Assessment of Oral Mucositis, Oral health Outcomes, and Implementation of a Standardized Oral Health Care Protocol for a Pediatric Inpatient Population Receiving Cancer Treatment

By

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Abstract

Rationale: Oral mucositis can compromise cancer treatment, reduce quality of life, and lead to debilitation among childhood cancer patients. Recent clinical trials have recognized oral care to prevent oral mucositis, however, few studies have reported oral health outcomes of children receiving cancer treatment. Aim and Objectives: This research was undertaken to assess oral mucositis incidence and oral care outcomes, and to explore possible risk factors for oral mucositis among inpatient children receiving cancer treatment at the Women's and Children Hospital, Adelaide, Australia. The objectives were to investigate the evidence on oral mucositis prevention, assess and validate the combined use of the Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) oral mucositis scale in recording oral mucositis incidence, develop and implement a standardized hospital oral care protocol, and to record prospectively oral mucositis incidence, oral health outcomes, and possible risk factors. Methods: A systematic review was conducted to assess the current evidence on oral mucositis prevention among children. Results of a previous retrospective study were used to design a prospective pilot study. The pilot study was carried out for seven months during which the new oral care protocol was implemented and the ChIMES and the WHO oral mucositis scale were validated through daily recording of oral mucositis in the oncology ward. Measures of reliability and compliance were assessed among nurses and dental staff involved in recording oral mucositis and oral health status. The pilot study was followed by a prospective clinical observational study and recorded measures of oral mucositis (12 months) and oral health status (24 months). Measures of oral health outcomes were assessed initially and then every three months through clinical examination to record dental caries and oral hygiene while

measures of oral mucositis was recorded daily during the hospital stay of recruited children. The incidence of oral mucositis, oral health outcomes, and dental treatment utilization were then analyzed to explore possible risk associations. Results: The systematic review supported the benefit of implementing a standardized oral care protocol to prevent oral mucositis among children. Thirty-eight children were conveniently sampled during the pilot study during which high levels of reliability and compliance (87%) in using ChIMES and WHO oral mucositis scales were achieved. Dental referrals increased from 53% to 100% after adopting the comprehensive oral care protocol. Sixty-seven children were recruited during the prospective part with oral mucositis incidence similar to that of the pilot study (33% versus 34%). Dental caries prevalence was 28% with absence of new carious lesions throughout the 24 months follow up. Regular dental reviews were significantly related to shorter duration of oral mucositis (adjusted rate ratio=0.94; 95% CI=0.89-0.99; P-value=0.026) and hence fewer days of hospital stay. On the other hand, an increase in days of hospital stay was significantly related to oral mucositis incidence (adjusted rate ratio=1.64; 95% CI=1.002-2.69; P-value=0.049). Conclusion: Implementing a comprehensive oral care protocol and consistent recording of oral mucositis have resulted in low rates of oral mucositis and dental caries incidence among inpatient children receiving cancer treatment.

Thesis declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Dedication

I dedicate the knowledge provided in this thesis and the benefits that can come out of it to the pure soles of the children who participated in this study and lost their battle to cancer. May Allah's blessings surround their soles in heavens, where they will have a prosperous and suffer-free eternal life in paradise.

I also dedicate this work to all children who are still fighting cancer. May Allah almighty grant them the strength, patience, and bravery throughout their treatment. May Allah almighty grant their families the capacity to accommodate this hardship and to see the smiles of their little angels shine on their faces for years to come.

I hope that Allah almighty accepts from me and counts this work as a good deed

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1.0 Introduction and background

1.1 Cancer in the pediatric population

Different types of cancer can affect children and adults. However, there are several important differences between childhood and adult cancers. These differences include the origins of these cancers and other clinical characteristics. Among these differences is the difference in types and prevalence/incidence rates of cancers affecting children and adults. Children can withstand and recover faster to their original body status after a period of bone marrow suppression due to cancer treatment when compared to affected adults. On the contrary, late effects of cancer treatment tend to affect children more than adults (1-3). Another clinical difference is the limited ability of children to describe the severity of clinical symptoms such as pain and discomfort thus posing a challenge to health personnel when assessing such measures.

Childhood cancer also differs biologically and histologically from that of adults (4). Biologically, cancer in affected children shows close relationship between abnormal development (teratogenesis) and cancer induction (oncogenesis) (4). Childhood cancer is usually associated with underlying genetic abnormalities (4). Most fetal and neonatal malignant cancer variants tend to regress or cytodifferentiate spontaneously (4). The biology of cancer among children also differs form that of adults in having better survival and remission rates (4).

The histology of cancer among children is unique because it tends to have a primitive rather than pleomorphic-anaplastic microscopic picture and it exhibits features of organogenesis that are specific to the origin of the cancer (5). In contrast to adult

cancers which are mostly carcinomas, childhood cancers are histologically very diverse and include embryonal tumors and sarcomas (5).

1.2 Classification and epidemiology of childhood cancer

It was recommended in the recent editions of the International Classification of Childhood Cancer (ICCC-3) and the International Classification of Diseases for Oncology (ICD-10) that childhood cancer are classified according to morphology rather than the site of origin that is usually used for adult cancers classification (6, 7). The ICCC-3 classification was based on morphology, topography and behavior. The classification was developed and presented on three levels. Level one included 12 main diagnostic groups, level two included 47 diagnostic subgroups and level three included extended classification.

The main diagnostic groups of childhood cancer include (7):

1) Leukemias, myeloproliferative diseases and myelodysplastic diseases
2) Lymphomas and reticuloendothelial neoplasms
3) Central nervous system and miscellaneous intracranial and intraspinal neoplasms
4) Neuroblastoma and other peripheral nervous system cell tumors
5) Retinoblastoma
6) Renal tumors
7) Hepatic tumors
8) Malignant bone tumors
9) Soft tissue and other extraosseous sarcomas
10) Germ cell tumors, trophoblastic tumors and neoplasms of gonads
11) Other malignant epithelial neoplasms and malignant melanomas
12) Other and unspecified malignant neoplasms

Childhood cancer is considered a rare disease that was found to affect only 0.5% of children under the age of 15 years (5). The age standardized annual incidence of childhood cancer for 0-14 years ranges between 70 and 160 per million (8). The worldwide annual number of new cases of childhood cancer was estimated to exceed 200,000 with 80% of it occurring among the developing world (9). Although cancer was responsible for 13% of worldwide deaths (10), the overall five-year survival rate for all childhood cancers combined was estimated at 75-79% (11).

Among the different types of childhood cancers, leukemias constitute approximately one third of all childhood cancers with an age standardized rate of 35-50 per million (8). Of all types of leukemias, acute lymphocytic leukemia (ALL) comprises around 80% of the total rate of childhood leukemia in most populations (8). In another epidemiological study, leukemias were found to constitute 31.5% of all childhood cancers followed by central nervous system neoplasms (17.6%), lymphomas (12.4%), sympathetic nervous system neoplasms (8.1%), soft tissue sarcomas (7.1%), renal tumors (6.4%), malignant bone tumors (5.0%), carcinomas (4.0%), germ cell neoplasms (3.2%), retinoblastomas (2.9%), hepatic tumors (1.3%), and other unspecified malignant neoplasms (0.5%) (12).

In Australia, although the proportional frequency of childhood cancer is relatively low, it was found to be the leading cause of death among children under the age of 14 years (13). Among the same age group, cancer (predominantly leukemias and central nervous system neoplasms) was responsible for 18% of the total number deaths in 2004.

The annual incidence of childhood cancer in Australia was estimated at 142.4 per million for all types of cancers among children aged 0-14 (8). The three types of

childhood cancer with the highest annual incidence were leukemias at 49.9/million, central nervous system tumors at 29.6/million, and lymphomas at 13.3/million. Neuroblastoma, soft tissue sarcomas and Wilms' tumor had an annual incidence of 9.1, 8.6 and 8.5 per million respectively. The annual incidences of the rest of the types of childhood cancer were reported at 4.2/million for retinoblastoma, 4.1/million for each of germ cell and all other tumors, 3.8/million for melanoma, 2.9/million for Ewing's sarcoma, 2.2/million for osteosarcoma, and 1.4/million for hepatic tumors.

1.3 Effects of cancer treatment in children

Benign neoplasms in most cases can be successfully treated leaving the treated individual with minimal immediate and late treatment effects. On the other hand, malignant neoplasms require intensive treatment therapies that are associated with aggressive immediate and late treatment effects. Childhood leukemia and lymphoma treatment, as in adults, is composed of intensive treatment and maintenance phase. During the intensive treatment phase that lasts for an average of six to nine months, patients exhibit signs and symptoms of acute effects of cancer treatment. These acute effects include: nausea, vomiting, loss of appetite, alopecia, xerostomia, neutropenia, and oral and gastrointestinal mucositis (14).

The maintenance phase lasts for longer periods of time and throughout this time the child shows evidence of complete remission. During the maintenance phase, patients usually do not exhibit signs and symptoms of acute effects to cancer treatment. However, during and after the maintenance phase patients my show signs and symptoms of late effects of cancer treatment. These late effects may range from psychiatric effects to secondary malignant neoplasms to disorders affecting several systems in the body including the central nervous system, the endocrine system, the

musculoskeletal system, the cardiac system, the respiratory system, the gastrointestinal system, and the urinary system (15). These late effects result from the fact that cancer treatment usually targets and kills rapidly dividing tumor cells and at the same time kills rapidly dividing normal cells in different body parts.

In children who are usually at different stages of their dental development, cancer treatment can affect the developing dentition as well as the salivary glands (16). This can occur in the form of malformed teeth, hypomineralized teeth, hypoplastic teeth or complete absence of permanent teeth as they fail to develop because of the toxic effects of cancer treatment. When salivary glands are affected they result in xerostomia that will predispose the patient to dental caries- the decay of a tooth- and other oral infections. It was found that 82% of children who were exposed to radiotherapy treatment developed dental abnormalities including root stunting and blunting, incomplete calcification of developing teeth, premature closure of root apices, delayed or arrested tooth development and dental caries (17).

The impact of radiotherapy and chemotherapy on developing dental abnormalities was investigated in detail among 9308 adult cancer survivors and 2951 survivors of childhood cancer (18). Those survivors showed different dental abnormalities that were significantly associated with their cancer treatment and included microdontia (odds ratio (OR)=3.0; 95% confidence interval (CI)=2.4-3.8), hypodontia (OR=1.7; 95% CI=1.4-2.0), root abnormalities (OR=3.0; 95% CI=2.2-4.0), abnormal enamel (OR=2.4; 95% CI=2.0-2.9), teeth loss ≥6 (OR=2.6; 95% CI=1.9-3.6), severe gingivitis (OR=1.2; 95% CI=1.0-1.5), and xerostomia (OR=9.7; 95% CI=4.8-19.7). It was also found in this study that exposure to radiation of ≥20 Gray significantly increased the risk of developing ≥1 dental abnormality. Dental abnormalities were also assessed in another study that followed up 423 children treated for acute lymphoblastic leukemia

(19). The majority of children who were ≤8 years of age and/or received total body irradiation (TBI) showed different dental late effects including root stunting (24.4%), microdontia (18.9%), hypodontia (8.5%), taurodontia (5.9%), and over-retention of primary dentition (4.0%).

Focusing on the management of acute effects of cancer treatment will help improve the quality of life of cancer patients during the treatment phase (20, 21). In this study, we will focus on oral mucositis as an acute effect of cancer treatment among children.

1.4 Oral mucositis overview

1.4.1 Definition and grading

Mucositis is defined as a painful inflammation and ulceration of any mucus membranes including that of the oral cavity and the gastrointestinal tract (22). Oral mucositis should be differentiated from the term stomatitis that is used to refer to inflammatory diseases of the oral cavity.

Oral mucositis is considered one of the major debilitating side effects of cancer treatment that can impact cancer treatment dosages (23), patients' quality of life (20, 21) and cancer treatment costs (24).

Several oral mucositis grading systems were established to represent the severity of this condition. Among these grading systems are the World Health Organization (WHO) and the National Cancer Institute Common Toxicity Criteria (NCI-CTC) grading systems (25, 26). The WHO grading system is composed of:

- Grade 0 (no oral mucositis): presents no signs or symptoms of oral mucositis.
- Grade 1 (mild oral mucositis): presents as oral soreness/erythema
- Grade 2 (moderate oral mucositis): presents as oral erythema, ulcers and the patient can consume solid and liquid diet.
- Grade 3 (severe oral mucositis): presents as oral ulcers and the patient can only consume liquid diet.
- Grade 4 (life threatening): presents as severe oral ulcers that will not allow the patient to consume any form of diet.

On the other hand the NCI has graded oral mucositis according to the type of cancer treatment as being chemotherapy-induced, radiation-induced or oral mucositis associated with hematopoietic stem cell transplantation (HSCT). Five grades of oral mucositis were described under each of these treatments (26). Grade zero and grade five were the same for all three types of cancer treatments where grade zero represents the absence of oral mucositis and grade five represents death due to toxicity. Grades one to four vary under each treatment based on the presentation of the severity of ulceration and erythema, and the difficulty in performing oral functions including eating, drinking and swallowing.

1.4.2 Epidemiology and risk factors

Oral mucositis occurs among patients receiving cancer treatment. Forty-nine percent of new cancer patients are considered to be at an intermediate risk of developing oral mucositis at some stage during their treatment phase (27). Among the rest of all new cancer patients, the proportion of patients who are at high and low risk of developing

oral mucositis were found to be at 8% and 43% respectively (27). Patients receiving radiotherapy for head and neck tumors and those who require HSCT or TBI constitute the majority of the high risk group with rates exceeding 50% (28). However these rates were found to be at 30-50% when TBI is excluded from the treatment regimen (22).

The incidence of oral mucositis was found to occur more among children (29) while its severity was found to favor adults (30). Incidence rates for oral mucositis among children were found to range between 52% and 80% (31-33). Despite the established literature on the epidemiology of oral mucositis among the adult population, few similar studies were conducted among the pediatric population due to the low number of cancer cases and the complexity of their treatment regimens (34).

The literature on the incidence of oral mucositis was repeatedly lacking in sample sizes. Another shortcoming of this literature was the use of different scales to record oral mucositis that resulted in the inability to compare the results of these studies. Furthermore, most of the literature on the incidence of oral mucositis has focused on recording WHO grade three and four due to lack of uniformity and the under reporting of WHO grades one and two (22).

The risk and incidence of oral mucositis vary according to several factors that usually fall under treatment-related and patient-related variables (28). Treatment-related factors include type, dose, and rout of administration of cancer treatment while patient-related variables involve age, gender, body mass, nutritional status, oral microflora, inflammation, and salivary function (28). In a recent meta-analysis it was found that the risk of developing low-grade oral mucositis was related to patients

receiving bevacizumab, erlotinib, sorafenib, or sunitinib (35). However, these agents are relatively new with few studies to support their use.

Risk factors of oral mucositis among children were investigated in a small number of studies. Prior oral mucositis episodes, high anxiety levels, and the level of neutropenia were found to be significant risk factors with adjusted relative risk values (ARR) of 3.94 (95% CI=1.49-10.39), 1.46 (95% CI=1.23-1.73), and 9.19 (95% CI=1.38-46.29) respectively (36). In another study, the risk of oral mucositis in children was associated significantly with low body weight (adjusted odds ratio (AOR)=0.91; 95% CI=0.84-0.98), low neutrophil count (AOR=0.33; 95% CI=0.16-0.68), and high creatinine levels (AOR=1.06; 95% CI=1.01-1.12) (37). The risk of oral mucositis in children was also found to be significantly associated with busulfan treatment (OR=2.1; 95% CI=1.3-3.0), germinal tumors (OR=1.4; 95% CI=1.2-1.7), and bacterial infections (OR=1.8; 95% CI=1.1-2.5) (38). These risk factors and others are yet to be explored and need larger sample sizes, better research designs, and appropriate statistical analysis.

1.4.3 Pathophysiology

The process by which oral mucositis develops is considered a complicated one. In the past, it was believed that oral mucositis is an epithelium-mediated event that affects dividing epithelial stem cells through the toxic effects of chemotherapy and radiotherapy (39). However, this belief has failed to describe the role of submucosal cells and extracellular matrix in the development of this condition (40). Vascular endothelial cell damage and the inhibition of platelet aggregation were strongly suggested to play a role in the pathogenesis of oral mucositis (41). Researchers are

still trying to understand in more depth the pathophysiology of oral mucositis to better diagnose, predict, prevent, and treat this debilitating condition.

However, for the sake of simplification, researchers have described the pathophysiology of oral mucositis in five phases that partially represent the complex pathophysiology of this condition. These five phases include initiation, message generation, signaling and amplification, ulceration, and healing phases (22, 27).

1) Initiation phase:

The process of oral mucositis starts by the generation of oxidative stress and reactive oxygen species (ROS) as a result of chemotherapy and radiotherapy agents. Cells, tissues and blood vessels are damaged directly by the activation of ROS that leads to stimulation of certain transcription factors responsible for further tissue damage.

2) Up-regulation and message generation phase:

This phase involves simultaneous events that occur at all levels of all affected tissues. The activation of ROS in the initiation phase will lead to DNA damage followed by clonogenic cell death in the basal epithelial cell layer. This prior event was not believed to be solely responsible for the genesis of oral mucositis. It was suggested that the genesis of oral mucositis is also a result of the activation of nuclear factor-κB (NF-κB) by chemotherapy or radiotherapy (22). Subsequently, this will lead to the up-regulation of many genes including those responsible for the production of proinflamatory cytokines (tumor necrosis factor-alpha TNF-α, interleukins-1 beta IL-1β, and IL-6) that indicate the extent of non-hematologic toxicity in the patient's body (42). This is followed by up-regulation of other genes causing

expression of adhesion molecules, activation of cyclooxeginase-2 pathway, and angiogenesis.

Pathways other than the NF-κB may also take place e.g. activation of sphyngomyelinase by ROS or activation of ceramide synthase pathway directly by chemotherapy. At the end, macrophages become activated causing tissue injury by matrix metalloproteinases.

3) Signaling and amplification phase:

The proinflamatory cytokines that were activated previously are indirectly responsible for amplifying the previously initiated tissue damage. The TNF-α can activate ceramide and caspase pathways resulting in more production of cytokines that may eventually lead to secondary TNF-α mediated tissue damage. All of this will lead to biological alteration of tissues regardless of their normal appearance.

4) Ulceration phase:

Polymorphonuclear and round inflammatory cells infiltrate the affected tissues that are populated by bacteria that have no clear role in this phase so far. However, the bacterial cell wall products are suggested to stimulate pathways leading to further tissue damage. During this phase, patients are considered to be at risk for bacteremia and sepsis because the ulceration will result in further amplification of cytokines, inflammation, and pain. Oral mucositis usually appears as early as the third day following cancer treatment and become established by day seven (43).

5) Healing phase:

Renewal of epithelial proliferation and differentiation that are coupled by reestablishment of normal oral flora takes place following signals from the extracellular matrix. Although the mucosa is healing, the patient will be at high risk for developing oral mucositis in future cycles (27).

1.5 Diagnosis and prediction of oral mucositis

Proper diagnosis of oral mucositis and its different grades of severity are of prime importance to clinicians and researchers. The ability to accurately diagnose oral mucositis has its implications on the prevention and management of this condition. It is also crucial for the advancement of the different levels of research including epidemiology, basic sciences, genetics, and clinical research.

Characteristics of an ideal diagnostic scale for oral mucositis include: clarity, simplicity objectivity, validity, acceptability, reliability (reproducibility, repeatability and consistency), quantifiability, high sensitivity and high specificity (44, 45). Currently there is no existing universal scale that bears all of the aforementioned characteristics (22).

Versions of oral mucositis scales have been developed and validated by epidemiologists and clinicians. These scales differed due to different perspectives and end outcomes specified by different researchers. As a result of these differences, comparisons of oral mucositis results became limited. Despite this lack of comparability, the development of different oral mucositis scales has helped

researchers identify strengths and weaknesses of different scales that will eventually aid in developing an optimal and unified scale.

The WHO oral mucositis scale was utilized in developing many oral mucositis scales that were used for clinical assessment of patients receiving cancer treatment (26). These scales included characteristics such as the overall health status of the mouth, severity of pain, and patient's oral functional status. The National Cancer Institute (NCI) has also developed a number of scales endorsed under the NCI-common toxicity criteria (NCI-CTC) (25).

Another group of scales has evolved from the WHO and the NCI-CTC scales. This group of scales utilized variables of objectivity, functionality and disease symptoms making them appropriate for use in clinical and research activities. The oral mucositis assessment scale (OMAS) is an example of this group of scales (46). Other scales were also developed with more details to suit clinical trials. About 43% of clinical trials utilized the NCI scale while 38% used the WHO scale (22). Study specific scales and cooperative group scales e.g. the radiation therapy oncology group, were used by 10% and 5% of clinical trials respectively (22). The remaining 4% of the trials have utilized the rest of the scales.

Children are quite unique when it comes to the diagnosis of oral mucositis due to their different stages of development and their inability to accurately describe the symptoms of oral mucositis. The WHO scale, the NCI-CTC version three, and the OMAS scale were among the few that were validated for the pediatric population (34).

The children's international mucositis evaluation scale (ChIMES) scale was developed in 2008 to target this special group of patients (47). This scale was recently evaluated for its understandability, content validity and acceptability by patients and their parents/guardians and was refined accordingly (48).

The ChIMES scale consists of three components that include assessment of pain, oral functions (swallowing, eating and drinking), and assessment of oral cavity appearance for the presence or absence of ulcers. The assessment of pain severity and levels of discomfort associated with oral functions were depicted in drawings of a range of facial expressions (Appendix 6). These drawings ranged from smiley faces to normal to crying faces in an attempt to allow the child to express his/her level of pain severity and level of oral functions' discomfort in a friendly and easy way. Despite this attempt to help children express their pain and discomfort levels during episodes of oral mucositis, the scale could not accommodate children ≤2 years of age; a challenge that needs to be addressed by researchers and clinicians treating children.

Prediction of oral mucositis can offer a useful aid in its diagnosis, prevention and treatment. However, few studies have been carried out on such topic especially among the pediatric population. Among the predictors of oral mucositis is the association between patients' genotypes of specific genes and the risk of developing different grades of oral mucositis.

Results from a clinical trial of 220 patients found that patients with lower activity of 5,10-methylenetetrahydrofolate reductase (MTHFR) gene (C677T, TT genotype) had 36% significantly higher mean of oral mucositis index (OMI) during days 1 to 18 following a chemotherapy cycle (49). Robien K. et al., investigated the association

between the severity of oral mucositis and certain predictive factors among 133 patents (≥18 y) who were undergoing allogeneic HSCT for chronic myelogenous leukemia (50). The results showed that TBI containing conditioning regimens, body mass index ≥25, and methylenetetrahydrofolate reductase (677 TT genotype) could predict higher scores of OMI.

In another study, the 677TT genotype, a variant of the methylenetetrahydrofolate reductase (MTHFR), was significantly over-expressed in patients with oral mucositis with odds ratio of 4.85 (95% CI=1.47-15.97) (51). The risk of developing grade three and four oral mucositis was doubled in all patients carrying the 677TT genotype (OR=8.13; 95% CI=1.61-41.04). Furthermore, patients with the same genotype and who had a combination of chemotherapy containing methotrexate have shown an increased risk of grade three and four oral mucositis (OR=24.6; 95% CI=2.49-87.41). However, those high odds ratio values should be interpreted with caution given the large width of confidence intervals that represent a lack of enough data points to explain the parameter under study.

Schwab M. et al., investigated 683 patients treated with five-fluorouracil (5-FU) for the predictive value of polymorphisms in dihydropyrimidine dehydrogenase (DPYD), thymidylate synthase (TYMS), and methylene tetrahydrofolate reductase (MTHFR) to predict severe leukopenia, diarrhea, and mucositis (52). DPYD was significantly associated with oral mucositis and leukopenia when the toxicity-type-based analysis was investigated. The multivariate analysis showed that genotype, being a female, mode of 5-FU administration, and modulation by folinic acid were independent risk factors for oral mucositis.

Investigating the association between the 677TT genotype variant of the MTHFR and polymorphisms in DPYD and the development of oral mucositis among the pediatric population may provide valuable information. Clinical trials testing such associations may help in the early prediction of children who are at risk of developing oral mucositis and hence allow for early prevention and management of this condition.

1.6 Guidelines for prevention and treatment of oral mucositis

The Mucositis Study Group (MSG) of the Multinational Association of Supportive Care in Cancer (MASCC) was established in 1998 and published its first guidelines on the prevention and treatment of mucositis in 2004 (23). These guidelines along with other recently published articles provided useful evidence based information and recommendations for the prevention and management of oral mucositis. However, since the pathophysiology of oral mucositis is still being investigated and is not fully understood, clinical trials of new preventative and treatment regimens and agents continue to grow in number.

1.6.1 Oral health care for cancer patients

The oral cavity was found to be a source of sepsis in the immunocompromised cancer patient making the use of oral hygiene measures of paramount benefit in reducing the risk of oral and systemic complications (53-55). In particular, the pediatric population is more prone to be affected by oral problems than adults (55). The immunosuppression in children receiving cancer treatment increases their risk of treatment complications if any underlying oral potential sources of infection are left untreated (56, 57). Oral care was also recognized in the meta-analysis of a Cochrane

review as an effective preventative regimen for oral mucositis in patients receiving cancer treatment (58).

Several studies have investigated different oral health protocols for patients receiving cancer treatment. The guidelines published by the MSG and the Australian and the American Academies of Pediatric Dentistry provided a strong foundation for oral health care in children receiving cancer treatment (23, 59). However, more research is needed to assess the outcomes of any suggested oral care protocol.

The most recent updated clinical practice guidelines of the MSG on the prevention and treatment of mucositis (60) recommended a basic oral care protocol for patients receiving cancer treatment. The protocol was based on expert opinions and limited published articles. The protocol recommended an initial and ongoing assessment of the oral cavity that runs parallel to the use of oral care regimens. The oral care regimen included regular brushing with a soft toothbrush that should be replaced on a regular basis, flossing, and use of rinses. The protocol also recommended regular assessment of oral pain with the use of topical anesthetics to promote oral comfort.

The MSG also advocated for an interdisciplinary approach to oral care that is shared by dentists, dental hygienists, physicians, nurses, pharmacists, and dietitians. This advocacy was based on the belief that this approach will provide a strong and well-coordinated support for oral health care of this group of patients.

The guidelines of the Australian and the American Academies of Pediatric Dentistry on dental management of patients receiving cancer treatment, that was revised in 2008, provided objectives for dental care before, during and after cancer treatment (59). The objectives of oral care before the initiation of cancer treatment were to

identify and eliminate any potential sources of infection or local oral irritants and to educate patients and their parents/guardians about the importance of maintaining an excellent oral health status. The objectives of oral care during cancer treatment were to maintain an excellent oral health status, to treat any oral side effects of cancer treatment, and to emphasize the importance of maintaining an excellent oral health status. At the end of cancer treatment, the objectives were to maintain an excellent oral health and to emphasize on the importance of maintaining an excellent oral hygiene.

These objectives were followed by recommendations for preventative oral strategies that covered oral hygiene, diet, fluoride, and oral health education. The first recommendation for oral hygiene included brushing of teeth and tongue two to three times a day using a manual or an electric soft toothbrush that should be replaced every two to three months (60). Brushing was suggested to be carried out at all times regardless of the hematological status of the patient. Brushing at different levels of platelet counts was not found to be associated with an increased risk of bleeding problems or septicemia (54, 61). The only time at which patients are encouraged to use foam toothbrush or super soft toothbrush soaked in chlorhexidine was when the patient develops moderate to severe oral mucositis and could not tolerate using the soft toothbrush or an end-tufted brush. The Academies recommended that such patients should shift back to the soft toothbrush once they can do so (59).

The second recommendation under oral hygiene was the daily use of chlorhexidine mouthwash for patients with poor oral hygiene and/or periodontal disease and that it should be discontinued when the patient develops oral mucositis. The reason for recommending the discontinuation of chlorhexidine mouthwash was because of its alcohol content that tends to dehydrate oral tissues and produce discomfort and pain

to those with established oral mucositis. The provision of alcohol-free chlorhexidine mouthwashes can be beneficial in avoiding such symptoms (62).

Teitelbaum AP et al., evaluated the effectiveness of mechanical and chemical control of dental biofilms and found statistically significant differences between the two techniques. It was found that use of dentifrices containing chlorhexidine resulted in significant reduction of gingival bleeding while dentifrices containing plaque-disclosing agents have resulted in a significant reduction of dental plaque (63).

The use of fluoridated toothpaste was recommended to be used at all times except when oral mucositis is established and the patient cannot tolerate the stinging sensation of the toothpaste. However, it was recommended that patients should continue to brush their teeth with a toothbrush and water. The use of professionally applied topical fluorides could be recommended according to patients' dental caries risk and their risk of developing xerostomia.

Both Academies have provided recommendations on diet that included advising patients and parents/guardians on the relationship between cariogenic diet and the development of dental caries (59). These recommendations were followed by others educating patients and parents/guardians about the importance of maintaining an excellent oral health status that was found to be closely related to fewer oral side effects of cancer treatment.

1.6.2 Prevention of oral mucositis

The scientific evidence on the prevention of oral mucositis is still building up and more research projects are needed to cope with the ongoing research on the

pathophysiology of this condition. The MSG clinical practice guidelines and the Cochrane systematic reviews provided the most updated evidence on preventing oral mucositis (60, 64).

The recommendations of the MSG clinical guidelines on the prevention of oral mucositis were provided under three main themes. The first theme was the prevention of oral mucositis in patients receiving radiotherapy. In this theme the MSG recommended the use of midline radiation blocks and three-dimensional radiation treatment to reduce mucosal injury. The MSG also recommended the use of benzydamine for the prevention of radiation-induced mucositis in patients with head and neck cancer and receiving moderate dose radiotherapy.

The second theme for the prevention of oral mucositis was designed for patients receiving standard dose chemotherapy. The MSG recommended a regimen of 30 minutes and 20-30 minutes of oral cryotherapy (ice chips) to prevent oral mucositis in patients receiving bolus 5-FU chemotherapy and bolus doses of edatrexate respectively. It is worth mentioning that 5-FU chemotherapy treatment is not being offered to treat children with cancer at the Women's and Children Hospital, Adelaide, Australia.

The third theme was designed for patients receiving high-dose chemotherapy with or without TBI and HSCT. The MSG recommended the use of ice chips for patients receiving high-dose melphalan treatment. It was also recommended under this theme to use keratinocyte growth factor-1 (Palifermin) for patients receiving high-dose chemotherapy and TBI with HSCT. However, the use of Palifermin was not approved for use in children. Low-level laser therapy (LLLT) was recommended for patients receiving high-dose chemotherapy or chemoradiotherapy before undergoing HSCT

to reduce the incidence of oral mucositis. The LLLT does require expensive equipment and special training thus rendering its use to be less frequent.

The MSG has also recommended against the use of certain agents for the prevention of oral mucositis including chlorhexidine mouthwash, granulocyte macrophage colony stimulating factor (GM-CSF) mouthwash, acyclovir, antimicrobial lozenges, and pentoxifylline. Although the MSG did not recommend the use of chlorhexidine mouthwash for the prevention of oral mucositis, the group still recommends its use as part of the basic oral care protocol to maintain an optimal oral hygiene.

The Cochrane review on the interventions to prevent oral mucositis found evidence to support the use of several preventative agents from 89 studies that comprised 7523 randomized patients (64). However, these agents were only effective with certain types of cancers and with specific cancer treatments. The evidence on amifostine, Chinese medicine, hydrolytic enzymes, and ice chips were found from more than one study that was included in the meta-analysis. Amifostine was found to have a minimal preventive effect on mild and moderate oral mucositis with relative risks of 0.95 (95% CI=0.92-0.98) and 0.88 (95% CI=0.80-0.98) respectively. Chinese medicine showed evidence of preventing mild, moderate, and severe oral mucositis with relative risks of 0.44 (95% CI=0.20-0.96), 0.44 (95% CI=0.33-0.59), and 0.16 (95% CI=0.07-0.35). Hydrolytic enzymes were found to reduce moderate and severe oral mucositis with relative risks of 0.52 (95% CI=0.36-0.74) and 0.17 (95% CI=0.06-0.52) respectively. Ice chips were also found to prevent all levels of oral mucositis with relative risks of 0.64 (95% CI=0.50-0.82), 0.38 (95% CI=0.23-0.62), and 0.24 (95% CI=0.12-0.48).

The rest of the effective preventative regimens were only supported by one study for each agent included in the meta-analysis. These preventative agents were benzydamine, calcium phosphate, etoposide bolus, honey, iseganan, zinc phosphate, and oral care. The authors of the Cochrane review (64) have recognized the need for further clinical trials with larger sample sizes to allow for subgroup analysis by type of cancer and by type of cancer treatment.

In a recent clinical trial, ice chips combined with an oral health protocol were administered to patients undergoing allogeneic HSCT and melphalan regimens (65). Ice balls were used 15 minutes prior and during the melphalan infusion but did not exert enough potency to prevent oral mucositis. The authors acknowledged that ice chips had a marginal supportive effect on the incidence of mucositis and that its efficacy might have been more difficult to assess in reduced-intensity HSCT than in conventional HSCT.

1.6.3 Treatment of oral mucositis

The updated MSG clinical practice guidelines did not include any treatment regimen for oral mucositis (60). At the same time the group recommended against the use of sucralfate for the treatment of radiation-induced oral mucositis. Chlorhexidine was also not considered for the treatment of established oral mucositis. However, the group still recommends its use as part of the basic oral care protocol to maintain an optimal oral hygiene.

Results of a meta-analysis of 26 clinical trials involving 1,353 patients have supported the use of different agents that were found effective for the treatment of oral mucositis (66). Four agents were found to be effective in improving the healing of

oral mucositis including allopurinol (RR=3.33), granulocyte-macrophage colony stimulating factor (RR=4.23), immunoglobulin (RR=1.81), and human placental extract (RR=4.50).

When pain control using patient controlled analgesia (PCA) was compared to continuous infusion method, no difference was found between the two methods (66). However, fewer opiates were utilized and shorter duration of pain was found with PCA. The duration of pain was also found to be shorter with pharmacokinetically patient-controlled analgesia (PKPCA) than with the regular PCA but more opiates were used with the former method.

At the Women's and Children Hospital the recommendations for the management of oral mucositis focus on pain management and include the use of viscous lignocaine mouth rinse and paracetamol or opiate analgesics e.g. morphine (orally, intravenous or as PCA) as required

The use of local anesthetic mouth rinses can be criticized for its risk of producing swallowing disorders and discomfort especially among younger children who have less comprehension of the numbing sensation. However, their use in older children has fewer complaints.

A detailed discussion of the treatment of oral mucositis will not be carried out since this study will be focusing more on the prevention of oral mucositis.

2.0 Study rationale, aim and objectives

2.1 Study rationale

The review of previous literature has indicated several shortcomings with regard to recording the incidence and severity of oral mucositis, recommending an optimal oral health care protocol, and exploring possible risk factors of oral mucositis among children receiving cancer treatment. This study is set to contribute valuable information to the scientific literature to help better understand oral mucositis among the pediatric population. The rationale for the study originates from and attempts to address the following:

- The debilitation and the reduced quality of life associated with oral mucositis in children receiving cancer treatment provide a strong impetus for clinical trials on this group of patients

- The increasing cost on health organizations and hospitals for treating and managing oral mucositis adds to the burden of illness in the pediatric population

- Oral mucositis can compromise the regimens of cancer treatment and limit the dose of medications used hence prolonging the cancer treatment time

- Only a few studies were reported to record the incidence of oral mucositis in the pediatric population due to the low numbers of childhood cancers and the complexity of their treatment regimens

- Currently at the Women's and Children Hospital, Adelaide, Australia, there is no standardized method or consistency in recording the incidence of oral mucositis for oncology inpatients

- The current hospital oral health care protocol that is meant to prevent oral mucositis is not based on current scientific evidence and lacks many of the recommendations endorsed by the Australian and the American Academies of Pediatric Dentistry on dental management of patients receiving cancer treatment

- The MSG in their most recent updated clinical practice guidelines on the prevention and management of oral mucositis has recognized a lack of outcome assessment of oral care protocols, thus a detailed assessment of oral health outcomes will address this lack

2.2 Study aim

This clinical trial sets out to assess the incidence of oral mucositis and oral care outcomes and to explore possible risk factors for oral mucositis among inpatient children receiving cancer treatment at the Women's and Children Hospital, Adelaide, Australia.

2.3 Study objectives

1) To investigate the scientific evidence on different agents and strategies used to prevent oral mucositis in children through a systematic review of the literature,

2) to assess and validate the combined use of ChIMES and WHO oral mucositis scale in recording the incidence, subjective, and objective outcomes of oral mucositis among inpatient children receiving cancer treatment,

3) to develop and implement a standardized hospital oral care protocol and standardize the recording of oral mucositis among inpatient children receiving cancer treatment, and

4) to record and assess prospectively the incidence of oral mucositis, objective and subjective outcomes of oral mucositis, oral health outcomes (dental caries and oral hygiene), and possible risk factors among inpatient children receiving cancer treatment.

3.0 Portfolio of publications

3.1 Publication 1 (published):

Prevention of oral mucositis in children receiving cancer therapy: A systematic review and evidence-based analysis

Statement of Authorship

Title of Paper	Prevention of oral mucositis in children receiving cancer therapy: A systematic review and evidence-based analysis
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By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

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3.2 Publication 2 (submitted for publication):

The rationale and validation of the combined use of the Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) oral mucositis scale for recording oral mucositis in children undergoing cancer treatment

Statement of Authorship

Title of Paper	The rationale and validation of the combined use of the Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) oral mucositis scale for recording oral mucositis in children undergoing cancer treatment
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Supportive Care in Cancer

The rationale and validation of the combined use of the Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) oral mucositis scale for recording oral mucositis in children undergoing cancer treatment

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Abstract:	Purpose: This prospective study was carried out to validate the combined use of the Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) oral mucositis scale for recording the incidence and severity of oral mucositis among pediatric inpatients undergoing cancer treatment in South Australia. Methods: All inpatients who were diagnosed with childhood cancer and were undergoing cancer treatment were included and followed up for seven months. Oral mucositis scales were recorded daily for all inpatients using the ChIMES and the WHO scales. Visual illustrations of the ChIMES scale were utilized to help young children express the subjective outcomes: levels of pain, difficulty in eating, drinking or swallowing while the WHO scale helped hospital staff to record the severity of oral mucositis. Results: A total of 38 patients were assessed and followed during the seven months period of the pilot study. The combined use of ChIMES and WHO scales gave a good synergistic outcome as one complemented the other. The ChIMES scale was appropriate for recording subjective outcomes with higher range of scores being recorded for children suffering from grade 3 and 4 oral mucositis as compared to those with grade 1 and 2. The WHO scale was appropriate for recording the incidence and severity of oral mucositis. The incidence of oral mucositis was 33% (12 patients) of whom 75% had WHO grade 1 and 2 and 25% had WHO grade 3 and 4. The rate of compliance of implementing the oral mucositis scale has improved from 41% to 87%. Conclusions: The combined use of the ChIMES and the WHO oral mucositis scales was successful in recording the subjective and objective outcomes of oral mucositis in children undergoing cancer treatment.
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Title:

The rationale and validation of the combined use of the Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) oral mucositis scale for recording oral mucositis in children undergoing cancer treatment

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Abstract:

Purpose: This prospective study was carried out to validate the combined use of the Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) oral mucositis scale for recording the incidence and severity of oral mucositis among pediatric inpatients undergoing cancer treatment in South Australia.

Methods: All inpatients who were diagnosed with childhood cancer and were undergoing cancer treatment were included and followed up for seven months. Oral mucositis scales were recorded daily for all inpatients using the ChIMES and the WHO scales. Visual illustrations of the ChIMES scale were utilized to help young children express the subjective outcomes: levels of pain, difficulty in eating, drinking or swallowing while the WHO scale helped hospital staff to record the severity of oral mucositis.

Results: A total of 38 patients were assessed and followed during the seven months period of the pilot study. The combined use of ChIMES and WHO scales gave a good synergistic outcome as one complemented the other. The ChIMES scale was appropriate for recording subjective outcomes with higher range of scores being recorded for children suffering from grade 3 and 4 oral mucositis as compared to those with grade 1 and 2. The WHO scale was appropriate for recording the incidence and severity of oral mucositis. The incidence of oral mucositis was 33% (12 patients) of whom 75% had WHO grade 1 and 2 and 25% had WHO grade 3 and 4. The rate of compliance of implementing the oral mucositis scale has improved from 41% to 87%.

Conclusions: The combined use of the ChIMES and the WHO oral mucositis scales was successful in recording the subjective and objective outcomes of oral mucositis in children undergoing cancer treatment.

Keywords:

Oral mucositis, Mucositis scale, Assessment, Childhood cancer, Children, Validity

Introduction:

Cancer treatment is associated with short and long-term complications that add to the burden of illness. The short-term complications of cancer treatment include nausea, vomiting, loss of appetite, alopecia, xerostomia, oral and gastrointestinal mucositis [1]. Among the previously mentioned complications, oral mucositis was found to be the most debilitating and distressing complication to patients and parents with an incidence of approximately 20-40% in adult patients undergoing standard dose chemotherapy regimens [2-5]. Studies have documented the negative effects of oral mucositis on the quality of life of affected individuals and cost repercussions on health care systems reflected mainly by increased length of hospital stay [6-9]. Beside the psychosocial and economical effects of oral mucositis on patients and health care systems, symptoms of oral mucositis such as pain, ulcerations, and functional difficulties, can further alter cancer treatment and pose risk of oral and systemic infections.

The importance of assessing and recording oral mucositis has been recognized from the nursing perspective to improve patient outcomes related to oral mucositis [10]. Furthermore, this importance can be further extended to include psychosocial, clinical, economical, and research perspectives. The systematic and regular assessment and recording of oral mucositis through a reliable scale can help 1) improve patients' objective and subjective outcomes such as pain and function (swallowing, drinking, eating, and speaking) through appropriate and timely medical interventions, 2) reduce the costs associated with managing oral mucositis such as reduced hospital stay, 3) reduce dose limiting interruptions in cancer treatment due to pain, dehydration, and reduced blood cell count, 4) standardize the medical and nursing management of oral

mucositis, 5) improve the quality of life of patients affected by oral mucositis, and 6) advance future research for effective prevention and management of oral mucositis.

Assessing and recording oral mucositis in children has its own challenges. These challenges mainly involve difficulty in assessing subjective outcomes of oral mucositis e.g. pain and function as well as behavior management of young children when attempting to examine the oral mucosa. Young children can find it difficult to verbally express pain severity and discomfort; this necessitates special consideration of which scales should be used to assess subjective outcomes of oral mucositis in children. Although these challenges were identified, few oral mucositis scales have been developed to address this condition in the pediatric population. Assessment scales, including the Oral Assessment Guide (OAG), Oral Mucositis Assessment Scale (OMAS), and Walsh Scale [11], generally rely on description of subjective outcomes of oral mucositis making it not applicable to young children (≤5 years). The Children's International Mucositis Evaluation Scale (ChIMES) is one of the recently validated scales for recording oral mucositis that incorporated the use of smiley faces to help capturing the subjective outcomes of oral mucositis in young children [12].

In this article, the rationale and validity of the combined use of the ChIMES scale and the World Health Organization (WHO) oral mucositis scale are discussed for the purpose of recording the incidence and severity of oral mucositis during a prospective pilot study among pediatric oncology inpatients.

Methods:

Ethics approval was obtained for the prospective study from the Human Research Ethics Committee (approval No. REC2256/2/13). The pilot study was conducted from January-July 2010 to implement an oral care protocol for the prevention of oral mucositis among pediatric inpatients undergoing cancer treatment and its results were reported in a previous publication [13]. The pilot study was also conducted to assess and validate the combined use of two validated oral mucositis scales; the ChIMES and the WHO oral mucositis scale [14;15] for the recording of the incidence and severity of oral mucositis among this patient population.

Several in-service presentations and training sessions were given at different intervals to the nursing and the medical staff at the oncology unit. These presentations and training sessions were aimed at calibrating and familiarizing the staff with the new oral mucositis scale, encouraging them to advocate for its implementation, and to answer any related questions or concerns.

The smiley faces of the ChIMES scale were utilized in recording the levels of pain and discomfort related to eating, swallowing and drinking while the WHO was used to record the severity of oral mucositis. This way the ChIMES scale could enhance the recording of the subjective part of the WHO scale and collectively give a comparable assessment of oral mucositis similar to that gained by using the WHO scale in adults.

The prospective study included all inpatients who were diagnosed with childhood cancer and were undergoing cancer treatment at the oncology ward of the Women's and Children's Hospital in Adelaide, Australia. Both scales were fitted as half page stickers that were pasted daily in the inpatient progress notes of the medical records of each patient to facilitate the daily recording of the incidence and severity of oral mucositis (Figure 1). The daily recording of oral mucositis was done by the nursing staff at the oncology ward and was then assessed for accuracy by a trained and calibrated dentist from the research team. This assessment for accuracy was done by daily auditing the medical records. The dentist performed daily clinical examination on all inpatients and cross-matched the clinical results (ulceration and/or erythema) recorded by the nursing staff in their medical records to ensure accurate recording of the incidence and severity of oral mucositis and to help assess inter-examiner reliability.

Results:

Thirty-eight patients were recruited and followed up during the pilot study from January to July 2010. These selected patients were known to be at risk of developing oral mucositis due to the use of multi-agent chemotherapy, intensive chemotherapy with or without radiotherapy and/ or bone marrow transplantation. Table 2 displays patients' demographics (age and gender) and the distribution of cancer diagnoses. The incidence of oral mucositis among the pilot study sample was 33%, of which 75% were scored as WHO grade 1 and 2 while 25% were scored as WHO grade 3 and 4.

The two selected oral mucositis scales have complemented each other in different domains when recording oral mucositis including capturing subjective and objective outcomes, recording the severity of oral mucositis, and ease of recoding by hospital staff, patients and parents (Table 1). The ChIMES scale captured the subjective outcomes of oral mucositis. Results of pain levels and levels of discomfort with eating swallowing and drinking were prevalent among patients who developed oral mucositis (12 children). As shown in Table 3, the range of pain levels for children affected by oral mucositis grade 1 and 2 were lower than that of those affected by grade 3 and 4. Similarly, levels of discomfort with eating swallowing and drinking were higher among children with grade 3 and 4 oral mucositis.

The inter- and intra-examiner reliability was regularly checked among staff throughout the study period with kappa results of 0.83 and 0.87 respectively i.e. almost perfect agreement. Besides the accurate recording of oral mucositis, the daily recording of the oral mucositis scale has helped in identifying affected children at an early stage and hence suggesting early intervention to manage pain and discomfort during episodes of oral mucositis. However, this study did not intend to assess or compare pain and discomfort management strategies for children with oral mucositis.

In the first phase of implementing the combined ChIMES/WHO oral mucositis scale during the period of January-April 2010, the rate of compliance of its daily recording for all oncology inpatients was 41%. This compliance rate has improved to 87% during the second phase of the prospective study from May to July 2010.

Discussion:

The ability to accurately diagnose oral mucositis has its implications in the prevention and management of this condition. It is also crucial for the advancement of the different levels of research including epidemiology, basic sciences, genetics, and clinical research.

Many versions of oral mucositis scales have been developed and validated by epidemiologists and clinical researchers. The differences between these scales emerged from the different perspectives and end results (outcomes) interpreted by different epidemiologists, clinicians and clinical researchers. This has resulted in the inability to compare the results from the rapidly growing literature on oral mucositis. The absence of a unified scale and the subsequent lack of comparability between research results have lead to the slow understanding and advancement of oral mucositis prevention and treatment. However, it is worth mentioning that the development of so many scales will allow researchers to identify strengths and weaknesses of each scale, which will subsequently help in the development of an optimal unified scale in the near future.

Characteristics of an ideal diagnostic scale for oral mucositis include: clarity, simplicity objectivity, validity, acceptability, reliability (reproducibility and consistency), quantifiability, high sensitivity and high specificity [16;17]. Currently there is no universal scale that bears all of the aforementioned characteristics [18]. Furthermore, such a scale should take into account the challenges faced when assessing children who cannot express pain or discomfort as accurately as an adult in addition to the behavior challenges when it comes to examining young children.

Most of the oral mucositis scales were developed based on the scale developed by the World Health Organization for the clinical assessment of patients receiving cancer therapy [19]. Characteristics such as the overall health status of the mouth, severity of pain and the patient's oral functional status were utilized in the development of most scales. The National Cancer Institute (NCI) has also developed a number of scales promoted under the NCI-common toxicity criteria (NCI-CTC) [20].

A second set of scales has evolved after the WHO and the NCI-CTC scales. This second set combined variables of objectivity, functionality and disease symptoms making them appropriate as clinical and research management tools. The oral mucositis assessment scale (OMAS) is an example of this second set of scales [21]. This was followed by a third set of detailed scales that were solely designed for clinical trials.

An inventory of the most commonly used scales in clinical trials found that 43% of clinical trials utilized the NCI scale followed by the WHO scale (38%) [18]. Study specific scales and cooperative group scales e.g. the radiation therapy oncology group, were used by 10% and 5% of clinical trials respectively. The rest of the scales were utilized by less than five percent of trials.

The pediatric population is quite unique when it comes to the diagnosis of oral mucositis because children at different stages of their development may or may not be able to describe accurately the different symptoms of oral mucositis. Diagnostic scales for oral mucositis are limited for the pediatric population. The WHO scale, the NCI-CTC version three and the OMAS scale were among the few that were validated for the pediatric population [22].

The ChIMES scale provided a lot of hope when it was developed in 2008 to target this special group of patients [23]. However, its major limitation relies in the fact that it doesn't objectively measure the severity of oral mucositis and hence limits the ability to properly manage affected patients. We have attempted in the planning stage of this pilot study to address this limitation by creating a scoring system from the different fields of the ChIMES scale that would help us assign an oral mucositis severity grade for each patient. We graded each category in the ChIMES scale as follows: five points for the assessment of pain, fifteen points for the assessment function (five points each), one point for each question about pain medication and two points for the assessment of mouth appearance. Grades of oral mucositis were assigned according to the collective points of ChIMES as follows:

- 0-4 points: No oral mucositis
- 5-9 points: Grade 1 oral mucositis
- 10-14 points: Grade 2 oral mucositis
- 15-19 points: Grade 3 oral mucositis
- 20-24 points: Grade 4 oral mucositis

We were hoping that in this way the ChIMES scale could then be compared to the WHO grades in other research projects. However, the grounds for such categorization were not empirically possible due to the subjectivity involved in the assessment of pain and oral functions.

The other limitation of the ChIMES scale and any other existing oral mucositis scale is the inability to assess oral mucositis in very young children (≤2 years of age) or similarly in children

who have either mental or developmental problems e.g. autism spectrum disorders. This second limitation may not be addressed even in future versions of oral mucositis scales due to the natural cognitive development of the pediatric population. In our study, the ChIMES scale was used to enhance the recording of the subjective outcomes of the WHO scale, which was also used for recording the severity and grading of oral mucositis. Using both scales would make the assessment of oral mucositis in children comparable to results obtained by using the WHO scale in the adult population.

Table 1, has illustrated the different suitability for the WHO and the ChIMES scales. These characteristics can help in designing future research projects to involve recording of oral mucositis for non-hospitalized children where parents can use the ChIMES scale at home and hospital staff can assess it and record the WHO scale when the child is reviewed or during the chemotherapy treatment in the outpatient clinics.

It has been a great achievement of this project to implement the use of an established scale to record oral mucositis for inpatients. Prior to this pilot study, consistent recording of oral mucositis was lacking and was mainly based on signs and symptoms of patients affected by severe grades of mucositis. Daily recoding of oral mucositis scale for all inpatients was a challenge with issues related to familiarization and compliance of the nursing staff. This was addressed by frequent in-service presentations and follow up sessions that helped in increasing the compliance rate from 41% to 87%.

This pilot study has facilitated planning for an ongoing prospective study which aims at properly reporting the incidence of oral mucositis among inpatients at the oncology ward of the Women's and Children's Hospital in Adelaide, Australia. Such results will be correlated to clinical outcomes in this patient population to explore risk associations.

Conclusion:

The combined use of ChIMES and WHO oral mucositis scales complemented each other and was successful in capturing objective and subjective outcomes of oral mucositis among an inpatient pediatric population undergoing cancer treatment. We strongly recommend the use of visual illustrations similar to that of the ChIMES scale when future oral mucositis scales are being developed for children because it significantly assists children in expressing the subjective outcomes of oral mucositis. Limitations of oral mucositis scales in children must be acknowledged for accurate recording and use in research to avoid over- or under-estimation of this condition among the pediatric population.

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Table 1: Comparison of the different domains of ChIMES and WHO oral mucositis scales

Domain	**ChIMES**	**WHO**
Capturing subjective outcomes (pain and function)	Suitable	Limited suitability
Capturing objective outcomes (erythema and ulcers)	Suitable	Suitable
Recording the severity of oral mucositis	Not suitable	Suitable
Ease of use by hospital staff	Suitable	Suitable
Ease of use by patients/parents	Suitable	Limited suitability

Table 2: Demographics and distribution of cancer diagnoses among the study sample

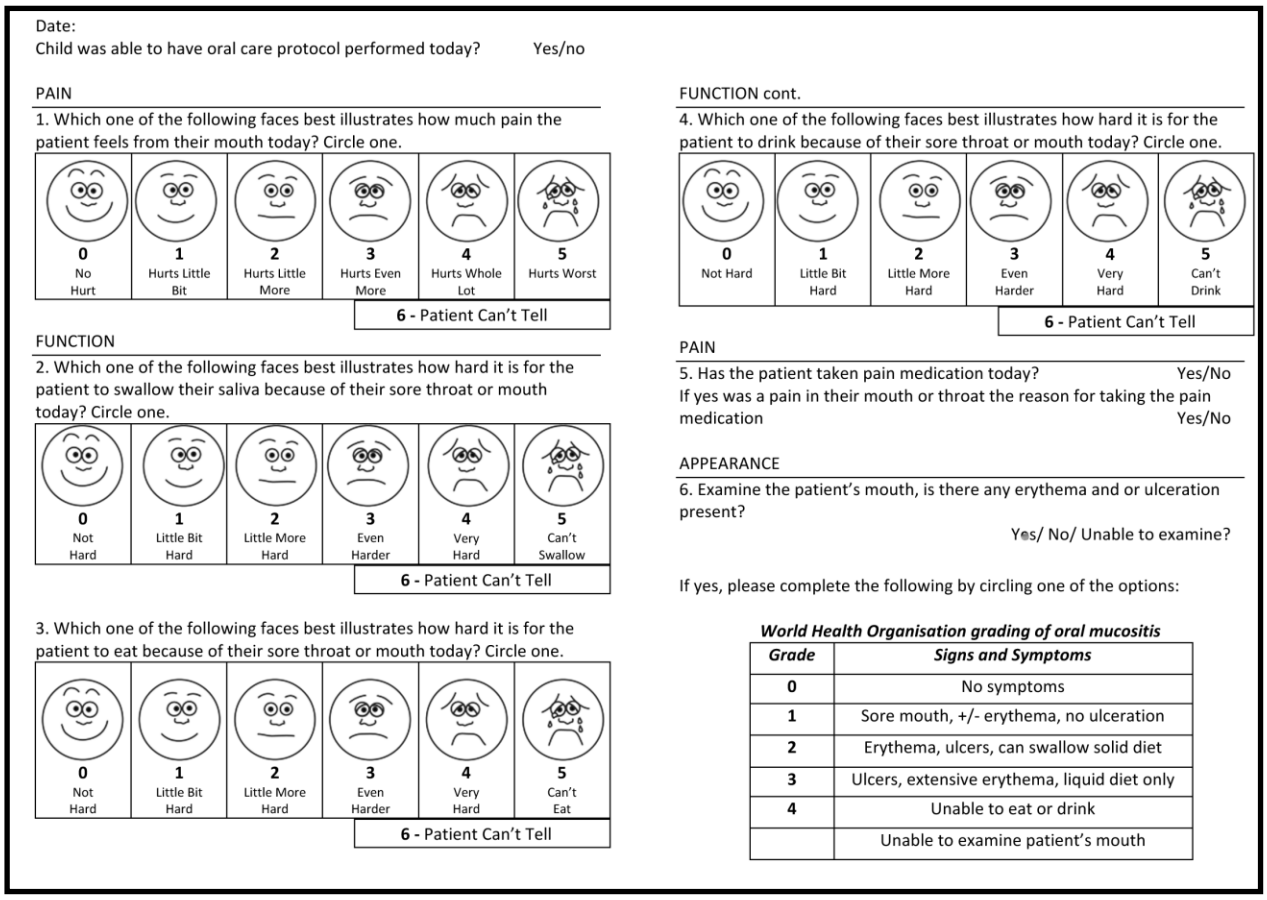
Total number of patients	Cancer diagnosis and frequency (%)	Age at diagnosis (years)	Gender ratio
38 patients	Acute lymphoblastic leukemia- ALL (55.3%)	Range: 3-15 Median: 9	1.5:1 male to female
	Acute myelogenous leukemia- AML (5.3%)		
	Central nervous system tumors (21.1%)		
	Lymphomas (10.5%)		
	Renal tumors (2.6%)		
	Hepatoblastoma (2.6%)		
	Osteosarcoma (2.6%)		

Table 3: Subjective outcomes of oral mucositis stratified by grade of oral mucositis

Grade of oral mucositis	Range of levels of pain[a]	Range of levels of discomfort[a]		
		Eating	Swallowing	Drinking
Grade 1 and 2 (9 children)	0-3	0-3	0-3	0-2
Grade 3 and 4 (3 children)	3-5	3-5	2-5	2-5

[a] Levels of pain and discomfort with eating, swallowing and drinking range from 0 (doesn't hurt/not hard) to 5 (hurts worst/ can't eat, swallow or drink) as shown in Figure 1

Figure 1: The combined Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) oral mucositis scale[a]



Date:

Child was able to have oral care protocol performed today? Yes/no

PAIN

1. Which one of the following faces best illustrates how much pain the patient feels from their mouth today? Circle one.

0	1	2	3	4	5
No Hurt	Hurts Little Bit	Hurts Little More	Hurts Even More	Hurts Whole Lot	Hurts Worst

6 - Patient Can't Tell

FUNCTION

2. Which one of the following faces best illustrates how hard it is for the patient to swallow their saliva because of their sore throat or mouth today? Circle one.

0	1	2	3	4	5
Not Hard	Little Bit Hard	Little More Hard	Even Harder	Very Hard	Can't Swallow

6 - Patient Can't Tell

3. Which one of the following faces best illustrates how hard it is for the patient to eat because of their sore throat or mouth today? Circle one.

0	1	2	3	4	5
Not Hard	Little Bit Hard	Little More Hard	Even Harder	Very Hard	Can't Eat

6 - Patient Can't Tell

FUNCTION cont.

4. Which one of the following faces best illustrates how hard it is for the patient to drink because of their sore throat or mouth today? Circle one.

0	1	2	3	4	5
Not Hard	Little Bit Hard	Little More Hard	Even Harder	Very Hard	Can't Drink

6 - Patient Can't Tell

PAIN

5. Has the patient taken pain medication today? Yes/No

If yes was a pain in their mouth or throat the reason for taking the pain medication Yes/No

APPEARANCE

6. Examine the patient's mouth, is there any erythema and or ulceration present?

Yes/ No/ Unable to examine?

If yes, please complete the following by circling one of the options:

World Health Organisation grading of oral mucositis

Grade	***Signs and Symptoms***
0	No symptoms
1	Sore mouth, +/- erythema, no ulceration
2	Erythema, ulcers, can swallow solid diet
3	Ulcers, extensive erythema, liquid diet only
4	Unable to eat or drink
	Unable to examine patient's mouth

[a] Adapted from Tomlinson D et al. 2009 [14] and the WHO handbook for reporting results of cancer treatment [15]

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Authorship disclosure form

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On behalf of the authors,

I, the principal author would like to state that there are no conflict of interest to be declared in regard to this manuscript.

Akram Fareed Qutob

3.3 Publication 3 (published):

Implementation of a hospital oral care protocol and recording of oral mucositis in children receiving cancer treatment: A retrospective and a prospective study

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Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

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Contribution to the Paper	Developed the work, collected, interpreted, and analyzed the data, wrote the manuscript, and acted as corresponding author		
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3.4 Publication 4 (submitted for publication):

Oral mucositis incidence, oral health outcomes, and related risk factors among inpatient children population undergoing cancer treatment: A prospective observational study

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Oral Mucositis Incidence, Oral Health Outcomes, and Related Risk Factors Among Inpatient Children Population Undergoing Cancer Treatment: A Prospective Observational Study

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Condensed abstract:

This observational clinical study was carried out to record the incidence of oral mucositis (OM), assess oral health outcomes, and explore possible risk factors of OM among children receiving cancer treatment. The study found low incidence rates of OM and dental caries and suggest that regular recording of OM and implementing a comprehensive oral care protocol may have played a role in reducing OM incidence and duration among children admitted to receive cancer treatment.

Abstract:

Background: Oral mucositis (OM) predisposes patients to infections, nutritional deficiencies, and increases their overall treatment time and cost. This study was conducted among children undergoing cancer treatment as inpatients at the Women's and Children's Hospital, Adelaide, Australia to record OM incidence and severity, investigate oral health status, and explore risk factors. **Methods:** This prospective observational study has utilized the Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) OM scale to record OM incidence and severity daily during the first 12 months. Dental caries and oral hygiene were recorded and followed up to 24 months. OM incidence, severity, duration, recurrence, and hospital stay were tested against confounders to explore risk associations. **Results:** Sixty-seven children were followed and OM incidence of 34% and incidence density of 129.2/100 person-years of observation were reported. The highest recorded OM severity grades were: 1 (9%), 2 (61%), and 4 (4%). Dental caries prevalence was 28% and was treated without further caries incidents occurring throughout the dental review time. Significant direct risk associations were evident for OM duration and clinical variables (OM severity, recurrence, type

of cancer treatment, pain and oral functional difficulty scores) except for prolonged dental reviews that had an inverse protective relationship by 6%. Children with OM, stayed in the hospital 1.64 times longer than children without OM. **Conclusion:** Continuous OM recording and implementing a comprehensive oral care protocol for children receiving cancer treatment may reduce OM incidence. Prolonged regular dental reviews can reduce OM duration and subsequently hospital stay.

Keywords:

Dental Caries, Oral mucositis, Incidence, Risk Factors, Child

Introduction:

Cancer treatment is usually associated with short and long-term physical, emotional, and financial hardships that affect patients and their circle of relatives and friends. These hardships can be even more devastating when a child is diagnosed with cancer. In Australia, over 600 children aged 0-14 years are annually diagnosed with childhood cancer.[1] Although childhood cancer incidence is relatively low in Australia when compared to adult cancers, it was found to be the leading cause of death among children under the age of 14 years with an average of 100 deaths per year.[2] These deaths were mostly related to leukemia and brain tumors.[2]

Cancer patients' hospital visits whether as an outpatient or as an inpatient become a big part of these patients' lives for treatments and/or regular follow-ups. During the cancer treatment phase, patients are prone to develop different acute side effects of treatment including oral mucositis (OM).[3] This side effect affects the oral mucous membranes and manifests clinically with different severity levels ranging from minimal erythema to severe ulcerations.[4] OM signs and symptoms usually occur at day 3-5 of administering chemotherapy/radiotherapy and reach their peak effects at days 7-14.[5] In affected patients, OM can lead to pain, difficulty swallowing, eating, and drinking thus reducing their quality of life during their treatment.[4] Such effects may also disrupt the progress of their cancer treatment, predisposes them to other oral infections, nutritional deficiencies, and increase the period of their hospital stay and overall treatment time and cost.[6-8]

The pathophysiology of OM is yet to be fully understood[9] and thus researchers continue to investigate this debilitating side effect to prevent it and find a proper treatment. Observational studies have been helpful in learning about the behavior and risk factors associated with OM. However there are only a limited number of studies on OM risk factors and incidence among children, with reported incidence rates of 52-80%.[10-12] Risk factors of OM include treatment-related variables (e.g. type and intensity of treatment) and patient related factors (e.g. age, gender, nutritional status, oral micro-flora, inflammation, and salivary function).[13] However, oral health outcomes, especially dental caries among affected children are underreported.

This prospective clinical observational study was conducted among children admitted to receive cancer treatment at the Women's and Children's Hospital, Adelaide, Australia. Our objectives were to: 1) record OM incidence, severity, recurrence, and duration, 2) investigate the status of oral health outcomes, and 3) investigate possible risk factors and confounders.

Methods:

Ethical approval was obtained from the human research ethics committee (HREC) of the Children, Youth, and Women's Health Services in Adelaide, Australia (approval No. REC2256/2/13). The approval was obtained to carry out a prospective clinical observational study over 24 months to record OM incidence and severity, and oral health outcomes of all pediatric inpatients receiving cancer treatment at the Oncology Department. The decision to focus on inpatients was made in order to help improve their quality of hospital stay through early recognition and management of OM.

Children from birth to <18 years of age were conveniently recruited after obtaining informed consent from parents/caregivers. Participants were recruited during the first 12 months of the study (August 2010-August 2011) with different entry time points. OM incidence, severity and other OM outcomes were recorded during the first 12 months while oral health outcomes (dental caries, oral hygiene, and dental treatments) were recorded and followed up to a maximum of 24 months or until August 2012. The length of follow up period for OM and oral health outcomes was dependent on patients' survival rates and different entry time points. At the time of entry (cancer diagnosis or ongoing cancer treatment), patients were referred to the Department of Pediatric Dentistry for initial oral examination and to give patients/caregivers instructions on the standardized oral care protocol. Details of the process of implementing the oral care protocol and the use of the OM scale were outlined in a previous publication.[14]

During the first oral examination, dental caries status was recorded by means of the number of decayed, missing, and filled teeth (DMFT/dmft) for permanent and primary dentitions. Oral hygiene status was recorded using the plaque index (PI) that scored patients' oral hygiene based on the amount of dental plaque adhering to selected teeth and their surrounding gingival tissues. The PI was preferred over other indices because it doesn't involve the use of dental instruments (periodontal probes) that may induce gingival bleeding and hence impose a risk to patients with low platelet and/or neutrophil counts. Required dental preventive (fissure sealants/fluoride) and/or curative treatments (restorations/extractions) were provided for patients soon after their first dental examination. Patients were then reviewed every three months until they finished cancer treatment.

OM incidence and severity were recorded daily for all inpatients at the oncology ward using the Children's International Mucositis Evaluation Scale (ChIMES) and the World Health Organization (WHO) OM scale.[15-17] These scales were pasted daily in inpatients' medical records. The smiley faces of the ChIMES scale helped children express their levels of pain and difficulties with oral functions (swallowing, eating, and drinking), thus enhancing the subjective measures of the WHO scale.

One trained examiner was responsible for the assessment and recording of oral health outcomes and the accuracy of recording OM incidence and severity. Nurses performed daily OM recording, however, objective clinical outcomes (erythema/ulceration) were re-assessed by the designated examiner to ensure accuracy. Calibration and inter-/intra-examiner reliability were checked at three time points throughout the study to ensure consistency and accuracy of recording.

Whenever a patient from the cohort was hospitalized, OM scales were recorded daily until discharge. Data on OM severity, duration, recurrence, and length of hospital stay were collected simultaneously.

Statistical software SAS-9.3 (SAS Institute Inc., Cary, NC, USA) was used to analyze data. Descriptive statistics were performed to explore normality of data distribution and to describe demographics, calculate OM incidence, and summarize patients' characteristics. This was followed by bivariate analysis to explore risk factors in relation to four main OM outcomes including incidence, severity, duration, and recurrence. Various models were used to explore

associations between OM outcome variables and several explanatory variables. Strength of association and significance values were tabulated along with statistical methods used to test these associations. Bivariate analysis results were then used as permissible to construct multivariate models to control for confounders and explain associations among significant risk factors.

Results:

Seventy children were recruited, however, three were excluded because they were eighteen years of age. The remaining children with a mean age of 6.9y (median=5y [min/max=0.2/17.0y]) were included in the analysis. Twenty-seven children (40%) completed the first 12 months review while 27% and 31% were followed for 3-6 months and 7-11 months respectively. The shortest follow up time was recorded for one child who was followed for a month and died due to disease progression.

Forty percent of children completed 24 months dental reviews except for the same child mentioned earlier who had only one month follow up. The remaining children were followed for 3-9 months (9%), 10-18 months (23%), and 19-23 months (26%). Differences in OM and dental follow up times were due to different entry points and survival rates of children. These differences in follow up times were accounted for in the analysis and reflected by reporting cumulative incidence and incidence density of OM.

Of the study sample, 58% were males and 42% were females with a male to female ratio of 1.4:1. The types of cancer diagnosis and the protocols of chemotherapy treatment were grouped into five main categories as shown in Table 1 to allow for statistical analysis.

OM cumulative incidence was 34% (34/100 over a one year period) with 23 children (11 males and 12 females) of the 67 reported to have OM during the first 12 months of the study. On the other hand, OM incidence density was 129.2 per 100 person years of observation based on a total number of 23 new cases over 17.8 person years of observation.

The average number of hospital admissions for all children was 6.5 with a median of 6 (SD=4; min/max=1/17). For these admissions, the average of cumulative days of hospital stay was 37.28 days with a median of 32 days (SD=30.47; min/max=2/186). Of these hospital days, the average days of OM was 4.3 days with a median of 11 days (SD=8; min/max=2/42). Details of the days of OM severity are displayed in Table 1.

Sixty-five percent of the 23 children who had OM incidence had repeated OM episodes. Only one patient had seven OM episodes while the number of children who had two, three, and four episodes was eight, four, and two respectively. The ratio of children who had OM recurrence to those who had a single episode was 1.9. Details of children affected by OM are displayed in Table 1.

Sixty-five percent of the children affected by grade one and two OM had pain scores of 1-2 while those who were affected by grades three and four (35%) had pain scores of 3-5. Similar findings were observed for the difficulty to perform oral functions among children affected by

grade one and two (65%) with difficulty scores of 1-3 for swallowing, 1-2 for eating, and 1-2 for drinking. Patients with grade three and four (35%) had difficulty levels of 4-5 for swallowing and 3-5 for both eating and drinking.

Oral hygiene was rated good for all children throughout the study period with the majority of children scoring between zero (no dental plaque) and one (a film of dental plaque) on the PI. Dental caries prevalence among the study sample was 28%. No statistical significant difference was found when the prevalence of dental caries was compared among children with or without OM, with prevalence rates of 39% and 23% respectively.

During the first dental examination, 69% of the sample had a score of dental caries index (DMFT/dmft) of zero that remained the same at the last dental examination. The rate of children who scored zero on the DMFT/dmft index and had OM was 61% compared to 73% for children without OM. Similar to the whole sample, those children remained caries free at the last dental examination. DMFT/dmft scores and details of the decayed (D/d), missed (M/m) and filled (F/f) components of this index at the first and last dental examinations are depicted in Figures 1 and 2.

At the last dental examination, the study sample mean rank of decayed teeth was significantly reduced (77 to 58) while that of filled teeth was significantly increased (59 to 76). These differences were statistically significant for the whole sample and for subgroup analysis based on the presence or absence of OM (2-sided Wilcoxon signed-rank test; P-value <0.0001). However, no significant difference was found for the number of missed teeth between the first and last dental examinations. The rates of the number of decayed teeth at the first dental examination

were 72%, 13%, 7%, and 8% corresponding to no decayed teeth, 1-3 decayed teeth, 4-7 decayed teeth, and 8-12 decayed teeth respectively.

Fifty-four percent of the study sample did not require any dental treatment. Among those who required dental treatments, 16% needed preventive treatments and 30% needed curative treatments. All children who required dental treatment whether preventive or curative have received it with 100% rate of utilization of dental services.

Among all explanatory variables tested in the bivariate analysis against OM outcomes (OM incidence, severity, duration, and recurrence), age and gender were not significantly associated. Similarly, no significant associations were found between OM incidence, severity, and recurrence and all explanatory variables. However, other associations were found significant when these latter variables were considered as explanatory variables (Tables 3 and 5).

Significant associations were found between OM duration and type of cancer treatment, dental review time, and higher pain and oral function difficulty scores (Table 2). Children who were treated with chemotherapy or chemotherapy/surgery had a comparable rate of OM duration that was four times greater than those treated with chemotherapy/radiotherapy/and surgery. Similarly, children who experienced high pain and oral function difficulty scores had a rate of OM duration 2.21 times greater than children with lower scores. Although there was no significant association between OM duration and dental caries status, if a child had one more day of dental review time his/her rate of OM duration would be expected to decrease by 6%. OM duration was also

significantly associated with OM severity (grade 2 and 4), total days of grade 1 and 2 OM, and OM recurrence with direct positive relationship leading to an increase in OM duration (Table 3).

Bivariate analysis of the number of OM episodes, that was used as a proxy measure for OM incidence density, revealed that for every additional day of grade 1, 2, or 4 OM, children's rate of additional OM episodes was increased by 23%, 25%, and 37% respectively (Table 4).

Exploring the effect of OM outcomes on the total days of hospital stay was examined in Table 5 with significant associations to OM incidence and severity (grade 2 and 4). Children who had OM or had experienced grade 2 or 4 OM had an increased rate of hospital stay of 2.18, 2.03, and 2.69 times greater than children who had no OM respectively.

Four multivariate models were constructed in Table 6 to examine the relationship between the number of OM episodes, OM duration, and the total days of hospital stay against significant covariates from the bivariate models, provided that they are not strongly correlated ($r \geq 0.6$) with the outcome variable of interest. The rate of OM episodes among children who had grade 1 or 4 OM was expected to increase by 20% and 24% respectively.

The two models that examined the relationship between OM duration and related covariates indicated a direct positive relationship among children treated with chemotherapy, those who had more days of grade 1 OM, and those who experienced pain scores of 3-5 with an increased likelihood by 3.69, 1.068, 2.18 times respectively. On the contrary, dental review time was

inversely related to OM duration with a decrease of 6% with each additional day of dental review.

The fourth multivariate model that tested the total days of hospital stay as an outcome measure found that by holding the total days of grade 1 and 3 OM constant, children who had OM had a rate of total days of hospital stay 1.64 times more than children who had no OM.

Discussion:

This prospective clinical study was able to estimate OM incidence and incidence density among children receiving cancer treatment at the Women's and Children's Hospital, Adelaide, Australia. This estimate of OM incidence (34%), the incidence density (129.2/100 person-years of observation), and other OM characteristics including OM severity, duration, and recurrence have helped in assessing the magnitude of this debilitating side effect of cancer treatment in children. These incidence figures were considerably lower than that of similar studies that reported a range of OM incidence of 52-80%.[10-12]

Such low OM incidence rate may be explained by the implementation of the comprehensive oral care protocol or by the fact that our hospital avoids using five-fluorouracil (5-FU) chemotherapy that has been documented to be related to high OM rates.[18] Another explanation of this low incidence might be related somehow to limiting OM recording for inpatients i.e. missing those who got OM while at home. Although OM was recorded for inpatients, children who were not hospitalized were also performing the comprehensive oral care protocol at homes. This might

have also contributed to the low incidence due to the preventative effect of the oral care protocol. One of the limitations of recoding OM, despite the utility of the ChIMES/WHO scale, was its limited applicability to children ≤2 years of age; a limitation worth investigating in future research.

Good collaboration between the dental and oncology departments played a big role in maintaining such good oral health measures throughout cancer treatment period. Regular dental reviews were essential to achieve such stability in oral health status and significantly reduce the rate of dental caries. Only one recent study has longitudinally assessed oral health status among children receiving cancer treatment and found similar findings in relation to the PI that did not change during the study period.[19] However, the mean number of decayed teeth has increased in contrast to our findings. The benefit of regular dental reviews was also endorsed by bivariate and multivariate analysis results that showed significant association between prolonged dental reviews and shortened OM duration.

Risk factors exploration through bivariate and multivariate analysis has revealed multiple risk factors for OM duration and the number of OM episodes. However, other associations among other OM outcomes could not be tested due to the relatively small sample size and low OM incidence. Risk factors exploration require large sample sizes to allow stratification without affecting the minimum number of observations required to run certain statistical tests per predictor. This problem was prevalent when the association between OM outcomes and type of chemotherapy protocols was tested. Such association was previously documented as a risk factor for developing OM among children.[20] Trend exploration for repeated OM episodes was limited

due to small rate of OM recurrence hence longer periods of observations and involvement of larger sample sizes may aid in explaining such occurrences.

Analyzing the effect of OM outcomes on days of hospital stay was essential to help reduce hospital costs in relation to OM management. Knowing that children with OM tend to stay longer emphasize the need to prevent this side effect. Correspondingly, ongoing regular dental reviews are considered essential because of its inverse relationship with OM duration hence less days of hospital stay.

Conclusion:

Continuous monitoring of OM incidence is essential for managing its symptoms. Implementing a comprehensive oral care protocol as a preventative tool might have played a role in lowering OM incidence. Prolonged regular dental reviews can significantly reduce OM duration among children receiving cancer treatment. Several risk factors have been identified, however, further exploration of risk associations requires larger sample sizes to allow proper statistical testing.

Table 1: Distribution of patients' characteristics among children with and without OM

Patient characteristics		With OM n=23	Without OM n=44	Total n=67
Type of cancer	Acute lymphoblastic leukemia (ALL)	48	48	48
	Acute myeloid leukemia (AML)	4	5	5
	Lymphoma	17	7	10
	Malignant solid tumors	22	27	25
	Central nervous system (CNS) tumors	9	14	12
Chemotherapy protocol	Standard-medium-risk ALL	35	30	31
	High-risk ALL & AML	26	25	25
	Lymphoma	13	0	5
	Malignant solid tumors	22	34	30
	CNS tumors	4	11	9
Cancer treatment type	Chemotherapy	65	61	63
	Chemotherapy & surgery	26	34	31
	Chemotherapy, radiotherapy, & surgery	9	5	6
Highest OM severity recorded	Grade 1	9	-	-
	Grade 2	61	-	-
	Grade 4	4	-	-
Total days of OM severity	Grade 1	Mean=1.43 Median=3 SD=3.34 Min/Max=1/17	-	-
	Grade 2	Mean=2.18 Median=6 SD=4.06 Min/Max=2/20	-	-
	Grade 3	Mean=0.27 Median=2 SD=1.18 Min/Max=1/8	-	-
	Grade 4	Mean=0.49 Median=4 SD=1.53 Min/Max=2/8	-	-
OM recurrence	Yes	65	-	-
	No	35	-	-
Total cumulative days of hospital stay		Mean=57.83 Median=51 SD=36.63 Min/Max=4/186	Mean=26.55 Median=25.5 SD=19.88 Min/Max=2/69	Mean=37.28 Median=32 SD=30.47 Min/Max=2/186

Table 2: Bivariate analysis of OM duration and explanatory variables

Outcome variable	Explanatory variables	Statistical method	Strength of association Measure; (95%CI)	Statistical measures n; Alpha=0.05; Pair-wise P-value *=Sig	Global P-value *=Sig
OM duration	Types of cancer *-Malignant solid tumors (reference)* *-ALL* *-AML* *-Lymphoma* *-CNS tumors*	Negative binomial regression[1]	 Rate ratio=1.02;(0.48-2.15) Rate ratio=1.10;(0.26-4.59) Rate ratio=0.93;(0.37-2.32) Rate ratio=0.23;(0.065-0.79)	n=23	0.14
	Chemotherapy protocol *-Standard-medium-risk ALL (reference)* *-High-risk ALL & AML* *-Lymphoma* *-Malignant solid tumors* *-CNS tumors*		 Rate ratio=1.32;(0.61-2.84) Rate ratio=1.22;(0.47-3.19) Rate ratio=1.22;(0.47-3.19) Rate ratio=0.43;(0.087-2.08)	n=23	0.70
	Type of cancer treatment *-Chemotherapy, radiotherapy, & surgery (reference)* *-Chemotherapy* *-Chemotherapy & surgery*		 Rate ratio=4.53;(1.47-14.0) Rate ratio=4.18;(1.23-14.15)	n=23 P=0.0086* P=0.022*	0.031*
	Dental caries status *-No (reference)* *-Yes*		 Rate ratio=1.17;(0.62-2.22)	n=23	0.63
	Dental review time		 Rate ratio=0.94;(0.89-0.99)	n=23 P=0.029*	0.029*
	Pain scores *-Score 1-2 (reference)* *-Score 3-5*		 Rate ratio=2.21;(1.27-3.85)	n=23 P=0.0049*	0.0049*
	Difficulty of swallowing, eating, & drinking *-Score 1-3 (reference)* *-Score 4-5*		 Rate ratio=2.21;(1.27-3.85)	n=23 P=0.0049*	0.0049*

[1] The number of days of OM review has been accounted for in this model

Table 3: Bivariate analysis amongst OM outcomes that may serve as explanatory variables

Outcome variables	Explanatory variables	Statistical method	Strength of association Measure; (95%CI)	Statistical measures n; Alpha=0.05; Pair-wise P-value *=Sig	Global P-value *=Sig
OM duration	OM severity (highest grade recorded) *-Grade 1 (reference)* *-Grade 2 vs reference* *-Grade 4 vs reference* *-Grade 4 vs Grade 2*	Negative binomial regression[1]	 Rate ratio=3.37;(1.13-9.98) Rate ratio=5.20;(1.67-16.17) Rate ratio=1.55;(0.85-2.81)	n=23 P=0.029* P=0.0044* P=0.15	0.015*
	Total days of OM severity by grade *-Grade 1* *-Grade 2* *-Grade 3* *-Grade 4*		 Rate ratio=1.07;(1.01-1.13) Rate ratio=1.09;(1.030-1.16) Rate ratio=1.14;(0.98-1.32) Rate ratio=1.11;(0.98-1.27)	n=23 P=0.028* P=0.0037* P=0.082 P=0.11	 0.028* 0.0037* 0.082 0.11
	OM recurrence *-No (reference)* *-Yes*		 Rate ratio=1.98;(1.05-3.71)	n=23 P=0.034*	0.034*
OM recurrence	OM severity (highest grade recorded) *-Grade 1* *-Grade 2* *-Grade 4*	Fisher's Exact Test[2]	 0 (0%),Recurrence=Yes 11 (79%),Recurrence=Yes 4 (57%),Recurrence=Yes	n=23	0.085

[1] The number of days of OM review has been accounted for in this model

[2] As a logistic model did not produce sensible results, a 2-way contingency table was created and Fisher's Exact Test performed

Table 4: Trend exploration of the repeated episodes of OM as a proxy for incidence density

Outcome variable	Explanatory variables	Statistical method	Strength of association Measure; (95%CI)	Statistical measures n; Alpha=0.50; Pair-wise P-value *=Sig	Global P-value *=Sig
Number of OM episodes	Total days of grade 1 OM	Negative binomial regression[1]	Rate ratio=1.23;(1.13-1.33)	n=67 P=0.0001*	<0.0001*
	Total days of grade 2 OM		Rate ratio=1.25;(1.12-1.40)	n=67 P=0.0001*	<0.0001*
	Total days of grade 3 OM		Rate ratio=1.33;(0.99-1.80)	n=67 P=0.061	0.061
	Total days of grade 4 OM		Rate ratio=1.37;(1.06-1.77)	n=67 P=0.015*	0.015*

[1] The number of days of OM review has been accounted for in this model

Table 5: Bivariate analysis of total days of hospital stay and OM outcomes

Outcome variable	Explanatory variables	Statistical method	Strength of association Measure; (95%CI)	Statistical measures n; Alpha=0.05; Pair-wise P-value *=Sig	Global P-value *=Sig
Total days of hospital stay	OM incidence *-No (reference)* *-Yes*	Negative binomial regression[1]	Rate ratio=2.18;(1.48-3.20)	n=67 P<0.0001*	<0.0001*
	OM severity (highest grade recorded) *-No OM (reference)* *-Grade 1* *-Grade 2* *-Grade 4*		Rate ratio=1.41;(0.48-4.13) Rate ratio=2.034;(1.29-3.20) Rate ratio=2.69;(1.48-4.89)	n=67 P=0.53 P=0.0022* P=0.0012*	0.0008*
	OM duration		Rate ratio=1.028;(0.99-1.06)	n=23	0.0617
	OM recurrence		Rate ratio=1.59;(0.96-2.64)	n=23	0.0721
	Number of OM episodes		Rate ratio=1.11;(0.91-1.35)	n=23	0.29

[1] The number of days of OM review has been accounted for in this model

Table 6: Multivariate analysis of OM outcomes controlling for confounders

Outcome variables	Covariates	Statistical method	Strength of association Measure; (95%CI)	Statistical measures n; Alpha=0.05; Pair-wise P-value *=Sig	Global P-value *=Sig
Number of OM episodes (as a proxy for incidence density)	Total days of grade 1 OM Total days of grade 4 OM	Multivariate negative binomial regression[1]	Adjusted rate ratio=1.20;(1.15-1.26) Adjusted rate ratio=1.24;(1.12-1.37)	n=67 P<0.0001* P<0.0001*	<0.0001*
OM duration	Dental review time Type of cancer treatment -*Chemotherapy, radiotherapy, & surgery (reference)* -*Chemotherapy vs reference* -*Chemotherapy & surgery vs reference* -*Chemotherapy & surgery vs chemotherapy*		Adjusted rate ratio=0.94;(0.89-0.99) Adjusted rate ratio=3.69;(1.29-10.58) Adjusted rate ratio=2.70;(0.83-8.76) Adjusted rate ratio=0.73;(0.39-1.38)	n=23 P=0.026* P=0.015* P=0.098 P=0.33	0.026* 0.039*
	Total days of grade 1 OM Pain scores -*Score 1-2 (reference)* -*Score 3-5*		Adjusted rate ratio=1.07;(1.02-1.12) Adjusted rate ratio=2.18;(1.38-3.44)	n=23 P=0.0057* P=0.0008*	0.0057* 0.0008*
Total days of hospital stay	OM incidence -*No (reference)* -*Yes vs reference* Total days of grade 1 OM Total days of grade 3 OM		Adjusted rate ratio=1.64;(1.002-2.69) Adjusted rate ratio=1.03;(0.97-1.097) Adjusted rate ratio=1.15;(0.97-1.38)	n=67 P=0.049* P=0.33 P=0.109	0.049* 0.33 0.109

[1] The number of days of OM review has been accounted for in this model

Figure legends:

Figure 1: DMFT/dmft index scores at the first and last dental examination

Figure 2: Details of decayed, missed, and filled teeth at the first and last dental examination

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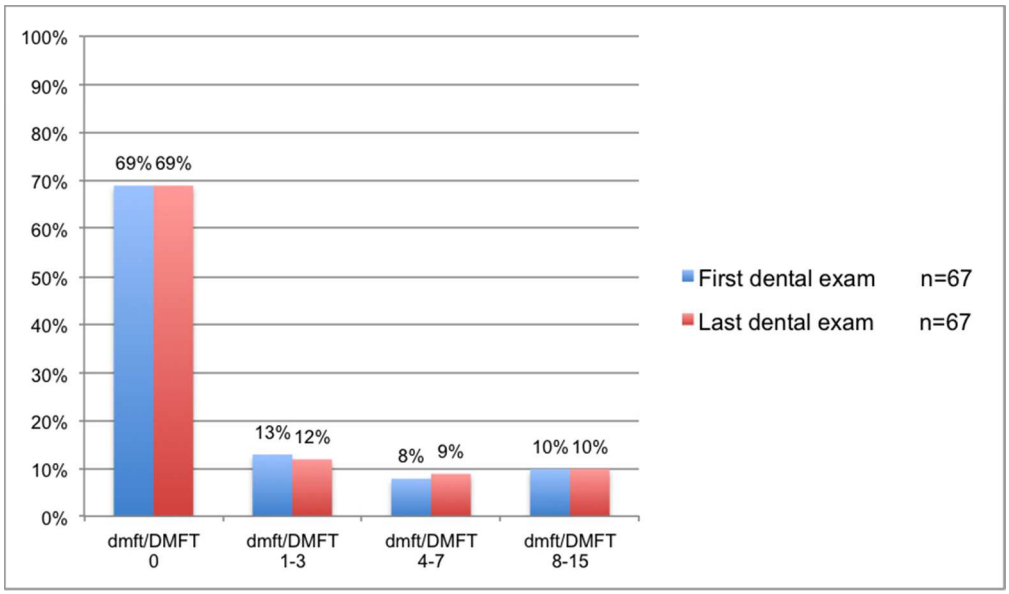

Figure 1
152x89mm (150 x 150 DPI)

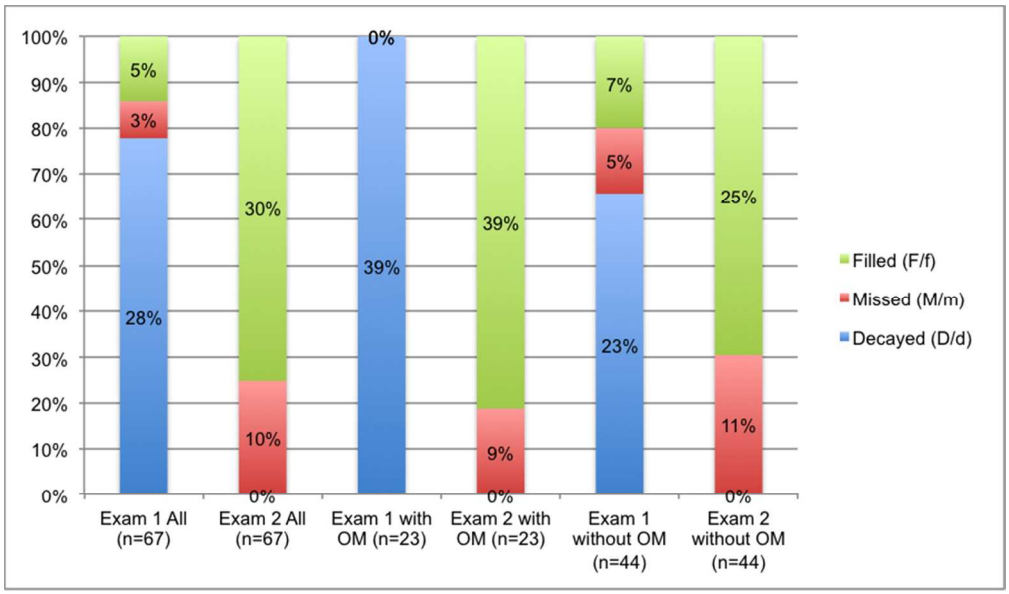

Figure 2
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4.0 General discussion

The initial review of the literature provided the background knowledge on childhood cancer and oral mucositis. It revealed that oral mucositis is one of the major debilitating side effects of cancer treatment. The understanding of the epidemiology, pathophysiology, risk factors, clinical presentation, prevention, and treatment of oral mucositis was critical in formulating the rationale, aim, and preliminary objectives of this study. These preliminary objectives were adjusted and amended at different time points based on recognizing and overcoming challenges encountered during and after each of the publications included in this thesis. The thesis is composed of a comprehensive literature review and four publications. At the conclusion of each publication, reflection and critical appraisal was made, and upon the results of that publication, these reflections were utilized to develop the study objectives and to generate the final study objectives as shown in section 2.3. This has provided valid justifications and insights for conducting subsequent publications.

The retrospective study of the incidence of oral mucositis was considered essential in documenting the deficiencies of clinical practices at the Women's and Children's Hospital in regards to both dental assessments as part of the overall cancer treatment plan and recording and managing of oral mucositis among children receiving cancer treatment. These deficiencies included a lack of consistent and standardized recording of oral mucositis, lack of collaboration and timely referrals between the Department of Clinical Hematology/Oncology and the Department of Pediatric Dentistry, and the absence of a standardized oral care protocol for children receiving cancer treatment. The realization of these deficiencies has provided evidence to conduct the systematic review on the prevention of oral mucositis in children (publication 1).

This systematic review was a comprehensive approach to investigate the different agents and strategies used to prevent oral mucositis in children. Moreover, it helped in the development of the standardized oral care protocol for children receiving cancer treatment based on scientific evidence. Many of the previous oral health recommendations that were given by the Oncology and Dental staff were modified after this systematic review to follow what the evidence suggests. The systematic review has also helped in gaining deeper understanding of the overall topic.

One of the key results of the systematic review was the finding that performing and maintaining optimal oral care among children receiving cancer treatment was considered an efficient, convenient, acceptable and accessible method of preventing oral mucositis: a finding that supported the development and implementation of the standardized oral care protocol in the hospital.

Following the discussion of the results of the systematic review and the retrospective study, Consultant medical and dental staff from the Department of Clinical Hematology/Oncology and the Department of Pediatric Dentistry agreed on the importance of conducting a prospective study to further investigate oral mucositis in children. This has led to the second and third publications of this thesis that were conducted simultaneously through the pilot study.

The second publication focused on validating the combined use of the ChIMES and the WHO oral mucositis scale and discussed justifications of their use. This idea of combining these two scales came about from the understanding gained from the literature review in the introduction part of the thesis. Knowledge of differences between cancer in children and in adults, especially when it comes to the limited ability of children to express pain and discomfort, gave reasoning behind utilizing oral

mucositis scales that can address this inherent problem. The smiley faces of the ChIMES scale helped in capturing children's expressions of subjective measures thus complementing subjective measures of the WHO scale.

Several training and calibration sessions with the nursing staff of the Department of Clinical Hematology/Oncology have resulted in reaching satisfactory reliability scores in the recording of oral mucositis among inpatients. The inter- and intra-examiner reliability kappa results were 0.83 and 0.87 respectively i.e. high agreement among staff involved in recording of oral mucositis. This high level of agreement has reflected on the accuracy of data collection of the fourth publication.

The third publication reported on the development and staged implementation of the hospital oral care protocol that was developed based on recommendations from the first publication. This third publication also reported the process of improving compliance for the daily recording of oral mucositis scales among children admitted to the Department of Clinical Hematology/Oncology. Continuous monitoring, ward rounds, in-service presentations, and meetings with the nursing staff have resulted in improved rate of compliance for recording oral mucositis scales from 41% to 87%. This third publication has also reported a significant increase in patients' referral rates from the Department of Clinical Hematology/Oncology to the Department of Pediatric Dentistry from 53% during the retrospective study to 100% at end of the prospective pilot study. This increase in the rates of compliance for the daily recording of oral mucositis and the improved rates of referral to the Department of Pediatric Dentistry have resulted in better outcomes during the data collection of the fourth publication.

The first three publications have allowed for better preparation and execution of the fourth publication that was carried out using a prospective observational research methodology among inpatients receiving treatment for childhood cancer. This last publication was centered on reporting oral mucositis incidence, incidence density, other oral mucositis characteristics, and oral health status including oral hygiene, dental caries, and dental treatment needs. The publication also explored possible risk factors that may play a role in the development of oral mucositis through statistical modeling to control for confounders. Sixty-seven children were recruited and included in the analysis with different entry and exit time points that were accounted for in the analysis.

The incidence of oral mucositis was reported at 34% while the prevalence of dental caries was reported at 28%. Both of these figures were considered low when compared with other studies and might be explained by the preventative effect of the comprehensive oral care protocol and by avoiding the use of 5-FU as chemotherapeutic agent at the Oncology Department.

When different risk factors were explored in the fourth publication, the duration of oral mucositis was significantly reduced when children were reviewed regularly at the Department of Pediatric Dentistry. This reflects the benefit of establishing and implementing the comprehensive oral care protocol in the third publication that included three-monthly dental reviews.

The results of the fourth publication were clearly affected by what have been achieved by the previous three publications. In the first publication, scientific evidence was established to support the development and implementation of a standardized oral care protocol in the third publication. Simultaneously, during the

critical appraisal of the literature for the first publication and the literature review in the thesis introduction, background knowledge was synthesized in regards to finding appropriate scales to record oral mucositis in children. This background knowledge was utilized to conduct the second publication. Moreover, mastering and improving research methods, raising the level of awareness of the importance of recording oral mucositis, maintaining an optimal oral care among patients, nurses, physicians, and dentists, and overcoming research obstacles during the first three publications, had a remarkable effect on shaping and improving the quality of the fourth publication.

5.0 Recommendations and future directions

Several recommendations and future directions can be endorsed based on the results of these publications and the shortcomings faced in this thesis. These recommendations are:

1) Future studies should include larger sample sizes. Increased sample size will allow extension of the period over which research projects are conducted, overcoming low incidence rates of childhood cancer. During the pilot study of this thesis, 38 children were recruited over seven months as reported in the third publication. This number was increased to 67 children during the prospective study in the fourth publication of which recruitment was carried out over twelve months. This means that on average, there is an increase of five new patients per extra month of observation. The increase in sample sizes would 1) allow for more accurate estimation and exploration of risk factors for oral mucositis, 2) permit more subgroups analysis 3) allow conducting research projects on oral mucositis genotyping to aid in the prediction of this condition. Such genetic studies require stratification of the sample based on patient-

related and cancer-treatment-related confounders e.g. age, gender, type of cancer, type of cancer treatment protocol, and frequency of chemotherapy and/or radiotherapy treatments; which subsequently necessitate larger sample sizes.

2) Patient recruitment should include both inpatients and outpatients to allow for more accurate estimation of oral mucositis incidence and other mucositis variables e.g. severity, duration, recurrence, and levels of pain and discomfort encountered by patients at home as well as during their hospital stay. Of course this will add a challenge to researchers to keep the children and their parents/caregivers motivated to record oral mucositis scales at home.

3) Compliance with the recording of oral mucositis at the Women's and Children's Hospital, Adelaide, Australia should continue to be monitored by appointed staff from the Department of Clinical Hematology/Oncology and the Department of Pediatric Dentistry to assure better patient management and allow for conduction of extended research projects.

4) The current outstanding collaboration between the Department of Clinical Hematology/Oncology and the Department of Pediatric Dentistry should be maintained because it is the key to constant success of such projects and improved patients' care.

5) Future research should invest in improving the assessment of subjective measures of oral mucositis e.g. pain and discomfort among very young children (≤ 2 years of age) and children with disabilities that prevent them from expressing subjective measures e.g. autism. Researches and clinicians need

to find innovative methods to address this problem e.g. inventing a scale that would incorporate crying tone, facial expressions and disturbed feeding and sleeping times to give estimates of pain and discomfort. Not only that such scale will improve the recording of oral mucositis but it will also revolutionize pain management in general for this group of patients.

6) Systematic reviews of the literature pertaining to prevention of oral mucositis in children, similar to the first publication, should be conducted regularly to update preventative strategies for this group of patients.

7) A systematic review of the literature and current national and international hospital protocols should be conducted in order to identify best practices in managing this debilitating condition and minimize the sufferings of affected children.

8) Multi-center research should be conducted nationally in Australia to survey the clinical guidelines currently used for the prevention and management of oral mucositis among children receiving cancer treatment. Such projects are essential to establish collaborations and allow for standardization of oral care protocols across Australia.

9) National bodies e.g. the Australian Academy of Pediatric Dentistry should take the lead in developing oral care guidelines for Australian children undergoing cancer treatment. Establishing such guidelines needs a group of experts who can build on and modify the guidelines developed by the American Academy of Pediatric Dentistry to incorporate unique Australian oral health policies in

relation to different oral care aspects e.g. applied topical fluorides and workforce utilization.

6.0 Conclusion

This prospective clinical study of 67 children hospitalized with cancer at the Women's and Children's Hospital, Adelaide, Australia, found a low incidence of oral mucositis and a low prevalence of dental caries. These low rates manifested through the implementation of a comprehensive oral care protocol and continuous monitoring of this condition. Results of the pilot study attested that the combined use of the WHO and the ChIMES scales was found to better record this condition while results of the systematic review supported the use of oral care protocol to prevent oral mucositis. Having regular dental reviews throughout the period of childhood cancer treatment were significantly related to shorter duration of oral mucositis and hence fewer days of hospital stay. An increase in incidence and severity of oral mucositis was significantly related to increasing total days of hospital stay. These results necessitate further investigation to better understand, prevent, and manage oral mucositis in children which will in return going to reflect on better patient care, improved quality of patients' life, and less cost on health care organizations.

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8.0 Appendices

8.1 Appendix 1: Ethical approval letters

Government of South Australia
SA Health

Women's & Children's Hospital

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4th February 2009

Dr S Gue
Paediatric Dentistry
CYWHS

Dear Sam

Re: Data base construction for recording oral findings and oral manifestations, including dental caries, preventive regimes, incidence of oral mucositis and oral mucositis management in paediatric patients undergoing oncology treatment. REC2112/10/11

I refer to my letter dated 27th January 2009 and advise that I have now received a copy of the National Police Certificate for Ms Allen. I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

If, in the future, the study involves other non CYWHS staff or students, a signed Confidentiality Agreement will be required and, if they visit any CYWHS site, a National Police Certificate provided to the Ethics Committee and the Human Resources Department. The study may proceed on this proviso.

I remind you approval is given subject to:
- immediate notification of any serious or unexpected adverse events to subjects;
- immediate notification of any unforeseen events that might affect continued ethical acceptability of the project;
- submission of any proposed changes to the original protocol. Changes must be approved by the Committee before they are implemented;
- immediate advice, giving reasons, if the protocol is discontinued before its completion;
- submission of an annual report on the progress of the study, and a final report when it is completed. Please note it is your responsibility to provide these reports – without reminder from the Ethics Committee.

Approval is given for three years only, and if the study is more prolonged than this, a new submission will be required. Please note the approval number above indicates the month and year in which approval expires and it should be used in any future communication.

If University of Adelaide personnel are involved in this project, you, as chief investigator must submit a Human Research Approval notification form online at http://www.adelaide.edu.au/ethics/human/guidelines/ within 14 days of receiving this ethical clearance to ensure compliance with University requirements and appropriate indemnification.

Yours sincerelv

TAMARA ZUTLEVICS (DR)
CHAIR
CYWHS HUMAN RESEARCH ETHICS COMMITTEE

Government of South Australia
SA Health

Women's & Children's Hospital

7th July 2010

A/Professor S Gue
Department of Paediatric Dentistry
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Dear Sam

Re: Assessment and validation of Diagnostic scale, oral care protocol, the prevention and treatment of oral mucositis in a paediatric population receiving cancer therapy. REC2256/2/13

I refer to a letter from Dr Qutob dated 23rd June 2010 responding to my letters dated 10th March and 8th June regarding matters raised by the CYWHS Human Research Ethics Committee at its February 2010 meeting. I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

I refer to advice in my letter dated 10th March 2010 letter regarding the institutional requirement for a National Police Check and the signing of a Confidentiality Agreement by students or non-CYWHS staff involved in research at CYWHS and provide further information below on the requirements.

a. **National Police Certificates for students (excluding students from University of South Australia) and non-CYWHS staff involved in the project on CYWHS sites.** The Certificates are to be provided to the CYWHS Human Resources Department for verification (telephone 81617249 for further information) and copies forwarded to the Ethics Committee.

b. **Confidentiality Agreements**. If the project involves patients/clients/staff of CYWHS or their personal information, signed Confidentiality Agreements are to be provided for all students and non CYWHS staff to the Committee. Please refer to http://www.wch.sa.gov.au/research/committees/humanethics/ConfidentialityAgreement.html

I note that two members of the research team are not CYWHS staff and presume that they will not be visiting the CYWHS site or have access to personal information, as above. If this is not the case, they should not be involved in the project until the requirements have been met. The above requirements also relate to any future students and non-CYWHS staff involved on the project. If students and non-CYWHS staff on this project are subsequently involved on other projects approved by the Committee, a copy of the National Police Certificate will need to be re-sent to the Committee and a Confidentiality Agreement signed for each specific project.

I remind you approval is given subject to:
- immediate notification of any serious or unexpected adverse events to subjects;
- immediate notification of any unforeseen events that might affect continued ethical acceptability of the project;
- submission of any proposed changes to the original protocol. Changes must be approved by the Committee before they are implemented;
- immediate advice, giving reasons, if the protocol is discontinued before its completion;
- submission of an annual report on the progress of the study, and a final report when it is completed. It is your responsibility to provide these reports – without reminder from the Ethics Committee.

Approval is given for three years only. If the study is more prolonged than this, an extension request should be submitted unless there are significant modifications, in which case a new submission may be required. Please note the approval number above indicates the month and year in which approval expires and it should be used in any future communication.

If University of Adelaide personnel are involved in this project, you, as chief investigator must submit a Human Research Approval notification form online at

http://www.adelaide.edu.au/ethics/human/guidelines/ within 14 days of receiving this ethical clearance to ensure compliance with University requirements and appropriate indemnification.

Yours sincerely

TAMARA ZUTLEVICS
(DR) CHAIR
CYWHS HUMAN RESEARCH ETHICS COMMITTEE

Cc: Dr A Qutob, Dental Dept, CYWHS

8.2 Appendix 2: Participant's consent form

NOTE:
This appendix is included on pages 163-164 of the print copy of the thesis held in the University of Adelaide Library.

8.3 Appendix 3: Participant’s information sheet

8.4 Appendix 4: Dental treatment booklet

NOTE:
This appendix is included on pages 169-178 of the print copy of the thesis held in the University of Adelaide Library.

8.5 Appendix 5: Oral care protocol

Oral Care Protocol for Children Receiving Cancer Treatment

Dental Visits	• **Attend the Department of Pediatric Dentistry shortly after cancer diagnosis to assess child's oral health prior to start of cancer treatment** • **Attend follow up dental visits every 3 months**
Tooth Brushing	• **Brush teeth and tongue 2-3 times daily, each session lasting for at least 2 minutes with a soft nylon toothbrush** • **Brushing should continue regardless of the child's blood cell and platelet counts** • **Toothbrushes are to be air dried between uses** • **Replace toothbrush every 2-3 months and/or after neutropenic cycle** • **Use super soft toothbrushes or oral sponges ONLY when the child cannot tolerate a toothbrush and should be soaked with aqueous 0.2% alcohol-free Chlorhexidine mouth rinse** ***(regular teeth brushing with soft brush should resume once tolerated)*** • **Use Small pea-sized amount of fluoridated tooth paste pushed down the brush by the thumb to be used to brush teeth in children over 18 months of age** **- *Prior to 18 months of age*: no tooth paste just warm water** **- *18 months – 6 years*: use junior/children's tooth paste (400ppm)** **- *Over 6 years*: use standard adult tooth paste (1000ppm)** • **Use a mint-free tooth paste if the child has stinging sensation**
Mouth Rinse	• **Rinse 2 times daily with aqueous 0.2% alcohol-free Chlorhexidine mouth rinse after brushing to reduce gum bleeding** **NOTE: Infants or children, who are unable to rinse their mouths should use jumbo probes soaked in the recommended mouth rinse**

8.6 Appendix 6: ChIMES/WHO oral mucositis scale

NOTE:
This appendix is included on page 182 of the print copy of the thesis held in the University of Adelaide Library.

8.7 Appendix 7: Dental examination form

Clinical Examination Form

Participant's ID

Appointment date: _ _ /_ _ / _ _ _ _

Dentist: _____

Attendance:		**1**: Attended **2**: Failed to attend- FTA
Appointment #:		
Cancer treatment phase:		**1**: Treatment phase **2**: Maintenance phase

For each of the following categories, please type the appropriate code number(s) that applies, in the boxes provided.

Plaque Index (PlI):

Codes

0 No plaque

1 A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be recognized only be running a probe across the tooth surface

2 Moderate accumulation of soft deposits within the gingival pocket, on the gingival margin and/ or adjacent tooth surface, which can be seen by the naked eye

3 Abundance of soft matter within the gingival pocket and/ or on the gingival margin and adjacent tooth surface

9 Not recorded (if no posterior or anterior teeth present to examine)

*** If the assigned tooth has a stainless steel crown (SSC) please record the tooth next to it**

55/16	11/51	65/26
85/46	71/31	75/36

Dentition Status (dmft/DMFT) after clinical and radiographic examination:

Codes

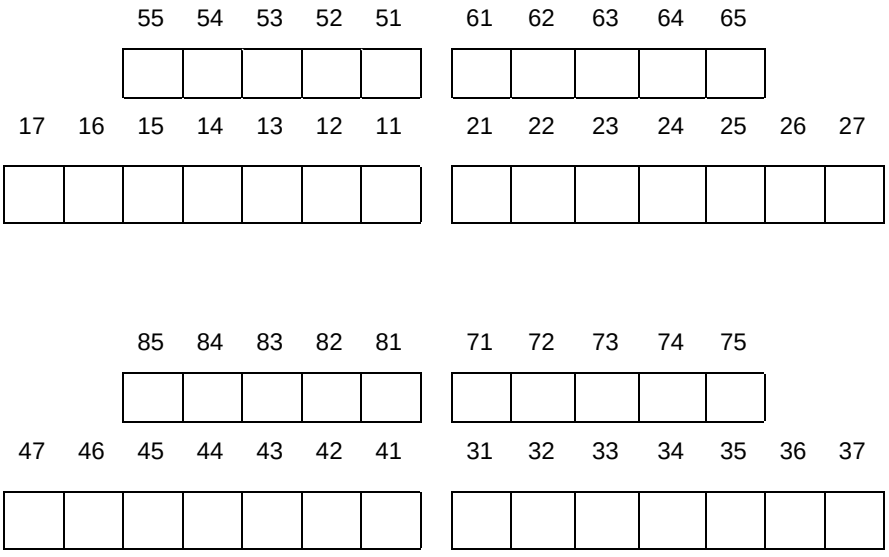
0	Sound
1	Initial caries (D1)
2	Enamel caries (D2)
3	Caries of dentin (D3)
4	Pulpal involvement (D4)
5	Filled- with decay
6	Filled- no decay
7	Missing- due to caries
8	Missing- any other reason
9	Fissure sealant
10	Exfoliated or un-erupted tooth
11	Soon to exfoliate
12	Partially erupted

Radiographs:

Bitewings ☐ 1: Yes 2: No

OPG ☐ 1: Yes 2: No

* Please record the deft/ DMFT after taking the diagnostic radiographs



Dental treatment needed: ☐ **1**: Yes **2**: No