Prophylaxis of oral mucositis in irradiated head-and-neck cancer patients: a proposed classification scheme of interventions and meta-analysis of randomized controlled trials

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Authors' objectives
To identify, classify and evaluate agents used in the prophylaxis of oral mucositis in irradiated head and neck cancer patients.

Searching
MEDLINE, EMBASE, CINAHL and Cancerlit were searched from 1966 to June 2000 using combinations of the following search terms: 'head and neck neoplasms', 'radiotherapy or drug therapy', 'stomatitis', and 'clinical trial'. The individual agents identified from this search were listed and then the search repeated for each agent. Unpublished studies were identified by searching Cancerlit for abstracts from major oncology conference proceedings, and ongoing studies were searched for on the National Cancer Institute's PDQ database. The reference lists of all the retrieved articles were also checked.

Study selection
Study designs of evaluations included in the review
All studies that met the eligibility criteria were included for the purpose of developing the classification scheme, and assessing trends in and possible future directions for research. Only randomised trials were included in the analysis of effectiveness.

Specific interventions included in the review
All interventions used for the prevention of oral mucositis were eligible for inclusion. The intervention had to be compared with a no-active treatment control.

Participants included in the review
Patients receiving radiotherapy to the head and neck, in whom any intervention to prevent oral mucositis were used, were eligible for inclusion. Studies where patients were treated with radiation therapy alone, but which included patients with disease at sites other than the head and neck, were deemed ineligible.

Outcomes assessed in the review
Studies were included if they reported the following: clinician-assessed oral mucositis scores; proxy measures of oral mucositis, such as radiotherapy interruptions or G-tube placements; or patient-assessed ratings of oral mucositis or other symptoms.

How were decisions on the relevance of primary studies made?
The citation lists generated by the searches were examined by three reviewers and all the relevant articles were obtained. Two reviewers then independently applied the inclusion and exclusion criteria. Agreement on the eligibility of the studies was measured using the Kappa-statistic, and any disagreements were resolved through discussion.

Assessment of study quality
Validity was assessed using the validated assessment tool developed by Jadad et al. (see Other Publications of Related Interest no.1), following a pilot test on a small sample of studies. Two reviewers independently assessed the methodological quality of all the selected randomised controlled trials (RCTs). A study with a quality score of less than 1 (on a scale of 0 to 5) was excluded from the analysis.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted for the following categories: population details; interventions and dose; and primary outcome measure for severe oral mucositis. In studies where dichotomous outcome measures were not reported, the data were derived by one of two methods. First, if individual patient data were available, this were extracted in a dichotomous format. Second, for continuous data, means from different scales were transformed to a common percentage scale using the method described by Eisenberg et al., and then dichotomised using the technique of Moore et al. (see Other Publications of Related Interest nos.2-3, respectively).

Methods of synthesis
How were the studies combined?
All the studies identified were used to construct a classification scheme, whilst the 15 RCTs were combined in a meta-analysis using RevMan software (version 3.1; Cochrane Collaboration). The odds ratios (ORs) were calculated using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.4), along with the 95% confidence intervals (CIs).

How were differences between studies investigated?
The chi-squared test was used to test for heterogeneity (significance level set at a p-value of 0.1).

Results of the review
Forty-two studies were included in the classification of agents, whilst 15 RCTs (n=1,002) were included in the analysis of effectiveness.

A large number of agents used for the prophylaxis of oral mucositis after head and neck radiotherapy were identified. These included: sucralfate (8 studies); prostaglandins (2 studies); beta-carotene (1 study); silver nitrate (2 studies); hydrogen peroxide (1 study); amifostine (4 studies); glutamine (1 study); low-energy laser (1 study); haematopoietic growth factors (9 studies); anti-inflammatories (3 studies); human immunoglobulin (1 study); broad-spectrum antimicrobials (3 studies); and narrow-spectrum antimicrobials (6 studies). The median quality of the RCTs was 3 (range: 1 to 5). Thirteen studies were included in the meta-analysis of the number of patients who developed severe mucositis; the pooled OR was 0.64 (95% CI: 0.46, 0.88; chi-squared 10.59, d.f.=11), indicating a beneficial effect of prophylactic interventions. When only studies with a quality score of at least 3 were included (8 studies), the OR compared with no-active treatment was 0.78 (95% CI: 0.54, 1.13).

Efficacy of antibiotics (5 studies, n=509): the OR was 0.47 (95% CI: 0.25, 0.92). This was made up of results from broad-spectrum antibiotics (3 studies) and narrow-spectrum antibiotics (2 studies), the ORs for which were 0.52 (95% CI: 0.14, 1.98) and 0.45 ((95% CI: 0.23, 0.86), respectively.

The ORs for the treatment effect were also presented for other subgroups.

Authors' conclusions
Overall, interventions chosen on a sound biological basis to prevent severe oral mucositis were effective. In particular, narrow-spectrum antibiotic lozenges appeared to be beneficial when oral mucositis was assessed by clinicians. Methodological limitations were evident in many of the studies.

CRD commentary
This review addressed an appropriate question using well-defined inclusion and exclusion criteria for the participants, intervention and study design. The search for relevant trials was comprehensive and included efforts to retrieve unpublished material. Some studies may have been missed since the full manuscripts were only obtained for English language articles. The validity of the studies was assessed appropriately, and the results of the assessment were incorporated into the review. Adequate details of the identified studies were presented, and the classification of all
interventions was helpful. The meta-analysis of the data from RCTs was conducted appropriately; however, the large number of subgroup analyses performed is of questionable validity.

This was a well-conducted systematic review. The authors' conclusions are supported by the results of the review.

Implications of the review for practice and research
Practice: The authors state that 'interventions chosen on a sound biologic basis to prevent severe oral mucositis are effective'.

Research: The authors state that further research using validated measurement tools in larger methodologically-sound trials is warranted.

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Other publications of related interest

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Record Status
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