Canadian Consensus Practice Guidelines for Bisphosphonate Associated Osteonecrosis of the Jaw


ABSTRACT. Objective. Following publication of the first reports of osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates in 2003, a call for national multidisciplinary guidelines based upon a systematic review of the current evidence was made by the Canadian Association of Oral and Maxillofacial Surgeons (CAOMS) in association with national and international societies concerned with ONJ. The purpose of the guidelines is to provide recommendations regarding diagnosis, identification of at-risk patients, and prevention and management strategies, based on current evidence and consensus. These guidelines were developed for medical and dental practitioners as well as for oral pathologists and related specialists.

Methods. The multidisciplinary task force established by the CAOMS reviewed all relevant areas of research relating to ONJ associated with bisphosphonate use and completed a systematic review of current literature. These evidence-based guidelines were developed utilizing a structured development methodology. A modified Delphi consensus process enabled consensus among the multidisciplinary task force members. These guidelines have since been reviewed by external experts and endorsed by national and international medical, dental, oral surgery, and oral pathology societies.

Results. Recommendations regarding diagnosis, prevention, and management of ONJ were made following analysis of all current data pertaining to this condition. ONJ has many etiologic factors including head and neck irradiation, trauma, periodontal disease, local malignancy, chemotherapy, and glucocorticoid therapy. High-dose intravenous bisphosphonates have been identified as a risk factor for ONJ in the oncology patient population. Low-dose bisphosphonate use in patients with osteoporosis or other metabolic bone disease has not been causally linked to the development of ONJ. Prevention, staging, and treatment recommendations are based upon collective expert opinion and current data, which has been limited to case reports, case series, surveys, retrospective studies, and 2 prospective observational studies. Recommendations: In all oncology patients, a thorough dental examination including radiographs should be completed prior to the initiation of intravenous bisphosphonate therapy. In this population, any invasive dental procedure is ideally completed prior to the initiation of high-dose bisphosphonate therapy. Non-urgent procedures are preferably delayed for 3 to 6 months following interruption of bisphosphonate therapy. Osteoporosis patients receiving oral or intravenous bisphosphonates do not require a dental examination prior to initiating therapy in the presence of appropriate dental care and good oral hygiene. Stopping smoking, limiting alcohol intake, and maintaining good oral hygiene should be emphasized for all patients receiving bisphosphonate therapy. Individuals with established ONJ are most appropriately managed with supportive care including pain control, treatment of secondary infection, removal of necrotic debris, and mobile sequestrate. Aggressive debridement is contraindicated.

Conclusion. Our multidisciplinary guidelines, which provide a rational evidence-based approach to the diagnosis, prevention, and management of bisphosphonate-associated ONJ in Canada, are based on the best available published data and the opinion of national and international experts involved in the prevention and management of ONJ. (First Release June 1 2008; J Rheumatol 2008;35:1391–7)

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Endocrinology and Metabolism, University of Calgary Health Sciences Centre, Calgary, Alberta, Canada; Columbia University and Regional Bone Center, Helen Hayes Hospital, West Haverstraw, New York, USA; Pediatrics and Human Genetics, McGill University and Genetics Unit, Shriners Hospital for Children, Montreal, Quebec; Departments of Oncology and Medicine, Michael G. DeGroot School of Medicine, McMaster University, Hamilton; Division of Oral and Maxillofacial Surgery, University of Toronto, Toronto, Ontario, Canada; University of Rochester Eastman Dental Center, Rochester, New York, USA; College of Medicine, Mayo Clinic, Rochester, Minnesota, USA; Osteoporosis Centre, Division of Endocrinology and Metabolism, St. Michael’s Hospital; Hospital for Sick Children and Bloorview Kids Rehabilitation, Women’s College Health Sciences Centre, Faculty of Dentistry, University of Toronto, Toronto, Ontario; Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; Texas Institute for Reproductive Medicine and Endocrinology, University of Texas Medical School, Houston, Texas, USA; Centre de Recherche, CHUM, Montreal, Quebec, Canada; and School of Clinical Medicine and Department of Medicine, University of Cambridge, Cambridge, UK.

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In 2003 the first reports describing bisphosphonate-associated osteonecrosis of the jaw (ONJ) were published. ONJ is associated with significant morbidity, and its association with bisphosphonate led to an urgent need for both the medical and dental scientific community to further understand this uncommon condition. Bisphosphonates are commonly used in the management of skeletal complications of malignancy including metastatic bone disease and hypercalcemia of malignancy. In patients with osteoporosis these agents are administered in low doses and effectively reduce the risk of vertebral and nonvertebral fracture. Bisphosphonates have become a cornerstone in the management of skeletal complications of malignancy as well as osteoporosis and metabolic bone disease, as these agents offer tremendous benefit to those with malignancy or metabolic bone disease. In the oncology patient ONJ has been temporally associated with use of high-dose intravenous (IV) bisphosphonates. A similar link has not yet been identified in the patient with osteoporosis in whom these agents are used in very low doses.

Due to limited and misleading public information regarding ONJ, many patients have discontinued bisphosphonate treatment, resulting in inadequate care of the underlying skeletal condition. Medical and dental practitioners have requested evidence-based multidisciplinary guidelines on which to base advice regarding diagnosis, prevention, and treatment of ONJ. It was recognized that the pathogenesis leading to ONJ is not well understood and the condition may arise in association with many etiologic factors. ONJ may also occur spontaneously without exposure to bisphosphonates. The incidence of the condition also required clarification. For these reasons, further study with respect to the appropriate evaluation and management of both spontaneously occurring lesions and those occurring with bisphosphonate use was required. An urgent need for evidence-based strategies to prevent and effectively manage this condition was therefore recognized nationally. Due to the paucity of good quality evidence regarding bisphosphonate-associated ONJ, it was recognized that evidence-based guidelines would focus on collective multidisciplinary expert opinion in addition to current published data.

The Canadian Association of Oral and Maxillofacial Surgeons in association with national and international multidisciplinary societies formalized a Canadian task force on ONJ. An evidence-based systematic review that was conducted by the task force is now close to completion; as well, the task force developed the present evidence-based guidelines for diagnosis, prevention, and management of bisphosphonate-associated ONJ.

The aim of these guidelines is to provide recommenda-
tions for diagnosis of bisphosphonate-associated ONJ, in both the oncology and osteoporosis patient populations, to dental and medical practitioners including dentists, oral surgeons, oral pathologists, general practitioners, and internal medicine specialists. The recommendations are practical and address both prevention and treatment strategies. Identification of the individual at risk is recommended, with implementation of appropriate measures enabling early identification and management of the condition. Recommendations for care address evaluation of the individual with exposed bone in the oral cavity, as well as appropriate medical and surgical intervention strategies.

These guidelines have been endorsed by the Canadian Association of Oral and Maxillofacial Surgeons, Canadian Society of Endocrinology and Metabolism, Ontario Society of Oral and Maxillofacial Surgeons, Canadian Academy of Oral and Maxillofacial Pathology and Oral Medicine, American Association of Clinical Endocrinologists, International Bone and Mineral Society, and the International Society of Clinical Densitometry.

The guidelines will be pilot-tested in Ontario, Canada, by oral surgeons to obtain feedback regarding practicality and usefulness.

MATERIALS AND METHODS
The multidisciplinary task force included representatives from the national and international societies representing the disciplines of oral surgery, dentistry, oral pathology, oral medicine, endocrinology, rheumatology, and oncology. Task force members were identified on the basis of their knowledge and expertise in the diagnosis and management of ONJ. Conflicts of interest were declared and included (Appendix). Following completion of the systematic review, the task force reviewed the data collected centrally and prepared discussion papers, which were reviewed by the entire task force.

The systematic review included a search of the medical literature for studies on bisphosphonate use and dental complications in either the cancer or osteoporosis population in Medline (1966 to January 2008) and Embase (1980 to January 2008). A manual search of the bibliography of key published articles was also carried out, and pharmaceutical companies were invited to submit relevant information.

Due to limited high quality evidence, all published studies were included; these comprised case reports, case series, surveys, retrospective studies, and 2 prospective observational studies.

The task force convened on June 2, 2007, in Toronto and each section was discussed in detail. Patient preferences were also strongly considered in the development of the prevention and management strategies. The recommendations presented in this document reflect the consensus of the task force on the target areas of discussion. Each task force member had a unique perspective, knowledge base, understanding, and experience with ONJ. Sharing of expertise was invaluable in enhancing a broader perspective of understanding of this condition among the task force members and led to considerable discussion and heated debate. Through discussion, dialogue, and exchange of ideas, consensus was achieved on the recommendations presented in this final consensus document, which synthesizes task force recommendations.

The guidelines document was subsequently distributed to all task force members and to several external experts from specialties within medicine and dentistry, and feedback was incorporated in the final document, which has been endorsed by all member societies and the task force members.

Twenty-five dental, medical, and oral pathology experts developed the draft guidelines. These were reviewed in detail at the June 2, 2007, meeting in Toronto. The evidence-based statements were considered acceptable if sufficient evidence to justify the recommendation was present and if each recommendation was agreed upon by the members of the task force. The recommendations were modified to ensure agreement and consensus at the meeting. Following incorporation of task force member feedback, the revised guidelines were circulated to all task force members for approval and reviewed by external experts. The process of the literature search, data analysis, and consultation with national and international experts in accordance with the modified Delphi model of gaining consensus in the development of the guideline is outlined in Figure 1.

RESULTS
The following clinical questions served as the starting point for the systematic literature review and areas of clinical care addressed by the Canadian task force on ONJ associated with bisphosphonates.

How is bisphosphonate-associated ONJ diagnosed?
The diagnosis is made clinically in the presence of exposed bone in the maxillofacial region for more than 8 weeks in the absence of radiotherapy to the jaw. If the exposed bone has been present for less than 8 weeks, it should be followed to confirm that soft tissues close; such a case would be described as a suspected case of osteonecrosis. It is important to consider the differential diagnosis as including the condition identified as spontaneous lingual mandibular sequestration with ulceration.

Spontaneous sequestration is a less aggressive and self-limited pathologic process that can develop without any obvious eliciting factor and is characterized by exposed necrotic bone involving the lingual mandible approximately at the level of the mylohyoid ridge. It can resemble bisphosphonate-associated ONJ. It is a self-limited condition that resolves spontaneously between 3 days and 12 weeks. Other conditions that can present with exposed bone include periodontal disease, local malignancies, and osteonecrosis secondary to radiotherapy. Trauma may also result in exposed bone and requires appropriate followup. Biopsies are only recommended if local malignancy is suspected. Radiographic findings may not be helpful in the early cases of ONJ, and features are not specific or diagnostic of bisphosphonate-associated ONJ.

Can ONJ associated with bisphosphonates be prevented in those with and without risk factors?
To date, no published studies allow us to answer this question. The task force made the following recommendations based on collective clinical experience:

(a) In all patients receiving bisphosphonate therapy, physicians should stress the importance of maintaining good oral hygiene.

(b) Lifestyle changes, such as stopping smoking and limiting alcohol intake, should be encouraged in patients at high risk for ONJ.

(c) In all cases, physicians are highly encouraged to
Figure 1. The development of national clinical practice guidelines for bisphosphonate-associated osteonecrosis of the jaw.

Taskforce members identified the key clinical questions to be addressed by the Panel

Compilation of information: Medical literature search was conducted using MEDLINE and EMBASE focused on answering the key clinical questions and all relevant literature retrieved. This consisted of case reports, case series, surveys, retrospective studies, prospective observational studies

Development of collective evidence
- Articles pertaining to each section were assessed by multiple experts (mentioned below) in the field, and discussion papers were prepared
- These papers were critiqued by all panel members

Establishing Consensus on key clinical questions
- Based upon the currently available evidence, and discussion, consensus was achieved on June 2, 2007 in Toronto at a face to face conference

Development of collective Guidelines
- A final document was drafted which incorporated revisions from the June meeting

Consensus exercise
Two rounds of feedback from in field experts and external specialists in medicine and dentistry

Development of final guidelines manuscript
- Guidelines manuscript was finalized incorporating all feedback from the taskforce members at the conference and external experts
discuss the very rare occurrence of ONJ (including risk factors and prevention strategies) with patients in whom they have recommended a bisphosphonate for non-cancer indications. For cancer patients receiving high-dose frequent IV bisphosphonate therapy, where the risk for ONJ appears to be substantially higher, more specific information should be provided.

For the oncology patient prescribed high-dose IV bisphosphonate therapy:

(a) Prior to the initiation of IV bisphosphonate therapy in the oncology patient, a thorough dental examination, including radiographs, should be completed.

(b) In oncology patients, if any invasive dental procedure (e.g., tooth extraction, surgery) is deemed necessary, it should be completed and optimal dental health achieved prior to initiating bisphosphonate therapy if the patient’s medical condition permits the delay\(^1,10\). This would apply to the pediatric population, as well.

(c) For oncology patients receiving IV bisphosphonate therapy who require an urgent invasive dental procedure, it is recommended that the procedure be completed and interruption of bisphosphonate therapy be considered during the healing period, if the medical condition permits\(^28\). If the procedure is non-emergent, it is recommended that one consider interruption of the bisphosphonate for 3 to 6 months prior to the procedure, and until the surgical site has healed, if the medical condition permits. While this may be difficult in patients at high risk for hypercalcemia of malignancy, other non-bisphosphonate options should be considered for the short-term medical management of these patients.

For the osteoporosis patient prescribed oral or IV bisphosphonate therapy:

(a) For the osteoporosis patient expecting to receive oral or IV bisphosphonate therapy who has practiced appropriate preventive dental care and reports no acute dental problems, routine followup dental examinations are appropriate. If appropriate dental care has not taken place, or if there is an acute dental problem, this should be addressed prior to initiating a bisphosphonate. As is recommended for all individuals, patients taking bisphosphonates should maintain good oral hygiene practices and attend semiannual dental examinations\(^27\). In osteoporosis patients receiving an oral or IV bisphosphonate who present with a true dental emergency, invasive surgery should not be delayed. Consideration should be given to interrupting the bisphosphonate during the healing period.

(b) For the osteoporosis patient requiring non-emergent invasive dental surgery, interruption of bisphosphonate therapy for several months prior to the procedure and throughout the healing period may be considered. However, there are no clinical trial data to guide the duration of cessation of therapy; and it should be emphasized that, at present, only anecdotal data exist to suggest discontinuing a bisphosphonate reduces risk.

Clearly, implementation of the above guidelines is dependent upon the type and extent of dental coverage a given patient may have. As the relationship between bisphosphonate use and ONJ in the patient with osteoporosis remains unproven, it is not recommended that bisphosphonate therapy be withheld for osteoporosis if a patient is unable to be in full compliance with these guidelines in the absence of other major risk factors for ONJ. Delaying the initiation of bisphosphonate therapy pending a dental evaluation rarely would seem necessary in the osteoporosis patient.

As bisphosphonates have longterm skeletal retention, it is not known if stopping treatment will alter the course of any ONJ lesions. No prospective data exist to address this question, but there are anecdotal reports of patients in whom ONJ seemed to resolve with appropriate dental care and cessation of the bisphosphonate\(^29\), suggesting that cessation of the drug is reasonable. Certainly the cessation of bisphosphonate therapy for several months does not seem to have a detrimental effect on osteoporosis management\(^30\).

What are evidence-based treatment strategies for bisphosphonate-associated ONJ?

Conservative approaches are most effective, and all patients should be evaluated and managed by a team including the dental specialist, the oral and maxillofacial surgeon, and the medical physician as well as the oncologist or osteologist, as necessary. Treatment goals focus around reassuring and educating each patient regarding the possibility of ONJ; and ensuring adequate nutritional intake and tube feeding if necessary. Addressing local pain and treating secondary infection are important approaches in the management of ONJ\(^30\).

Individuals with exposed or necrotic bone with pain and evidence of infection should be treated with a 3-week course of antibiotics\(^17,20\).

Elimination of sharp and ragged bone surfaces with surgical debridement is necessary to limit trauma to adjacent soft tissues. Readily identifiable sequestrae should be removed. Extraction of symptomatic teeth in the necrotic zone is not expected to exacerbate established ONJ. Segmental resection may be required to remove large portions of necrotic or fractured bone; however, aggressive debridement is contraindicated. Bone grafting may be problematic due to potential bone necrosis that may occur at the site of necrosis in the patient. Dietary supplementation or tube feeding should be considered as necessary in those individuals who have Stage III disease with exposed necrotic bone in the presence of pain, infection, pathologic fracture, extraoral fistula, or osteolysis. If metastatic disease is suspected then biopsy is advised.
Interruption of bisphosphonate therapy may be of value, although there are limited data to confirm this recommendation. In a recent review of 60 cases of ONJ, 7 patients did demonstrate improved outcomes with cessation of bisphosphonate therapy over at least 6 months. Table 1 summarizes the staging and treatment strategies recommended.

**Conclusion**
ONJ is a rare clinical entity that remains poorly understood. The underlying pathogenesis also requires clarification. A number of risk factors have been identified that appear to contribute to the development of ONJ, and recently bisphosphonates have been implicated in the development of this rare condition. ONJ has been temporally associated with high-dose IV bisphosphonates in the oncology patient population. A few cases have been described in osteoporosis patients receiving low-dose bisphosphonates, but a direct causal link has not been established in this patient population. ONJ has been documented as occurring spontaneously in the absence of known risk factors. The background incidence of ONJ in the general population is currently not known. In those individuals at high risk for development of ONJ in association with bisphosphonate use it is necessary to emphasize the importance of maintaining good dental hygiene and of limiting dental procedures to essential intervention only. Aggressive debridement is contraindicated. In those at low risk for the condition a focus on good dental hygiene should be taken in accordance with the dental recommendations for the general population.

Current knowledge gaps include a comprehensive understanding of the pathogenesis and the true incidence of ONJ occurring spontaneously as well as in association with bisphosphonates. Acquisition of prospective data will enable stratification of the risk factors leading to ONJ, and enable further refinement of the prevention and management recommendations. The Canadian task force on osteonecrosis of the jaw also recommends that a registry be maintained of all identified cases, as this will provide valuable information regarding the strength of association of risk factors for ONJ. The registry will also serve as a basis for obtaining prospective data regarding natural history and effects of intervention. Close international collaboration among medical and dental experts will be needed to further close the existing knowledge gaps.

**Appendix**

*Disclosure:* A.A. Khan has consulted for Amgen, Novartis, Merck, Eli Lilly, Procter & Gamble (P&G), Servier, and has received support from Merck, Novartis, and P&G. D. Dempster has consulted for Eli Lilly, Merck, Amgen, Sanofi-Aventis/P&G, GlaxoSmithKline (GSK)-Roche, and Novartis. D.A. Hanley has consulted for Amgen, Sanofi-Aventis, Procter & Gamble, Eli Lilly, Wyeth-Ayerst, Novartis, NPS Pharmaceuticals, and

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**Table 1. Staging and treatment strategies.**

<table>
<thead>
<tr>
<th>Staging</th>
<th>Treatment Proposed</th>
<th>Level of Evidence*</th>
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<tbody>
<tr>
<td>Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection</td>
<td>Baking soda and water rinse*</td>
<td>RCS</td>
</tr>
<tr>
<td></td>
<td>Quarterly clinical followup</td>
<td>EO</td>
</tr>
<tr>
<td></td>
<td>Patient education and review of indications for continued BP therapy</td>
<td>EO</td>
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<tr>
<td></td>
<td>Biopsy, if metastasis suspected</td>
<td>EO</td>
</tr>
<tr>
<td>Stage 2: Exposed/necrotic bone in patients with pain and clinical evidence of infection, such as erythema in the region of the exposed bone, with or without purulent drainage</td>
<td>Symptomatic treatment with broad-spectrum oral antibiotic (culture, if necessary)</td>
<td>RCS</td>
</tr>
<tr>
<td></td>
<td>Antibacterial mouth rinse</td>
<td>RCS</td>
</tr>
<tr>
<td></td>
<td>Pain control</td>
<td>RCS</td>
</tr>
<tr>
<td></td>
<td>Only superficial debridement to relieve soft tissue irritation</td>
<td>RCS</td>
</tr>
<tr>
<td></td>
<td>Patient education and review of indications for continued BP therapy</td>
<td>EO</td>
</tr>
<tr>
<td>Stage 3: Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border</td>
<td>Antibiotic therapy (culture, if necessary)</td>
<td>RCS</td>
</tr>
<tr>
<td></td>
<td>Surgical debridement/resection for longer-term palliation of infection and pain without grafting</td>
<td>RCS</td>
</tr>
<tr>
<td></td>
<td>Pain control</td>
<td>RCS</td>
</tr>
<tr>
<td></td>
<td>Removable prosthesis to protect the site</td>
<td>EO</td>
</tr>
<tr>
<td></td>
<td>Dietary supplementation or tube feeding, if necessary</td>
<td>EO</td>
</tr>
<tr>
<td></td>
<td>Patient education and review of indications for continued BP therapy</td>
<td>EO</td>
</tr>
<tr>
<td></td>
<td>Biopsy, if metastasis suspected</td>
<td>EO</td>
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</tbody>
</table>

* 1 teaspoon of baking soda with 12–14 ounces of water. RCS: retrospective case study or case series; EO: expert opinion. BP: bisphosphonate.
Nycomed, and has received support from Amgen, Sanofi-Aventis, P&G, Eli Lilly, Wyeth-Ayerst, Novartis, and NPS Pharmaceuticals. F.H. Glorieux has consulted for Novartis and P&G, and has received support from Novartis.

T. Paul has consulted for GSK. S. Khosla has consulted for Novartis and has received support from P&G. R.G. Josse has consulted for Eli Lilly, P&G, Sanofi-Aventis, Novartis, Merck, Amgen, and has received support from Servier and Amgen. D. Kendler has consulted for Amgen, Servier, Novartis, Eli Lilly, Wyeth, Pfizer, and has received support from Amgen, Servier, Novartis, Eli Lilly, Wyeth, Pfizer, Takeda, and Zelos. S. Petak has consulted for Eli Lilly, Novartis, and Roche/GSK, and has received support from P&G. L.G. Sr-Marie has consulted for the Alliance for Better Bone Health and P&G, and has received support from Alliance for Better Bone Health. P&G, Sanofi-Aventis Canada Inc., Amgen Canada, AstraZeneca Inc., Eli Lilly Inc., GSK, Merck Frosst, Pfizer Inc., Novartis Pharma Inc., Servier Inc., Sanofi-Aventis Canada Inc., Eli Lilly Inc., Hoffmann-LaRoche Limited, Merck Frosst, Novartis Pharma Inc., NPS Allelix, Pfizer Canada Inc., Zelos Therapeutics Inc., and Servier Inc. J. Brown has consulted for Amgen, Arthrolab, Sanofi-Aventis Canada, Boehringer Ingehelm/Roche, Bristol-Myers Squibb (BMS), Eli Lilly Canada, Genizon, GSK, Merck Frosst, Nico, Novartis, Pfizer, P&G, Servier, and Wyeth, and has received support from Amgen, Arthrolab, Sanofi-Aventis Canada, Boehringer Ingelheim/Roche, BMS, Eli Lilly Canada, Genizon, GlaxoSmithkline, Merck Frosst, Nico, Novartis, Pfizer, Procter & Gamble, Servier, and Wyeth. J.E. Compston has consulted for Amgen, Novartis, Eli Lilly, MSD, Nycomed, Servier, Shire, Wyeth, GSK/Roche, Pfizer, P&G, Alliance for Better Bone Health, Crescent Diagnostics, and received support from Servier and P&G.

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