, although this is difficult to achieve, especially with patients who require radiation to the neck [38].

Although there is a large literature on xerostomia in adult oncology, there are few such publications concerning the paediatric population. What is available recommends using a combination of treatments including synthetic salivary substitutes, stimulation of the remaining salivary tissue, meticulous oral hygiene daily and topical fluoride [1,2]. There are several salivary substitutes available, but patients do just as well by carrying a bottle of water or some other liquid with them from which to take frequent sips [37]. The newest treatment for xerostomia is the use of pilocarpine to stimulate any remaining salivary tissue. Pilocarpine is a cholinergic parasympathomimetic agent that can be used to stimulate salivary flow [37,39]. There is one case report of the use of pilocarpine in a 9-year-old patient with nasopharyngeal carcinoma who received a total of 5940 cGy to the head and neck. He was started on pilocarpine at the beginning of his radiation therapy, at a dose of 5 mg orally three times a day, and 7 months

after its completion he had no symptoms of xerostomia [38].

5. Dental abnormalities

Kaste and colleagues found dental abnormalities, including root stunting, microdontia, hypodontia, enlarged pulp chambers and over-retention of primary teeth, in children treated for acute lymphoblastic leukaemia [40]. The same investigators found similar abnormalities in 71% of children treated for neuroblastoma, as well as excessive caries and enamel hypoplasia [41]. In another study, 83% of children treated for acute lymphoid leukaemia were found to have dental abnormalities, including delayed eruption, microdontia, hypoplasia, agenesis, and V-shaped and shortened roots [42]. In addition to the above abnormalities, bony hypoplasia/facial asymmetry, trismus, velopharyngeal incompetence, tooth and root agenesis and an underdeveloped mandible were observed in children receiving chemotherapy and radiation for head-and-neck rhabdomyosarcoma [43]. Histological changes in dental structures, including incremental lines in dentine and enamel, as a result of chemotherapy and radiation have been documented in animals as well as man [41,43]. The child's age at the beginning of therapy as well as the type, intensity and frequency of the therapy administered are factors involved in the genesis of these dental abnormalities [42,43]. Advanced techniques such as magnetic resonance imaging and intensity-modulated radiotherapy are refining treatment for patients with head-and-neck cancer and show promise in reducing late dental effects [43].

6. Preventive intervention

The most effective measure in the prevention and treatment of the oral complications of cancer therapy is meticulous oral hygiene. Recent studies document the benefit of preventative mouth care in children. In a study by Bonnaure-Mallet and colleagues on children receiving cancer therapy following an oral-care programme, mouth lesions were more numerous in the group that did not tooth brush than in the group that brushed [7]. Levy-Pollack and colleagues, in their study of children with acute lymphocytic leukaemia, found a significant decrease in the incidence of mucositis following a preventive protocol of dental cleaning, aqueous chlorhexidine rinses, topical applications of iodopovidone and nystatin rinses [35]. In a study of child patients with acute lymphoblastic leukaemia or lymphoma, one group of which was boosted with oral physiotherapy, fluoride mouthwashes and topical applications of myconazole oral gel and the other group with instructions for oral physiotherapy, there were no significant differences between the groups but less mucositis was seen overall [44]. Cheng and colleagues found a significant reduction in the incidence of ulcerative lesions in children receiving high-dose or combination chemotherapy for haematological and solid malignancies following an oral care protocol consisting of tooth brushing and a saline rinse followed by a chlorhexidine rinse after each meal and before bedtime [8].

A multidisciplinary team approach is recommended for children receiving stomatotoxic therapy. A complementary oral-health team should include oncology physicians and nurses and dentists. Before beginning therapy a preventative approach should start with an examination by a dentist to remove plaque, treat existing caries and examine removable prostheses or orthodontics. Restorative dental procedures should be performed at least 3 weeks before the start of mucosatoxic therapy [11]. Although they have not been evaluated in clinical trials, topical fluorides are frequently applied to prevent caries and mucositis in the course of radiotherapy because they induce fluoride incorporation into tooth enamel and dentine and reduce the oral bacterial load [11].

Nurses may take the lead in providing systematic oral preventative care. A nurse-initiated preventative programme in adult patients has been found to be a time-efficient, cost-effective way to reduce cancer morbidity. In the PRO-SELF Mouth Aware Program (PMSA), patients are given didactic information on mouth care, taught self-care and then supported by nurses, with a review of information and a mouth examination at each visit [45]. A basic premise of the PSMA program is the belief that once a relationship with the nurse has been established, patients will be receptive to supportive nursing that offers encouragement and problem-solving assistance in their self-care [45].

Child oncology patients and their caregivers need to be instructed in oral hygiene by tooth brushing with a soft brush and fluoride toothpaste. Incorporating the principles of good oral hygiene from the PMSA program, families can be taught to use a new toothbrush for each cycle of chemotherapy, consistent, thorough tooth brushing for 90 s, daily flossing and which oral conditions should be brought to the attention of the nurse. Very soft brushes, moistened gauze or sponge 'toothettes' used during periods of thrombocytopenia and neutropenia will maintain good hygiene while minimising gingival trauma [41]. Rinses with salt water and baking soda following each meal and before bedtime, the use of lip lubricants and sugar-free products will decrease the cariogenic oral flora [11]. A thorough oral examination should be performed at each visit to detect oral lesions early and step up care as needed for signs of mucositis or infection. In addition, dental protocols for children receiving stomatotoxic therapy

(frequent dental follow-ups, early detection of caries, and the prevention of periodontal disease) could decrease or eliminate the need for invasive dental procedures in survivors of childhood cancer [43].

7. Conclusion

Unfortunately, there are few new treatments for child patients experiencing oral complications of chemotherapy and radiation. Comprehensive research reviews of the options for the prevention and treatment of oral mucositis reveal that most of the newer interventions have not been widely used or studied in the paediatric population. Furthermore, limitations in study design and a lack of consistency in measurements in adult studies make comparisons of antimicrobials, coating agents and anti-inflammatory agents difficult. Extrapolation of these research results to paediatric care is even more difficult and offers opportunities for more, well-designed trials in children to assess the effectiveness of old and new interventions for oral complications. As always in medicine, prevention remains the best treatment. Dental evaluation at diagnosis and meticulous oral hygiene during oncotherapy, with a multidisciplinary team approach, will minimise the oral complications of childhood cancer and improve the quality of life in survivors.

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