Mouth Care for Children and Young People with Cancer: Evidence-based Guidelines

Guideline Report

Version 1.0 February 2006

Produced by the UKCCSG-PONF Mouth Care Group

This Guideline Report has been produced by members of the UKCCSG-PONF Mouth Care Group and is open for comment.

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1 BACKGROUND

The United Kingdom Children's Cancer Study Group (UKCCSG) and the Paediatric Oncology Nurses Forum (PONF) have a combined Supportive Care Group. In June 2001, a sub-committee of this group was established and designated the Mouth Care Group. The principal aim of the UKCCSG-PONF Mouth Care Group was to produce comprehensive evidence-based guidelines on mouth care for children and young people being treated for cancer.

Treatment of childhood cancer is becoming increasingly effective, with survival rates reported at 70-75% in parts of Europe and North America.[1] Despite advances in chemotherapy and radiotherapy, cancer treatment still remains associated with clinically important, sometimes dose-limiting, side effects. Oral complications occurring during and following cancer treatment are common and can cause pain, difficulty in swallowing and phonation and poor nutrition. They clearly can impact severely on a patient's quality of life.[2]

One of the most common side effects of cancer treatment is **mucositis**, a painful inflammation and ulceration of the mucous membrane. The oral mucosa consists of rapidly dividing cells that are especially susceptible to the damaging effects of cytotoxic therapy. Oral complications during chemotherapy and radiotherapy can arise from direct injury to the oral mucosa, but they also result from cytotoxic induced myelosuppression which produces profound neutropenia.[3]

The prevalence of chemotherapy induced oral mucositis has been shown to range from 30-75% of patients, depending upon treatment type.[4, 5] In about 50% of patients with mucositis, lesions can be severe causing significant pain, interfering with nutrition and often requiring modification of the chemotherapy regimen. In addition, mucositis may predispose a child to fungal infection (most commonly), viral infection (for example due to herpes simplex virus) and bacterial infection, which may lead on to life-threatening systemic infection.

Candidiasis is an opportunistic yeast infection, usually limited to the skin and mucous membranes and most commonly caused by *Candida albicans.* Radiotherapy

and chemotherapy may predispose a patient to candidiasis by altering their immune status. In addition, changes to the oral mucosal environment such as mucositis, xerostomia and poor oral hygiene may increase a patient's risk of developing oral candidiasis.

Pseudomembranous candidiasis is the most common form of oral candidiasis, occurring on the buccal mucosa, dorsal tongue and palate. It appears as soft, creamy white to yellow, velvety plaques that are easily wiped off, leaving an erythematous, eroded or ulcerated surface. The plaques can increase in number and size and may lead to systemic infection.

Infection with **herpes simplex virus** (HSV) can cause pain and blistering on or around the lips and within the mouth. Orofacial lesions are most commonly caused by HSV type 1, although not exclusively. It is estimated that around 80% of the population are asymptomatic carriers of the virus.[6] Following primary infection, which may be asymptomatic, the virus enters sensory nerve endings and travels up the axon and becomes latent in the trigeminal ganglion. The virus can lie dormant for many years until triggered by a stimulus such as sunlight, stress, common cold, febrile illnesses, menstruation or immunosuppression. The activation of the virus under conditions of immunosuppression can lead to severe oral and occasionally, disseminated infections. It is thought that approximately 50 to 90 percent of bone marrow transplantation (BMT) patients who are seropositive for HSV will develop HSV infections, usually within the first five weeks after transplantation.[7] A large proportion of patients with acute leukaemia or those receiving high dose chemotherapy will reactivate HSV during periods of immunosuppression.

An additional oral complication following cancer treatment is **salivary gland dysfunction**, which can be caused by both chemotherapy and radiotherapy. Cytotoxic drugs can alter both the flow and composition of the saliva, causing **xerostomia** (a sensation of dryness in the mouth). Radiotherapy treatment to the head and neck region can cause damage to the salivary glands. Such radiotherapy damage develops soon after the initiation of treatment, progresses during treatment (and for some time after treatment), and is essentially permanent. Both salivary gland damage and xerostomia impact on a patient's quality of life, causing oral discomfort, taste

disturbances, difficulty chewing and swallowing and speech problems. In addition, patients suffering from xerostomia/salivary gland damage are at greater risk of oral infections, including oral candidiasis. Long-term consequences of salivary gland damage include dental caries.

The careful oral management of children treated for cancer can improve quality of life during treatment. However, there is 'confusion and conflict' surrounding what constitutes appropriate mouth care.[3] At diagnosis of cancer it is important that a child receives a dental assessment of the oral cavity in order to identify existing dental disease. By treating dental disease early, the risk of oral infections during cancer treatment may be reduced.[8] Collard and Hunter question the ability of health professionals other than dentists to conduct oral assessment and diagnose a range of oral pathology.[8] It is probably optimal for the initial assessment of the oral cavity at diagnosis of cancer to be conducted by a dentist.[8, 9] It is acknowledged, however, that not all cancer centres are linked to dental services, and that due to the often rapid start of cancer treatment, an oral assessment by a member of the dental team prior to cancer treatment onset is not always feasible. Consideration needs to be given to the frequency of oral assessments throughout cancer treatment and communication between the cancer team and routine dental provider.

Despite the lack of research evidence with regard to what constitutes effective basic oral hygiene and what dental care is appropriate for children being treated for cancer, a recent survey[10] showed little variation in the advice given to parents/patients on basic oral hygiene. Oral hygiene advice should be given to all children and parents prior to starting cancer treatment and this should be provided both verbally and in writing. Currently, parent/patient information leaflets are distributed at 73% of the UKCCSG centres.[10] Such leaflets can empower patients/parents, and may lead to a better understanding of what to expect and why. The provision of information leaflets may also improve patient compliance.[11] This advice should be given either by a designated member of the dental team or an appropriately trained member of the cancer team (medical/nursing team). Given the large amount of information parents and patients are provided with on diagnosis of cancer, verbal advice may need to be repeated throughout the cancer treatment. It has been suggested that the oral management of children receiving treatment for cancer requires a team approach.[12]

Nurses may be best placed to provide the continued advice and currently are the key staff involved in providing advice on basic oral hygiene and preventative measures both at diagnosis and throughout treatment. If nurses are to play such a major role in the provision of oral care, there is a need for continuing education, ideally in collaboration with dentists.[13]

Given that the research evidence to support an optimal oral hygiene routine for paediatric oncology patients is limited, a 'common sense' approach may have to be taken with regard to certain aspects of care, drawing upon evidence from other populations. With regard to the use of pharmacological interventions for prevention and treatment of oral complication, a wide variety of agents are used, only some of which have been shown to be effective. A systematic appraisal of the research evidence for these agents, and the development of evidence based guidelines can help inform decision making in this area, but should not limit or replace clinical judgement. The potential benefits of such guidelines include improved patient care, consistency of care, the promotion of interventions of proved benefit and reduction in use of ineffective or potentially harmful practices.

This document presents a summary of the methods and recommendations outlined in the full Methodological Report. The Methodological Report is available as a pdf file from www.ukccsg.org.uk.

2 AIMS

To develop comprehensive, evidence-based guidelines on oral care for children and young people who have undergone or are receiving chemotherapy and/or radiotherapy for a malignancy (including head and neck cancers), or stem cell transplant (including bone marrow and peripheral blood stem cell transplants).

3 GUIDELINE DEVELOPMENT PANEL

The UKCCSG-PONF Mouth Care Group is multidisciplinary in nature and consists of nationally and internationally recognised experts in the fields of paediatric oncology, oral care and evidence-based practice. Members include:

Barry Pizer (Chair) (BP)	Paediatric Oncologist (Alder Hey Hospital, Liverpool)
Liz Auld (EA)	Paediatric Oncology Research Nurse (Manchester Children's Hospital)
Jan Clarkson (JEC)	Senior Lecturer in Dental Primary Care (Dental Health Services Research Unit, Dundee)
Jean Craig (JC)	Research Associate (Alder Hey Hospital, Liverpool)
Suzanne Coulson (SC)	Sister in Paediatric Oncology (St James' University Hospital, Leeds)
Tim Eden (TE)	Professor of Paediatric Oncology (Central Manchester and Manchester Children's University Hospitals)
Faith Gibson (FG)	Lecturer in Children's Nursing Research (Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, London)
Anne-Marie Glenny (AMG)	Lecturer in Evidence Based Dentistry (University of Manchester)
Tasneem Khalid (TK)	Principal Pharmacist Haematology/Oncology Services (Manchester Children's Hospital)
Helen Worthington (HW)	Professor of Evidence Based Care (University of Manchester)

It was felt of extreme importance to ensure the guidelines benefited from patient input and that the most appropriate way of doing this was to enlist a group of patients to whom the guidelines would be sent for review. It was agreed that it would not be desirable to just have a single patient representative on the Mouth Care Group.

No conflicts of interest were identified for any member of the Mouth Care Group.

4 GUIDELINES DEVELOPMENT PROCESS

The guidelines have been developed following the methods outlined by the Scottish Intercollegiate Network (SIGN).[14] However, for certain questions addressed in the guidelines, the SIGN methods were not deemed applicable so adapted, or alternative, methods were used. This section outlines the generic methods initially employed for each section. Details of any alternative methods used for specific questions are presented in summary within the relevant sections. A more detailed description of the methods is presented in the Methodological Report (www.ukccsg.org.uk).

4.1 Identification of questions

A consensus approach was used to establish the scope and basic structure of the guidelines. Three key areas to be addressed were identified:

- Dental care and basic oral hygiene
- Methods of oral assessment
- Drugs and therapies used in treatment/prevention of the oral effects of cancer treatment

4.2 Searches

Scoping searches were initially undertaken to gain an overview of the volume of literature available, identify further questions that may need to be addressed and

establish the research methodologies used within each area. They did not aim to identify all relevant information but provide a basis upon which to make certain organisational and methodological decisions with regard to the guideline development process.

The searches were refined to reflect the final list of questions identified. The following electronic databases were searched for each key area:

The Cochrane Library (Issue 2, 2004)
MEDLINE (OVID BIOMED 1966 to March 2004)
EMBASE (OVID BIOMED 1980 to March 2004)
CINAHL (OVID BIOMED 1982 to March 2004)

English language articles only were included due to resource implications for reliable translation. Details of search strategies used are presented in the Methodological Report (www.ukccsg.org.uk).

4.3 Assessment of relevance

The screening process of all titles and abstracts was carried out independently and in duplicate. The full article of those records thought relevant, or potentially relevant to the subject area were retrieved.

4.4 Assessment of validity

The full paper copies of each article identified as being relevant (or potentially relevant) for inclusion in the guidelines were assessed independently and in duplicate to identify the study design. The appropriate SIGN checklist was attached to each article and the articles distributed for full validity assessment. As for the assessment of relevance, the validity assessment of each article was undertaken independently

and in duplicate. Disagreements in the validity assessment process were resolved through discussion between the reviewers.

4.5 Data extraction

Studies to be included in the guidelines were data extracted independently and in duplicate. Details to be extracted included characteristics of the study population, characteristics of the study setting, and details of any interventions, exposures or prognostic factors evaluated and the outcomes assessed.

4.6 Development of evidence tables

The results of the validity assessment and data extraction process were used to develop evidence tables. Within the evidence tables, each study was coded as illustrated in Table 1. Subsequently, Considered Judgement forms were developed. These forms considered the volume of evidence, the applicability of the identified evidence, its generalisability, consistency and clinical impact. The forms included provisional Evidence Statements.

4.7 Grading of recommendations

The recommendations produced by the Mouth Care Group were graded according to the guidelines produced by SIGN[14] (see Table 2). Much of the identified research was undertaken in adult populations, and not the target population. For this reason, the extrapolation of evidence was required and recommendations were often 'down graded'. For example, evidence from high quality RCTs of recruiting adults was graded 'B' rather than 'A', as illustrated in Table 2.

For certain guidelines it was felt appropriate to grade them as 'Best Practice'; these were assigned the symbol '√'. Recommendations on general care and preventative

strategies were colour coded green, with the recommendations regarding the treatment of specific oral complications colour coded blue.

Once the recommendations were provisionally approved by the Mouth Care Group, two versions of the guideline were initially produced:

- The Methodological Report, detailing all the methods used throughout the guideline development process, to be used as a reference document.
- The Guideline Report, an abbreviated document focusing on the recommendations, to be available on the ward.

4.8 Peer- review

A list of named referees from the guideline's major stakeholders was drawn up. Both the Methodological Report and the Guideline Report were distributed electronically along with a cover letter and feedback form to all named referees. Comments were also requested from families whose children were undergoing cancer treatment, four of whom had received a BMT. The feedback form was structured so as to gather information on specific issues, and allow for the respondent to provide additional comments as necessary. A period of eight weeks was provided for feedback.

Table 1. Grading systems used for levels of evidence [14]

1++	High quality meta-analyses/systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well conducted meta-analyses/systematic review of RCTs, or RCTs with low risk of bias
1-	Meta-analyses/ systematic reviews of RCTs, or RCTs with high risk of bias
2++	High quality systematic reviews of case-control or cohort studies; high quality case-control or cohort studies with a very low risk of confounding, bias or chance and high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case series, cross-sectional surveys
4	Expert opinion/non-systematic review article

Table 2. Grading systems used for recommendations (adapted from SIGN guidelines[14])

Grade	
A	At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
√	Best Practice (based on clinical expertise of the guideline group)

5 DENTAL CARE AND BASIC ORAL HYGIENE

Research Questions:

Q1. What basic oral hygiene should children who have been diagnosed with cancer (and/or their parents) be advised to undertake during and post cancer treatment?

Q2. At the time of cancer diagnosis, during treatment and post treatment, which member(s) of the team caring for the patient should be responsible for giving:

- advice on dental attendance
- advice on oral care
- dental treatment (e.g. abscess, dental caries)
- treatment of oral complications associated with cancer treatment (candidiasis, mucositis and xerostomia).

5.1 Inclusion criteria

Q1. Any study reporting on the effectiveness of basic oral hygiene in children or adults undergoing treatment for cancer was considered. Due to the lack of evidence in this area, there was no restriction on study design.

Q2. Any study reporting on the role of health professionals involved in the care of children or adults undergoing treatment for cancer with regard to dental and/or oral advice and/or treatment. There was no restriction on study design.

5.2 Amendments to guideline development process

Following the literature search, the paucity of evidence addressing either of the above questions led to the decision to obtain the views from health professionals working in the area. It was decided that a Delphi style/opinion gathering approach would be undertaken. A list of statements regarding basic oral hygiene and dental care was drawn up by members of the Mouth Care Group, reflecting the opinions of the group

members involved, or the results obtained through a survey of UKCCSG centres with regard to current oral care practice.[10] The list was distributed electronically to members of the UKCCSG and PONF, paediatric dentists and dental hygienists.

5.3 Opinion based statements

A total of 73 responses was obtained. The median value achieved for 29/32 (90.6%) of the statements was four or five, indicating that the majority of the respondents agreed with the statements to some extent. The results of the opinion gathering are presented in the Methodological Report (www.ukccsg.org.uk). These responses, alongside comments received were used to develop the recommendations.

RECOMMENDATIONS FOR ORAL CARE AT TIME OF CANCER DIAGNOSIS	
For paediatric dental units working with a cancer centre there should be a mechanism of notification for new patients.	√
All children should undergo a dental assessment at the time of cancer diagnosis and, if possible, before cancer treatment commences.	√
The possible long-term dental/orofacial effects of childhood cancer and treatment should be discussed.	√
The people most suitable to undertake the initial dental assessment are a paediatric dentist or a dental hygienist.	√
If any invasive dental treatment is required, this should be undertaken by either a consultant or specialist paediatric dentist.	√
All children diagnosed with cancer should be registered with a General Dental Practitioner or community dental service. Registration should be maintained during and following the cancer treatment.	√
All children diagnosed with cancer should have access to an NHS General Dental Practitioner.	√
The routine dental care provider in the general or community dental service should be notified of the cancer diagnosis and arrangements for care during cancer treatment as directed by the hospital dental team.	√
If there is not a paediatric dental unit liaising with a cancer centre there should be clear communication between the cancer centre and routine dental provider.	√
Appropriate training in oral assessment should be available within the cancer centre, ideally in collaboration with a member of the dental team.	√

RECOMMENDATIONS FOR ORAL HYGIENE AT DIAGNOSIS AND DURING CANCER TREATMENT	
Oral hygiene advice should be given to children and parents prior to commencing cancer treatment and this should be provided both verbally and in writing.	√
Oral hygiene advice should be given by a designated member of the dental team or, in the absence of a dentally trained individual, a member of the medical or nursing team who has received appropriate training.	√
Advice should be to brush at least twice a day, with a fluoride toothpaste (containing 1,000 ppm fluoride +/- 10%).[a]	√
The toothbrush should be for the sole use of the child and changed on a 3 monthly basis, or when bristles splay if earlier. A child's toothbrush should be changed following an oral infective episode.	√
If the child has a sore mouth a soft brush with a small head should be used.	√
For children up to the age of 6 years, parents/carers should be instructed on how to brush their child's teeth.	√
For babies without teeth, parents/carers should be instructed on how to clean the mouth with oral sponges. The sponge should be moistened with water.	√
For children where it is not possible to brush teeth, parents/carers should be instructed on how to clean the mouth with oral sponges, as a temporary measure. The sponge should be moistened with water or an antimicrobial agent such as diluted chlorhexidine.	√
Additional aids, such as flossing and fluoride supplements should only be prescribed according to risk assessment by a member of the dental team.	√
The need to restrict sugary food and drink to meal times only should be emphasised.[b]	√

[a] Data regarding fluoride concentration comes from: Scottish Intercollegiate Guidelines Network (SIGN). Prevention and management of dental decay in the pre-school child. Edinburgh: SIGN Report 83; November 2005
NB. There is no evidence to suggest when teeth should be brushed in relation to meal times

[b] Following peer review it was felt necessary to include an additional statement with regard to diet. The SIGN publication Number 47 has previously appraised the research evidence with regard to dietary advice for children at high caries risk and the recommendations to reduce the frequency of sugar intake has been incorporated into this document.

RECOMMENDATIONS FOR DENTAL/ORAL CARE DURING CANCER TREATMENT	
A dental assessment should be undertaken every three to four months by a member of the dental team.	√
The dental team should be consulted on any dental, or difficult to manage oral problems arising during cancer treatment and the cancer team should be informed of the type and extent of dental treatment required.	√
If there is not a dedicated dental team there needs to be clear communication between the cancer team and a routine dental provider.	√

RECOMMENDATIONS FOR DENTAL/ORAL CARE AFTER CANCER TREATMENT	
Parents and children should be informed of the possible long-term dental/orofacial effects of childhood cancer and treatment.	√
Children's oral/dental health should continue to be monitored during the period of growth and development.	√
Children should be referred back to their routine dental provider who should be advised of the specific oral/dental care recommended by the consultant/specialist paediatric dental team and advised of future care arrangements and systems for referral as necessary.	√

6 ORAL ASSESSMENT

Research Questions:

What are the most appropriate methods of oral assessment?
What oral assessment tools are available and how reliable and valid are these tools?
What areas of the mouth should be included in the assessment?
What tools should be used to examine the mouth?
Who should undertake oral assessment?
How often should a child's mouth be assessed?
How should assessment be taught for reliability?
How should assessment influence decision-making and management?
How can assessment be used to monitor response to therapy?
How acceptable to children/teenagers is the assessment process?

6.1 Inclusion criteria

In order to be included a study had to meet the following criteria:

- describe any aspect of oral assessment for patients (adults or children) treated for cancer with chemotherapy and/or radiotherapy

Given the nature of the topic and the types of study designs identified through the scoping searches, there was no restriction with regard to study design.

In addition, randomised controlled trials and systematic reviews identified for the drugs and therapies section of the full guidelines were also screened to identify any assessment tools not identified through the electronic searches.

6.2 Amendments to guideline development process - data extraction/validity assessment

Due to the nature of the research identified, it was felt inappropriate to assess the identified articles using SIGN checklists. Instead, each study was screened and all assessment tools described within each study were recorded.

The oral assessment tools were evaluated independently and in duplicate by two reviewers. The included tools were examined for structure and any studies providing some form of validity or reliability testing were subsequently assessed using an adaptation of the SIGN 'Diagnostic studies' checklist (see Methodological Report www.ukccsg.or.uk).

6.3 Results

No studies were identified with regard to the most appropriate timing or frequency of oral assessment, who should conduct the oral assessment and what instruments should be used during the assessment. Similarly, the acceptability of the assessment process to the children/teenagers was not addressed in the literature.

Twenty-seven individual oral assessment tools were identified. Table 3 provides an overview of the component recorded in each tool. The signs recorded for each component, and the grading system used varied across all assessment tools. Twelve tools required the calculation of a compound score (based upon the scores of individual components/signs and symptoms). Whilst many of the calculations were straightforward, two tools required complex calculations to be carried out, precluding the tool from use in everyday clinical practice[15, 16]. The methods of evaluation included visual observation, auditory observation, palpation, use of spatula, use of ruler (for measuring the size of lesions), stimulated/unstimulated saliva collection and self-assessment by the patient. Several studies reported the importance of good lighting when conducting the oral assessment.

Seven studies were identified as providing some assessment of validity and/or reliability testing of specific oral assessment tools. An evaluation of these studies, the focus of this section, is presented in Table 4.

With regard to the subjective assessment of 'usefulness' of each tool, only one tool was identified by the Guideline Development Group as being appropriate for use in children, both for clinical practice and research purposes.[17] The Oral Assessment Guide (OAG) produced by Eilers et al[18] covers eight categories (voice, ability to swallow, lips, tongue, saliva, mucous membrane, gingival and teeth/dentures), and was developed through consultation with experts and a review of the literature. It was considered to be user friendly and appropriate for everyday clinical practice with both adults and children, as well as a useful research tool. It has been shown to have good nurse/nurse,[18] nurse/dental hygienist[19] and nurse/dentist[20] inter-rater reliability.

Table 3. Components covered

	Lips	Tongue	Mucous membrane	Gingiva	Teeth	Hard/soft palate	Saliva	Voice	Swallow/dysphagia	Taste	Diet	Self-care	Pain	Dry mouth	Comments
Beck[21]	Y	Y	Y	Y	Y		Y	Y	Y						Each component graded 1-4 Compound score (15-64) Includes patient reported outcomes
Bruya[22]	Y	Y	Y	Y	Y		Y	Y		Y					Each component (and sub-component) graded 1-3 No compound score
Byfield[23]			Y						Y		Y				Mucositis scale Components used to grade mucositis 1-4 Developed for research
Chapko[24]													Y		Part of behavioural measure of mouth pain, nausea and well-being
Cox[25] (RTOG/EORTC)			Y												Part of RTOG/EORTC late radiation scoring scheme. Each organ tissue included scored from 0-4 Used for clinical trials
Dibble[26] (MacDibbs)							Y	Y	Y	Y	Y		Y	Y	Each component graded 0-3 Compound score (0-21) Includes patient reported outcomes
Donnelly[27]			Y						Y				Y		Mucositis scale Compound scale (0-15)

	Lips	Tongue	Mucous membrane	Gingiva	Teeth	Hard/soft palate	Saliva	Voice	Swallow/dysphagia	Taste	Diet	Self-care	Pain	Dry mouth	Comments
Dudjak[28]	Y		Y	Y			Y		Y		Y	Y			Adaptation of earlier tools. Each component graded 1-4 Compound score (7-28) Reports difficulties in monitoring change
Eilers[18] (OAG)	Y	Y	Y	Y	Y		Y	Y	Y						Each component graded 1-3 Compound score (8-24) Developed for research use and clinical practice
Hickey[29]			Y						Y		Y		Y		Signs used to grade mucositis (Grade 1-3)
Kolbinson (OMRS)	Y	Y	Y	Y									Y	Y	Developed as research tool
Lievens[30]			Y						Y						Part of broader toxicity scale Each component graded No compound score
Maciejewski[31] (Dische system)			Y						Y						Each sign (within component) graded 0-3 or 0-4 Compound score (0-24)
CTCAE v3[32]			Y	Y	Y		Y	Y	Y	Y	Y		Y	Y	Part of broader toxicity scale Each component graded 1-5 No compound score Developed for research use
Ohrn[33]*	Y			Y			Y	Y	Y	Y		Y	Y	Y	Patient reported outcomes (VAS) Incorporates OMI No compound score
Passos[34]	Y	Y	Y		Y		Y								Each component graded from 1-3 (normal to severe)

	Lips	Tongue	Mucous membrane	Gingiva	Teeth	Hard/soft palate	Saliva	Voice	Swallow/dysphagia	Taste	Diet	Self-care	Pain	Dry mouth	Comments
Schubert[35] (OMI)	Y	Y	Y	Y											Structured according to signs rather than components Includes patients based assessment Compound score (max 34)
Seto[36]			Y		Y								Y		Oral debris categorised as 'Excellent', 'Good', 'Fair' or 'Poor' Signs used to grade mucositis (Grade I-IV)
Sonis[15]	Y	Y	Y						Y		Y		Y		Each component graded Compound score – weighted mean mucositis score calculated Scoring complex for clinical practice
Spijkervet[16]			Y												Components graded 0-4 Mucositis score calculated according to signs/size of ulcerations Developed as a research tool Use of ruler for measuring size of ulcers reduces tolerability and use in clinical practice
Tardieu[37]	Y	Y	Y	Y			Y	Y	Y				Y		Each component graded 0-3 Compound score (daily index of mucositis) (0-48) – used to grade mouth status
Van der Schueren[38]			Y												Signs used to grade mucositis (Graded Level I-IV)
Van Drimmelen[39]	Y	Y	Y	Y	Y	Y									Each component graded from 1-3 (normal to worst condition)

	Lips	Tongue	Mucous membrane	Gingiva	Teeth	Hard/soft palate	Saliva	Voice	Swallow/dysphagia	Taste	Diet	Self-care	Pain	Dry mouth	Comments
WCCNR[40, 41]			Y								Y		Y	Y	Each component graded 0-3 No compound score Staging system from 'Healthy mouth' to 'Stage 3' Developed for research use and clinical practice for evaluating management of stomatitis
Walsh[42]	Y	Y	Y	Y	Y	Y	Y	Y	Y				Y		Each component graded 0-2 Compound score (0-21) – used to grade mouth status Used to inform oral hygiene regime
WHO[43-45]			Y								Y		Y		Components used to grade mucositis (Grade I-IV)

Table 4. Assessment of studies reporting validity/reliability testing of oral assessment tools

	Dibble 1996	Donnelly 1992	Eilers 1988	Sonis 1999	Spijervet 1988	Tardieu 1996	WCCNR 1991
PARTICIPANTS							
Was selection bias avoided?	**N**	**Y**	**Y**	**Y**	**U**	**Y**	**U**
Did the study include an appropriate spectrum of participants?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
RELIABILITY							
Inter-rater measured?	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**N**
Was the duration between assessments suitable so as not to have allowed a true change in oral health status?	U	-	Y	Y	Y	Y	U
Intra-rater measured?	**N**	**N**	**N**	**N**	**N**	**Y**	**N**
Was the duration between assessments suitable so as not to have allowed a true change in oral health status?	-	-	-	-	-	U	-
VALIDITY							
Was face validity reported?	**N**	**N**	**N**	**Y**	**Y**	**N**	**N**
Do you feel the tool appears to measure the condition of the mouth?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**

	Dibble 1996	Donnelly 1992	Eilers 1988	Sonis 1999	Spijervet 1988	Tardieu 1996	WCCNR 1991
Was content validity reported?	**Y**	**N**	**Y**	**Y**	**N**	**N**	**Y**
Were appropriate experts consulted in the development of the tool and/or a rigorous evaluation of the literature?	Y	-	Y	Y	-	-	Y
Does the tool address all the attributes of the concept under investigation?	Y	-	Y	Y	-	-	Y
Does the tool include any irrelevant items?	N	-	N	N	-	-	N
Was criterion validity reported?	**N**	**N**	**N**	**N**	**Y**	**N**	**Y**
Was the test compared with a valid reference standard?	-	-	-	-	Y	-	Y
Were the test and reference standards measured independently (blind) of each other?	-	-	-	-	U	-	U
Was the choice of patients for assessment by the reference standard independent of the test's results?	-	-	-	-	Y	-	U
Was the reference standard measured before any interventions were started with knowledge of test results?	-	-	-	-	U	-	Y
Was construct validity reported?	**N**	**N**	**N**	**N**	**Y**	**N**	**N**
Do you feel there is good justification for the theoretical construct used?	-	-	-	U	Y	-	
OVERALL OPINION							
Would you use this tool in everyday clinical practice with adults?	**N**	**N**	**Y**	**N**	**N**	**Y**	**N**

	Dibble 1996	Donnelly 1992	Eilers 1988	Sonis 1999	Spijervet 1988	Tardieu 1996	WCCNR 1991
Would you use this tool in everyday clinical practice with children?	**N**	**N**	**Y**	**N**	**N**	**N**	**N**
Would you use this tool in research with adults?	**Y**	**N**	**Y**	**N**	**N**	**N**	**N**
Would you use this tool in research with children?	**N**	**N**	**Y**	**N**	**N**	**N**	**N**

; Y – Yes N – No; U - Unclear

RECOMMENDATIONS FOR ORAL ASSESSMENT DURING CANCER TREATMENT	
There is a variety of oral assessment tools from which to choose. Using those which have been shown to be valid and reliable would be most valuable.	√
The Eilers' Oral Assessment Guide[18] offers a valid, reliable and clinically useful tool for assessing oral status.	D
The adaptation of the Eilers' Oral Assessment Guide (APPENDIX 1) is recommended for use in children and young people.	√
Those responsible for assessment of the oral cavity should be appropriately trained in the use of the selected assessment tool.	√
Nursing staff are best placed for the regular assessment of the child's oral status.	D
The frequency with which a child's mouth is assessed should be determined on an individual basis. Frequency should increase at the onset of oral complications.	D
Oral assessment should be used to check good basic oral hygiene is being maintained.	√
For a child with oral complications (e.g. as indicated by an OAG score of greater than 8) an appropriate pain assessment tool should be used to ensure adequate pain control and therapeutic interventions are available.	√
The timing of assessment should be consistent in relation to the child's oral hygiene routine.	D

7 DRUGS AND THERAPIES

Research Questions:

Which interventions are effective or ineffective in preventing or treating the following diseases, of the tongue or oronaso-pharynx, in children who are having, or who have had, treatment for cancer or related conditions:

Mucositis
Candidiasis (and other fungal infections)
Xerostomia
Salivary gland damage
Herpes virus infection

7.1 Inclusion criteria

Given that this section of the guideline deals with the effectiveness of interventions, it was felt appropriate to focus on evidence from systematic reviews (SR) or randomised controlled trials (RCT) only. The included SRs and RCTs could assess the effectiveness of any intervention to either prevent or treat a disease of the tongue or oronaso-pharynx, arising as a result of cancer treatment.

Children and young people who have undergone or are receiving chemotherapy and/or radiotherapy for a malignancy (including head and neck cancers), or bone marrow transplant were the focus of the guidelines. However, due to the paucity of trials in this area recruiting children with cancer, trials including adults with cancer were also included.

7.2 Evidence statements and recommendations

A total of 973 articles were identified through the electronic searches. Following the screening of the titles and abstracts, 111 full articles were retrieved as they were considered to be potentially relevant. These articles were distributed along with the

appropriate SIGN checklist, for validity assessment and data extraction. Evidence tables were produced and recommendations drawn up as outlined in 4.6 and 4.7.

Certain decisions were made with regard to the recommendation of interventions:

1. The guidelines would not support routine use of an intervention for use in children for which there was evidence of clinically important harm from either trials of adults or children

2. Where there is weak/insufficient/no evidence from trials in adults or children the guidelines would recommend use of an intervention only within the constraints of an RCT

3. Where there is strong evidence in adults or children, the guidelines would recommend the use of an intervention in children unless there is a contra-indication to therapy in this age group

The following definitions were used when determining the evidence in support of a given intervention:
No evidence: *no trials; or trials showing no statistically significant difference*[c]
Weak evidence: *limited number of trials and/or trials at risk of bias*
Strong evidence: *several high quality RCTs showing the same direction of effect*

[c] Several interventions have been assessed predominantly in trials recruiting adults only. When trials have shown no statistically significant difference between interventions for adults, this has been classified as 'no evidence' with regard to effectiveness for children.

7.2.1 Mucositis

Prevention

There is a large volume of evidence addressing both the prevention and treatment of oral mucositis in patients receiving treatment for cancer. Given the impact oral mucositis can have on a child's quality of life and their tolerance of the chemotherapy regimen, prevention of mucositis is of great importance. Parents and patients should be informed of the importance of keeping the mouth clean through basic oral hygiene. Two systematic reviews have identified a wide variety of prophylactic interventions used for the prevention of mucositis.[46, 47] The review by Clarkson et al[46] included any patients receiving chemotherapy and/or radiotherapy, whilst Sutherland et al[47] included only those patients undergoing radiotherapy to the head and neck region. The evidence supporting these prophylactic interventions varies and is drawn mainly from trials of adults. To date, no interventions have demonstrated a clear benefit for the prevention of mucositis in children receiving treatment for cancer. However, several interventions have been shown to be potentially beneficial for the prevention of mucositis in adult populations. These include: amifositine (Ehthyol®); allopurinol mouthwash; ice-chips; granulocyte-macrophage colony stimulating factor (GM-CSF) or granulocyte colony stimulating factor (G-CSF) (Neupogen®, Granocyte®, Neulasta®); benzydamine hydrochloride (Difflam®); polymyxin E, tobramycin and amphotericin (PTA) paste/lozenges; povidone iodine (Betadine ®); pilocarpine (Salagen®); hydrolytic enzymes.

The role of these interventions for the prevention of oral mucositis in children has not been investigated in RCTs.

Numerous other interventions have been investigated for the prevention of mucositis for patients with cancer.[46, 47, 48, 49] There is currently no evidence to support the use of the following interventions for either adults or children: lozenges containing Bacitracin, clotrimazole, and gentamicin (BcoG); propathelene; chlorhexidine; fluconazole; amphotericin B; sucralfate; prednisone; glutamine; pentoxifyline; Na-sucrose gel; traumeel; chamomile

There is weak evidence that i.v. folinic acid (an antimetabolite) may actually promote mucositis in adults receiving chemotherapy for cancer, and therefore cannot be recommended as an intervention for preventing mucositis in children receiving treatment for cancer.[46] However, i.v/oral folinic acid may be prescribed for the prevention of systemic toxicity following methotrexate. No trials were found assessing the effectiveness of folinic acid mouthwash for the prevention of mucositis. Prostaglandin E may promote mucositis, and can therefore not be recommended as a prophylactic agent.[46]

Treatment/pain control

With regard to the treatment of oral mucositis, several interventions were identified as being potentially beneficial for the treatment of mucositis in adult populations.[50] These include: allopurinol mouthwash; polyvalent intramuscular immunoglobulin; vitamin E oil.

None of these interventions have been evaluated in RCTs of children with mucositis following treatment for cancer. Human placental extract was also found to be potentially beneficial in a trial of adults with head and neck cancer. However, it may not be feasible, for ethical reasons, to consider this as a potentially useful treatment for oral mucositis.

Oral mucositis can cause severe pain. Given the lack of clear evidence for the treatment or prevention of mucositis, pain control is of utmost importance. An appropriate pain assessment tool should be used. Opiates are often required for the relief of mucositis pain. There is no evidence that patient controlled analgesia (PCA) is better than continuous infusion for controlling oral pain in children treated for cancer, although less opiate may be used per hour and the duration of pain control may be shorter. Further trials of PCA versus continuous infusion for controlling oral pain in children are required.

RECOMMENDATIONS FOR THE PREVENTION OF ORAL MUCOSITIS	
Parents and patients should be informed of the importance of keeping the mouth clean and encouraged to practice good, basic oral hygiene.	√
The following have all been shown to be potentially beneficial for the prevention of mucositis in adult populations. Their use in children for the prevention of radiotherapy and/or chemotherapy induced mucositis can only be considered within the constraints of an RCT; Amifostine[46] Allopurinol mouthwash (for 5-FU therapy)[46, 51] Ice-chips[46] GM-CSF/G-CSF[46, 52] Benzydamine[46, 51] Antibiotic pastilles/pastes (containing polymyxin E, tobramycin and amphotericin (PTA))[46, 51] Povidone-iodine[46] Pilocarpine (not currently available in a form suitable for children) Hydrolytic enzymes.[46]	B
RCTs of allopurinol mouthwash are not recommended for children receiving cancer treatment other than 5-FU.	D
Prostaglandin E is not recommended for the prevention of chemotherapy or radiotherapy induced mucositis as there is evidence that it may promote mucositis.[46, 51]	B
i.v. folinic acid is not recommended for the routine prevention of chemotherapy or radiotherapy induced mucositis as there is evidence that it may promote mucositis.[46]	B
However, i.v./oral folinic acid (rescue) should be used for the prevention of methotrexate toxicity according to the treatment protocol.	√

There is no evidence to support or refute the use of folinic acid mouthwash for the prevention of mucositis	
There is no evidence[d] to support the use of the following agents for the prevention of chemotherapy or radiotherapy induced mucositis in children; Lozenges containing Bacitracin, clotrimazole, and gentamicin (BCoG)[53] Propathelene[46] Chlorhexidine[46] Fluconazole[49] Amphotericin B[49] Sucralfate[46, 54] Prednisone[46] Glutamine[46] Pentoxifyline[46] Na-sucrose gel[48] Traumeel[46] Chamomile[46] Their use in children for the prevention of radiotherapy and/or chemotherapy induced mucositis can only be considered within the constraints of an RCT	B

[d] Trials of these interventions have predominantly been conducted in adult populations. No statistically significant benefit has been shown to date.

RECOMMENDATIONS FOR THE TREATMENT OF ORAL MUCOSITIS	
Appropriate pain control is recommended together with the continuation of good oral hygiene, as tolerated.	√
Pain associated with mucositis can be severe. Opiates are required for the control of such pain.	√
RCTs of patient controlled analgesia versus continuous infusion for controlling oral pain in children are required.[50]	B
The following have been shown to be potentially beneficial for the treatment of mucositis in adult populations. Their use in children receiving radiotherapy and/or chemotherapy can only be considered within the constraints of an RCT; Vitamin E[50] Immunoglobulin[50] Allopurinol mouthwash (for 5-FU therapy).[50]	B
RCTs of allopurinol mouthwash are not recommended for children receiving cancer treatment other than 5-FU.	D
There is no evidence[e] to support the use of the following for the treatment of chemotherapy or radiotherapy induced mucositis in children; Benzydamine[50] Chlorhexidine[50] Sucralfate[50] Tetrachlorodecaoxide[50] 'Magic' (lidocaine solution, diphenhydramine hydrochloride and aluminium hydroxide suspension).[50] Their use in children for the prevention of radiotherapy and/or chemotherapy induced mucositis can only be considered within the constraints of an RCT.	B
The use of folinic acid for the treatment of mucositis following treatment with methotrexate has not been assessed in RCTs.	

[e] Trials of these interventions have predominantly been conducted in adult populations. No statistically significant benefit has been shown to date.

7.2.2 Candidiasis

There is a large volume of evidence addressing the prevention and treatment of oral candidiasis in patients receiving treatment for cancer. Two high quality systematic reviews were identified.[55, 56] A third systematic review[57] of weaker methodological quality and a single RCT[58] not included in any of the reviews were also identified. Due to the volume of literature presented in the higher quality systematic reviews, this section focuses on the higher quality systematic reviews.

Some groups of patients are more likely to get candidiasis than others and a decision needs to be made by the clinician on whether to prevent or treat candidiasis according to patient risk. If the incidence of oral candidiasis is likely to be high for a particular patient subgroup (for example, those receiving certain cancer treatments), then evidence suggests that prevention is the best strategy, with a drug absorbed, or partially absorbed, from the GI tract being administered at the start of cancer treatment.[56] Further trials are required to identify risk factors.

Prevention

Antifungal agents are often used during the treatment of cancer to prevent superficial infections such as oral candidiasis.[56] There is strong evidence from systematic reviews of RCTs of both adults and children that certain categories of antifungals are effective for the prevention of oral candidiasis. These include drugs fully absorbed by gastrointestinal (GI) tract (fluconazole, ketoconalzole and itraconazole) and those partially absorbed by the GI tract (miconazole and clotrimazole).

There is no overall evidence to support the use of drugs not absorbed from the GI tract for the prevention of oral candidiasis in either adults or children.[56] Drugs assessed were nystatin, chlorhexidine, nystatin plus chlorhexidine, nystatin plus amphoterecin B, thymostimulin, natamycin, norfloxacin plus amphoterecin B.

There is weak evidence that oral amphotericin B may be effective at preventing oral candidiasis, however, the evidence draws predominantly on its evaluation in adults with leukaemia.[56]

Treatment

With regard to the treatment of oral candidiasis, the evidence on the most effective interventions is unclear due to the limited number of trials in this area.[55]

RECOMMENDATIONS FOR THE PREVENTION OF ORAL CANDIDIASIS	
Preventative therapy is not recommended for most patients (for example, those receiving treatment for solid tumours). A decision needs to be made by the clinician on whether to prevent candidiasis according to patient risks. Further studies are recommended to identify risk factors.	D
When choosing an antifungal agent for the prevention of candidiasis, one that is absorbed from the GI tract is recommended (for example fluconazole, itraconazole or ketoconazole).[56]	A
Drug doses should be prescribed according to the British National Formulary for Children.	√
Oral amphotericin B is recommended for the prevention of candidiasis only within the constraints of an RCT.[56]	B
There is no evidence to support the use of nystatin or chlorhexidine for the prevention of candidiasis in children treated for cancer.[56]	A

RECOMMENDATIONS FOR THE TREATMENT OF ORAL CANDIDIASIS	
There is no research evidence to demonstrate the effect of either topical or systemic antifungal agents for the treatment of oral candidiasis. Based on evidence for prevention of oral candidiasis, absorbed or partially absorbed antifungal agents could be used for the treatment of visible oral candidiasis.	D
Further controlled trials assessing the effectiveness of current antifungal agents and new interventions for treating oral candidiasis are required.	D

7.2.3 Xerostomia

A review of the research literature identified two systematic reviews[59, 60] and a set of evidence based guidelines[61] addressing the treatment of xerostomia. One systematic review included patients with xerostomia/salivary gland damage from a wide range of aetiologies.[59] The age of the patients included in the trials is unclear. The second review recruited patients with post-radiation xerostomia, but again, the ages of those included in the trials is unclear.[60] The guidelines focused on adult patients with head and neck cancers and symptomatic post-radiation therapy.[61]

A further four RCTs not included in the guidelines and systematic reviews were identified. All four RCTs assessed the prevention of xerostomia as opposed to treatment, and recruited adult patients with cancers of head, neck or 'mantle'.[62-65]

Prevention

For the prevention of xerostomia and salivary gland damage, three interventions (amifostine, biperidin and pilocarpine) have been evaluated in adults with cancer of the head and neck.[62-65]

The evidence for amifostine, biperidin and pilocarpine for the prevention of xerostomia/salivary gland damage is inconclusive.[62-66]

Treatment

With regard to the treatment of xerostomia/salivary gland damage there is strong evidence that pilocarpine (5mg three times daily) can reduce symptomatic xerostomia in adult patients with post-radiation xerostomia.[60, 61] However, pilocarpine is not currently available in a form suitable for children.

The results of the trials are fully applicable to adult oncology units within the UK, however, the applicability to paediatric oncology units needs to be considered cautiously.

RECOMMENDATIONS FOR THE PREVENTION OF XEROSTOMIA	
There is insufficient evidence to support the use of amifostine for the prevention of salivary gland damage, or pilocarpine (not currently available in a form suitable for children) or biperiden for the prevention of xerostomia, in children treated for cancer. [62-66] Future use of any such pharmacological agents for the prevention of salivary gland damage and xerostomia should be within the constraints of an RCT.	B

RECOMMENDATIONS FOR THE TREATMENT OF XEROSTOMIA	
Consideration should be given to the use of saliva stimulants, artificial saliva, chewing sugar free gum or frequent sips of water for the relief of dry mouth.	D

7.2.4 Herpes Simplex Virus

There are currently no systematic reviews addressing the prevention or treatment of herpes simplex virus in patients being treated for cancer. However, 16 RCTs have been identified[67-86] Twelve of these trials included patients with cancer, the remaining four recruited immunocompromised patients due to a variety of associated diseases.[67, 68, 79, 85, 86].

Prevention

For the prevention of HSV in patients with cancer, aciclovir has been evaluated in 11 RCTs. The trials provide strong evidence that aciclovir given orally, intravenously or as a combination of intravenous followed by oral administration is effective at reducing the frequency of herpes simplex infections in both adults and children with haematological malignancies.

Treatment

There is also strong evidence that aciclovir administered orally, intravenously or topically reduces the duration of viral shedding, new lesion formation, increases partial and total healing, and reduces time to eradication of pain.[79, 83, 85]

Given the effectiveness of the treatment, it may be advisable to only prescribe aciclovir as a prophylactic agent for those patients at high risk of HSV, for example those undergoing high dose chemotherapy and stem cell transplant.

There is weak evidence that from a single trial that thymostimulin reduces the recurrence of herpes simplex labialis infections in immunodeficient adults and children.[67] Similarly, there is evidence from a single trial that vidarabine accelerates loss of pain from HSV infection in immunocompromised adults and children.[86] However, the evidence is insufficient to support the use of thymostimulin or vidarabine for the treatment of HSV in children treated for cancer.

RECOMMENDATIONS FOR THE PREVENTION OF HERPES SIMPLEX VIRUS	
Aciclovir is only recommended as a preventative strategy for herpes simplex in patients undergoing high dose chemotherapy with stem cell transplantation.[69-74, 81, 84, 87, 88]	B
Aciclovir is not recommended for routine use due to rarity of problem and cost.	D

RECOMMENDATIONS FOR THE TREATMENT OF HERPES SIMPLEX VIRUS	
Aciclovir is effective for the treatment of herpes simplex virus in patients receiving chemotherapy and/or radiotherapy.[79, 83, 85]	A
Mild and non-progressing lesions on the lip should be treated with topical aciclovir.	D
Progressing and severe lesions on the lip should be treated with oral aciclovir.	D
Intra-oral lesions should be treated with oral aciclovir.	D
For severe cases, or where oral administration is not tolerated, i.v. aciclovir should be used.	D
Drug doses should be prescribed according to BNF for Children.	√
Thymostimulin and vidarabine are not recommended for routine treatment of herpes simplex unless within the constraints of an RCT[67, 86]	B

8 IMPLEMENTATION, AUDIT AND RESEARCH

In order to assist with the implementation of the guidelines, Trusts may need to review current practice against the guideline recommendations and assess any differences. The recommendations may need to be interpreted at a local level to allow for variations in organisation of care. The production of supporting documentation (e.g. parent/patient information leaflets) is encouraged. Some care factors that may help implementation are:

- Establishment of an implementation group to develop local translation of the guidelines and a plan for active implementation

- Stage the implementation and invest time to develop a perception of a performance gap

- Build on existing structures such as audit

- Be proactive; develop a plan and timetable for formulation and implementation

- Manage supporters and detractors (e.g. identify key stakeholders, assess their attitudes towards the change, assess their power to affect the change)

- Use all means of education interventions and forums for dissemination, posters in prominent places, regular teaching sessions, ward rounds, chemotherapy prescribing meetings etc.

- Use a variety of implementation interventions; focus on what has worked for your team in the past

- Set achievable small goals so that progress can be seen fairly quickly

- Develop and use a system of reminders (manual or computerised) and feedback; share progress and challenges with the team

It is not the purpose of these guidelines to present how future research should be undertaken, but merely to highlight gaps in current knowledge. The guideline development process has highlighted many areas where further research is required. Listed below are some of the issues that need addressing.

- Further research into the most valid and reliable assessment tools for monitoring a child's oral health during cancer treatment is required. The tolerability of oral assessment, its timing and use for informing the decision-making process need to be explored.

- There is currently insufficient evidence to support the use of many of the interventions used for the prevention/treatment of oral mucositis. Further RCTs should focus on interventions that have been shown to be beneficial/potentially beneficial in adults.

- RCTs of patient controlled analgesia versus continuous infusion for controlling oral pain in children are required.

- Further studies are recommended to identify factors that may help determine whether it is appropriate to prevent or treat oral candidiasis.

- Further RCTs assessing the effectiveness of current antifungal agents and new interventions for treating oral candidiasis are required.

9 UPDATING THE GUIDELINES

In order to incorporate new, emerging research evidence, the guidelines will be updated every two years. An update of the searches will be undertaken Spring 2007, with the aim of producing the next version of the guidelines Winter 2007.

The guidelines will be available in several formats:

Methodological report – containing the full details of methods used in the production of the recommendations

Guideline report – an abbreviated document focusing on the recommendations

'At a glance' – a user-friendly guide, providing a summary of the key issues (Appendix 3)

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APPENDIX 1: Adaptation of Eilers' Oral Assessment Guide

Oral Assessment Guide for Children and Young People

Category	Method of assessment	1	2	3
Swallow	Ask the child to swallow or observe the swallowing process. Ask the parent if there are any notable changes.	Normal. Without difficulty	Difficulty in swallowing	Unable to swallow at all. Pooling, dribbling of secretions
Lips and corner of mouth	Observe appearance of tissue	Normal. Smooth, pink and moist	Dry, cracked or swollen	Ulcerated or bleeding
Tongue	Observe the appearance of the tongue using a pen-torch to illuminate the oral cavity	Normal. Firm without fissures (cracking or splitting) or prominent papilla, pink and moist	Coated or loss of papillae with a shiny appearance with or without redness and/or oral *Candida*	Ulcerated, sloughing or cracked
Saliva	Observe consistency and quality of saliva	Normal. Thin and watery	Excess amount of saliva, drooling	Thick, ropy or absent
Mucous membrane	Observe the appearance of tissue using a pen-torch to illuminate the oral cavity	Normal. Pink and moist	Reddened or coated without ulceration and/or oral *Candida*	Ulceration and sloughing, with or without bleeding
Gingiva	Observe the appearance of tissue using a pen-torch to illuminate the oral cavity	Normal. Pink or coral with a stippled (dotted) surface. Gum margins tight and well defined, no swelling.	Oedematous with or without redness, smooth	Spontaneous bleeding
Teeth (If no teeth score 1)	Observe the appearance of teeth using a pen-torch to illuminate the oral cavity	Normal. Clean and no debris	Plaque or debris in localised areas	Plaque or debris generalised along gum line
Voice	Talk and listen to the child. Ask the parent if there are any notable changes	Normal tone and quality when talking or crying	Deeper or raspy	Difficult to talk, cry or not talking at all

APPENDIX 2: Quick reference guide to full recommendations

MOUTH CARE FOR CHILDREN AND YOUNG PEOPLE WITH CANCER
Quick Reference Guide
(Recommendations taken from the Evidence-based Guidelines produced by the UKCCSG-PONF Mouth Care Group, 2005)

ORAL CARE AT TIME OF CANCER DIAGNOSIS	
For paediatric dental units working with a cancer centre there should be a mechanism of notification for new patients.	√
All children should undergo a dental assessment at the time of cancer diagnosis and, if possible, before cancer treatment commences.	√
The possible long-term dental/orofacial effects of childhood cancer and treatment should be discussed.	√
The people most suitable to undertake the initial dental assessment are a paediatric dentist or a dental hygienist.	√
If any invasive dental treatment is required this should be undertaken by either a consultant or specialist paediatric dentist.	√
All children diagnosed with cancer should be registered with a General Dental Practitioner or community dental service. Registration should be maintained during and following the cancer treatment.	√
All children diagnosed with cancer should have access to an NHS General Dental Practitioner	√
The routine dental care provider in the general or community dental service should be notified of the cancer diagnosis and arrangements for care during cancer treatment as directed by the hospital dental team.	√
If there is not a paediatric dental unit liaising with a cancer centre there should be clear communication between the cancer centre and routine dental provider.	√
Appropriate training in oral assessment should be available within the cancer centre, ideally in collaboration with a member of the dental team.	√
ORAL HYGIENE AT DIAGNOSIS AND DURING CANCER TREATMENT	
Oral hygiene advice should be given to children and parents prior to commencing cancer treatment and this should be provided both verbally and in writing.	√
Oral hygiene advice should be given by a designated member of the dental team or, in the absence of a dentally trained individual, a member of the medical or nursing team who has received appropriate training.	√
Advice should be to brush at least twice a day, with a fluoride toothpaste (containing 1,000 ppm fluoride +/- 10%).	√
The toothbrush should be for the sole use of the child and changed on a 3 monthly basis, or when bristles splay if earlier. A child's toothbrush should be changed following an oral infective episode.	√
If the child has a sore mouth a soft brush with a small head should be used.	√
For children up to the age of 6 years, parents/carers should be instructed on how to brush their child's teeth.	√
For babies without teeth, parents/carers should be instructed on how to clean the mouth with oral sponges. The sponge should be moistened with water.	√
For children where it is not possible to brush teeth, parents/carers should be instructed on how to clean the mouth with oral sponges, as a temporary measure. The sponge should be moistened with water or an antimicrobial agent such as diluted chlorhexidine.	√
Additional aids, such as flossing and fluoride supplements should only be prescribed according to risk assessment by a member of the dental team.	√
The need to restrict sugary food and drink to meal times only should be emphasised.	√
DENTAL/ORAL CARE DURING CANCER TREATMENT	
A dental assessment should be undertaken every three to four months by a member of the dental team.	√
The dental team should be consulted of any dental, or difficult to manage oral problems arising during cancer treatment and the cancer team should be informed of the type and extent of dental treatment required.	√
If there is not a dedicated dental team there needs to be clear communication between the cancer team and a routine dental provider.	√
DENTAL/ORAL CARE AFTER CANCER TREATMENT	
Parents and children should be informed of the possible long-term dental/orofacial effects of childhood cancer and treatment.	√
Children's oral/dental health should continue to be monitored during the period of growth and development.	√
Children should be referred back to their routine dental provider who should be advised of the specific oral/dental care recommended by the consultant/specialist paediatric dental team and advised of future care arrangements and systems for referral as necessary.	√
ORAL ASSESSMENT DURING CANCER TREATMENT	
There is a variety of oral assessment tools from which to choose. Using those which have been shown to be valid and reliable would be most valuable.	√
The Eilers' Oral Assessment Guide offers a valid, reliable and clinically useful tool for assessing oral status.	D
The adaptation of the Eilers' Oral Assessment Guide is recommended for use in children and young people.	√
Those responsible for assessment of the oral cavity should be appropriately trained in the use of the selected assessment tool.	√
Nursing staff are best placed for the regular assessment of the child's oral status.	D
The frequency with which a child's mouth is assessed should be determined on an individual basis. Frequency should increase at the onset of oral complications.	D
Oral assessment should be used to check good basic oral hygiene is being maintained.	√
For a child with oral complications (e.g. as indicated by an OAG score of greater than 8) an appropriate pain assessment tool should be used to ensure adequate pain control and therapeutic interventions are available.	
The timing of assessment should be consistent in relation to the child's oral hygiene routine.	D
THE PREVENTION OF ORAL MUCOSITIS	
Parents and patients should be informed of the importance of keeping the mouth clean and encouraged to practice good, basic oral hygiene.	√
The following have all been shown to be potentially beneficial for the prevention of mucositis in adult populations. Their use in children for the prevention of radiotherapy and/or chemotherapy induced mucositis can only be considered within the constraints of an RCT.; Amifostine, allopurinol mouthwash (5-FU only), ice-chips, GM-CSF/GCSF, benzydamine, antibiotic pastilles/pastes (containing PTA), povidone-iodine, pilocarpine (not currently available in a form suitable for children), hydrolytic enzymes.	B
RCTs of allopurinol mouthwash are not recommended for children receiving cancer treatment other than 5-FU.	D
Prostaglandin E is not recommended for the prevention of chemotherapy or radiotherapy induced mucositis as there is evidence that it may promote mucositis.	B
i.v. folinic acid is not recommended for the routine prevention of chemotherapy or radiotherapy induced mucositis as there is evidence that it may promote mucositis.	B
However, i.v./oral folinic acid (rescue) should be used for the prevention of methotrexate toxicity according to the treatment protocol.	√

There is no evidence to support or refute the use of folinic acid mouthwash for the prevention of mucositis	
There is no evidence to support the use of the following agents for the prevention of chemotherapy or radiotherapy induced mucositis in children; Lozenges containing bacitracin, clotrimazole, and gentamicin (BcoG), propathelene, chlorhexidine, fluconazole, amphotericin B, sucralfate, prednisone, glutamine, pentoxifyline, Na-sucrose gel, traumeel, chamomile. Their use in children for the prevention of radiotherapy and/or chemotherapy induced mucositis can only be considered within the constraints of an RCT.	B

TREATMENT OF ORAL MUCOSITIS	
Appropriate pain control is recommended and the continuation of good oral hygiene, as tolerated.	√
Pain associated with mucositis can be severe. Opiates are required for the control of such pain.	√
RCTs of patient controlled analgesia versus continuous infusion for controlling oral pain in children are required.	B
The following have been shown to be potentially beneficial for the treatment of mucositis in adult populations. Their use in children receiving radiotherapy and/or chemotherapy can only be considered within the constraints of an RCT; Vitamin E, immunoglobulin, allopurinol mouthwash (5-FU only).	B
RCTs of allopurinol mouthwash are not recommended for children receiving cancer treatment other than 5-FU.	D
There is no evidence to support the use of the following for the treatment of chemotherapy or radiotherapy induced mucositis in children; benzydamine, chlorhexidine, sucralfate, tetrachlorodecaoxide, 'Magic' (lidocaine solution, diphenhydramine hydrochloride and aluminum hydroxide suspension). Their use in children for the prevention of radiotherapy and/or chemotherapy induced mucositis can only be considered within the constraints of an RCT.	B
The use of folinic acid for the treatment of mucositis following treatment with methotrexate has not been assessed in RCTs.	

PREVENTION OF ORAL CANDIDIASIS	
Preventative therapy is not recommended for most patients (for example, those receiving treatment for solid tumours). A decision needs to be made by the clinician on whether to prevent candidiasis according the patients risks. Further studies are recommended to identify risk factors.	D
When choosing an antifungal agent for the prevention of candidiasis one that is absorbed from the GI tract is recommended (for example fluconazole, itraconazole or ketoconazole).	A
Drug doses should be prescribed according to Medicines for Children.	√
Oral amphotericin B is recommended for the prevention of candidiasis only within the constraints of an RCT.	B
There is no evidence to support the use of nystatin or chlorhexidine for the prevention of candidiasis in children treated for cancer.	A

TREATMENT OF ORAL CANDIDIASIS	
There is no research evidence to demonstrate the effect of either topical or systemic antifungal agents for the treatment of oral candidiasis. Based on evidence for prevention of oral candidiasis, absorbed or partially absorbed antifungal agents could be used for the treatment of visible oral candidiasis.	D
Further controlled trials assessing the effectiveness of current antifungal agents and new interventions for treating oral candidiasis are required.	D

PREVENTION OF XEROSTOMIA	
There is insufficient evidence to support the use of amifostine for the prevention of salivary gland damage, or pilocarpine or biperiden for the prevention of xerostomia, in children treated for cancer. Future use of any such pharmacological agents for the prevention of salivary gland damage and xerostomia should be within the constraints of an RCT only.	B

TREATMENT OF XEROSTOMIA	
Consideration should be given to the use of saliva stimulants, artificial saliva, chewing sugar free gum or frequent sips of water for the relief of dry mouth.	D

PREVENTION OF HERPES SIMPLEX VIRUS	
Aciclovir is only recommended as a preventative strategy for herpes simplex in patients undergoing high dose chemotherapy with stem cell transplant.	B
Aciclovir is not recommended for routine use due to rarity of problem and cost.	D

TREATMENT OF HERPES SIMPLEX VIRUS	
Aciclovir is effective for the treatment of herpes simplex virus in patients receiving chemotherapy and/or radiotherapy.	A
Mild and non-progressing lesions on the lip should be treated with topical aciclovir.	D
Progressing and severe lesions on the lip should be treated with oral aciclovir.	D
Intra-oral lesions should be treated with oral aciclovir.	D
For severe cases, or where oral administration not tolerated, i.v. aciclovir should be used.	D
Drug doses should be prescribed according to Medicines for Children.	√
Thymostimulin and vidarabine are not recommended for routine treatment of herpes simplex unless within the constraints of an RCT.	B

A At least one meta analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
√ Best Practice

(**1++** High quality meta-analyses/systematic reviews of RCTs or RCTs with a very low risk of bias; **1+** Well conducted meta-analyses/systematic review of RCTs, or RCTs with low risk of bias; **1-** Meta-analyses/ systematic reviews of RCTs, or RCTs with high risk of bias; **2++** High quality systematic reviews of case-control or cohort studies; High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and high probability that the relationship is causal; **2+** Well conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal; **2-** Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal; **3** Non-analytic studies, e.g. case series, cross-sectional surveys; **4** Expert opinion/non-systematic review article)

APPENDIX 3: At-a-glance document

This document is available in electronic format for local adaptation.
(**www.ukccsg.org.uk)**

(TRUST LOGO)

MOUTHCARE FOR CHILDREN AND YOUNG PEOPLE WITH CANCER: EVIDENCE BASED GUIDELINES.

DENTAL CARE / TREATMENT

AT DIAGNOSIS: Oral & dental assessment	• Ideally by a dentist or dental hygienist linked to the cancer centre. • Any treatment required should be undertaken by a consultant or specialist paediatric dentist. • If there is not a paediatric dental unit liaising with the cancer centre there should be clear communication between the cancer centre and the routine dental provider.
DURING ONCOLOGY TREATMENT: Dental assessment every 3 – 4 months	• Ideally by a dentist linked to the cancer centre (retain registration and communication with usual dental provider). • Any treatment required should be undertaken ideally by dentist linked to the cancer centre. • If not available, then by usual dental provider with clear communication & guidance from the cancer centre.
POST TREATMENT	• By usual dental provider with clear communication & guidance from the cancer centre.

BASIC ORAL CARE

AT DIAGNOSIS & DURING TREATMENT	• Brush teeth well twice a day using fluoride toothpaste and soft toothbrush. • Whilst in-patient, oral assessment using OAG and score recorded. Frequency of assessment determined by individual need. • **OAG score >8 means increased risk of oral complications.** • Use of additional aids e.g. floss, fluoride tablets and electric toothbrushes – by recommendation of dental team only. Chlorhexidine is not recommended unless – see below. (If unable to brush teeth, clean mouth with oral sponges moistened with water or diluted chlorhexidine)

ORAL COMPLICATIONS

	PREVENTION	TREATMENT
MUCOSITIS	• Basic oral care (as above).	• Basic oral care (as above). • Appropriate pain control.
CANDIDIASIS	• Basic oral care. *Clinical decision required. If antifungal agent to be used, choose one absorbed from GI tract e.g. fluconazole, itraconazole or ketoconazole.* • Check treatment protocols. • Nystatin is not recommended.	• Basic oral care, plus *Clinical decision required about which antifungal agent to use, choose one that is absorbed from the GI tract eg fluconazole, itraconazole or ketoconazole.* • Check treatment protocols. • Nystatin is not recommended.
XEROSTOMIA	• Basic oral care	• Basic oral care. • Consider saliva stimulants/artificial saliva.
HERPES	• Basic oral care • Aciclovir is only recommended as a preventative strategy for herpes simplex in patients undergoing high dose chemotherapy with stem cell transplant / BMT	• Basic oral care, plus Mild and/or non progressive lip lesions: topical aciclovir. Moderate/severe and/or progressive lip lesions & for Mild/Moderate oral lesions: oral aciclovir. Severe oral lesions or if oral cannot be tolerated: IV aciclovir. (*for doses see BNF – Children*)

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