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American Association of Oral and Maxillofacial Surgeons

Position Paper



Medication-Related Osteonecrosis of the Jaw—2014 Update

Special Committee on Medication-Related Osteonecrosis of the Jaws:

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Introduction

The Special Committee recommends changing the nomenclature of bisphosphonate-related osteonecrosis of the jaw (BRONJ). The Special Committee favors the term **medication-related osteonecrosis of the jaw (MRONJ)**. The change is justified to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies.

MRONJ adversely affects the quality of life, producing significant morbidity. Strategies for management of patients with, or at risk for, MRONJ were set forth in the American Association of Oral and Maxillofacial Surgeons (AAOMS) updated *Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws* and approved by the Board of Trustees in 2009.¹ The *Position Paper* was developed by a Special Committee appointed by the Board and composed of clinicians with extensive experience in caring for these patients and basic science researchers. The knowledge base and experience in addressing MRONJ has expanded, necessitating modifications and refinements to the previous *Position Paper*. This Special Committee met in September 2013 to appraise the current literature and revise the guidelines as indicated to reflect current knowledge in this field. This update contains revisions to diagnosis, staging, and management strategies, and highlights current research status. AAOMS considers it vitally important that this information be disseminated to other relevant health care professionals and organizations.

Purpose

The purpose of this updated position paper is to provide:

1. Risk estimates of developing MRONJ
2. Comparisons of the risks and benefits of medications related to osteonecrosis of the jaw (ONJ) in order to facilitate medical decision-making for the treating physician, dentist, dental specialist, and patients
3. Guidance to clinicians regarding:



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- a. the differential diagnosis of MRONJ in patients with a history of exposure to antiresorptive and/or antiangiogenic agents
- b. MRONJ prevention measures and management strategies for patients with MRONJ based on the disease stage

Background

Antiresorptive medications

Intravenous (IV) bisphosphonates (BPs) are antiresorptive medications used to manage cancer-related conditions including hypercalcemia of malignancy, skeletal-related events (SRE) associated with bone metastases in the context of solid tumors such as breast cancer, prostate cancer and lung cancers, and for management of lytic lesions in the setting of multiple myeloma.²⁻¹³ While the potential for bisphosphonates to improve cancer-specific survival remains controversial, these medications have had a significant positive effect on the quality of life for patients with advanced cancer involving the skeleton.

IV BPs, ie once yearly infusion of zoledronate (Reclast®) and a parenteral formulation of ibandronate (Boniva®) administered every three months, have FDA approval for management of osteoporosis.¹⁴

Oral bisphosphonates are approved for treatment of osteoporosis and are frequently used to treat osteopenia as well.¹⁵ They are also used for a variety of less common conditions such as Paget's disease of bone, and osteogenesis imperfecta.^{16,17} The most common use, however, is for osteopenia and osteoporosis.^{18,19}

RANK ligand inhibitor (denosumab) is an antiresorptive agent that exists as a fully humanized antibody against RANK ligand (RANK-L) and inhibits osteoclast function and associated bone resorption. When denosumab (Prolia®) is administered subcutaneously every 6 months there is a reduction in the risk of vertebral, non-vertebral, and hip fractures in osteoporotic patients.^{20,21} Denosumab (Xgeva®) is also effective in reducing SRE related to metastatic bone disease from solid tumors when administered monthly.^{22,23} Denosumab therapy is not indicated for the treatment of multiple myeloma. Interestingly, in contrast to bisphosphonates, RANK ligand inhibitors do not bind to bone and their effects on bone remodeling are mostly diminished within 6 months of treatment cessation.

Antiangiogenic medications

Angiogenesis inhibitors interfere with the formation of new blood vessels by binding to various signaling mol-

ecules disrupting the angiogenesis-signaling cascade. These novel medications have demonstrated efficacy in the treatment of gastrointestinal tumors, renal cell carcinomas, neuroendocrine tumors and others.

Risks of jaw necrosis related to antiresorptive therapy

Oral and maxillofacial surgeons first recognized and reported cases of non-healing exposed bone in the maxillofacial region in patients treated with IV bisphosphonates.^{24,25} In September 2004, Novartis, the manufacturer of the IV bisphosphonates pamidronate (Aredia®) and zoledronic acid (Zometa®), notified healthcare professionals of additions to the labeling of these products, which provided cautionary language related to the development of osteonecrosis of the jaws.²⁶ This was followed in 2005 by a broader drug class warning of this complication for all bisphosphonates including the oral preparations.^{27,28} More recently, other antiresorptive agents and novel anti-cancer drugs have been linked to the development of jaw necrosis (Appendix I, II).

MRONJ Case Definition

In order to distinguish MRONJ from other delayed healing conditions and address evolving clinical observations and concerns about under-reporting of disease, the working definition of MRONJ has been modified from the 2009 *AAOMS Position Paper*:¹

Patients may be considered to have MRONJ if all of the following characteristics are present:

1. Current or previous treatment with antiresorptive or antiangiogenic agents;
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks; and
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

It is important to understand that patients at risk for or with established MRONJ can also present with other common clinical conditions not to be confused with MRONJ.

Commonly misdiagnosed conditions may include, but are not limited to: alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology, fibro-osseous lesion, sarcoma, chronic sclerosing osteomyelitis, and TMJ disorders. It is also important to remember that ONJ occurs in patients not exposed to antiresorptive or antiangiogenic agents.

Pathophysiology

Although the first MRONJ case was reported over a decade ago, the pathophysiology of the disease has not been fully elucidated.^{24,25} A source of great debate among clinicians and researchers are the potential mechanisms underlying MRONJ pathophysiology.²⁹⁻³² Proposed hypotheses that attempt to explain the unique localization of MRONJ exclusively to the jaws include altered bone remodeling or oversuppression of bone resorption, angiogenesis inhibition, constant microtrauma, suppression of innate or acquired immunity, vitamin D deficiency, soft tissue BP toxicity, and inflammation or infection.^{29,33-40}

A. Inhibition of osteoclastic bone resorption and remodeling

Bisphosphonates (BP), and other antiresorptives such as denosumab, inhibit osteoclast differentiation and function, and increase apoptosis, all leading to decreased bone resorption and remodeling.⁴¹⁻⁴⁵ Osteoclast differentiation and function plays a vital role in bone healing and remodeling in all skeletal sites, but osteonecrosis of the jaws only occurs primarily within the alveolar bone of the maxilla and mandible.⁴⁶ An increased remodeling rate in the jaws may explain the differential predisposition to ONJ compared to other bones in the axial or appendicular skeleton. Long term studies in the large animal model demonstrate decreased intracortical bone turnover with dynamic histomorphometry.^{30,47} The central role of bone remodeling inhibition is further corroborated by a similar incidence of ONJ observed with other antiresorptive medications such as denosumab.⁴⁸⁻⁵⁰ Preliminary evidence exists demonstrating the improved extraction socket healing in animals receiving systemic zoledronic acid when treated with parathyroid hormone, possibly due to its positive effect on osteoclasts to increase bone remodeling.^{51,52}

B. Inflammation/Infection

Both systemic and local oral risk factors have been implicated in ONJ pathogenesis, where several human studies have implicated dental disease or bacterial

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infection.⁵³⁻⁵⁵ Although tooth extraction was performed in most of the initial reported cases of ONJ, these teeth commonly had existing periodontal or periapical disease.^{1,56-59} From these clinical studies, several animal models have been developed to demonstrate that both inflammation or bacterial infection and systemic antiresorptives are sufficient to induce ONJ.^{46,60-64}

Inflammation or infection has long been considered an important component of ONJ. Early studies identified bacteria, especially *Actinomyces* species, in biopsied specimens of necrotic bone removed in patients with ONJ.⁶⁵ The presence of bacteria has prompted studies to evaluate the possibility of a complex biofilm on exposed bone.⁶⁶ These studies have identified bacteria in combination with fungi and viruses, which may require more sophisticated therapies to combat the multiorganism ONJ-associated biofilm.⁶⁷⁻⁷⁰

C. Inhibition of Angiogenesis

Angiogenesis is a process that involves growth, migration and differentiation of endothelial cells to form new blood vessels. Angiogenesis favorably influences tumor growth and also influences tumor invasion of vessels, resulting in tumor metastasis. Angiogenesis requires binding of signaling molecules such as vascular endothelial growth factor (VEGF) to receptors on the endothelial cells. This signaling promotes new blood vessel growth.

Osteonecrosis is classically considered an interruption in vascular supply or avascular necrosis, and therefore, it is not surprising that inhibition of angiogenesis is a leading hypothesis in ONJ pathophysiology.^{30-32,71} In vitro experiments consistently demonstrate a reduction in angiogenesis in response to zoledronic acid.^{40,72} Studies in cancer patients treated with zoledronic acid support these data with decreased circulating VEGF levels.⁷³ Moreover, there is a growing body of literature linking osteonecrosis of the jaw and other bones in patients receiving novel antiangiogenic drugs (tyrosine kinase inhibitors and monoclonal antibody targeting VEGF). However, inhibition of angiogenesis has not been reported with denosumab.

D. Other Hypotheses

1. Soft tissue toxicity

Although BPs primarily target the osteoclast and bind to hydroxyapatite in bone, soft tissue toxicity has been reported.^{29,74} Multiple cell types underwent increased apoptosis or decreased proliferation after exposure to BPs in vitro including cervical, prostate, and oral epithelial cells.⁷⁵⁻⁷⁷ Since BPs are excreted renally after only a few hours in the circulation, their concentration in tissues outside bone is minimal.⁷⁸ In contrast to BP's, no soft tissue toxicity has been reported with denosumab.

2. Innate or acquired immune dysfunction

The first animal model could not consistently induce ONJ unless BPs were combined with steroids in a tooth extraction defect.³⁷ Since then, many other studies showed mucosal ulceration, delayed healing, exposed bone, and histologic necrosis and inflammation when BPs and chemotherapy are administered in rodents undergoing extractions.^{34,63,79,80}

As described above, many hypotheses exist, and many of the animal models above show evidence that the disease may be multifactorial. To begin to develop effective therapies for patients with ONJ, clinically relevant animal models are paramount. Whether it is early diagnosis, prevention, or targeted therapy, therapeutic strategies cannot be developed or tested without these models. As more studies uncover the mechanisms, large animal models will be critical in closely replicating human MRONJ with frank bone exposure and stage 0 disease.

Risk factors for MRONJ

A. Medication-related risk factors

To interpret MRONJ disease frequency estimates, two parameters need to be considered: therapeutic indications and type of medications. The therapeutic indications are grouped into two categories: osteoporosis/osteopenia or malignancy. Medications will be grouped into two categories, BP and non-BP (other antiresorptive or antiangiogenic medications). Disease frequency will be reported as incidence (number of new cases per sample [or population] per unit time) or prevalence (number of cases in the sample [or population] reported as a percentage).

Given the proliferation of data since MRONJ was originally reported in 2003, the committee has tried

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to limit the inclusion of studies to: 1) those published since the last report (2009), 2) studies with the highest levels of evidence for the available topic, eg systematic reviews of several randomized control trials (RCTs) or prospective cohort studies, individual RCTs, prospective cohort studies, retrospective cohort studies, or case-control studies, and 3) studies with clinical ascertainment of MRONJ. Older studies, case reports and case series, and studies that rely on medical record review or insurance-claim data were excluded from analyses.

Due to the low frequency of disease, studies with small samples (<500 subjects) need to be interpreted cautiously. It is particularly challenging to obtain good estimates of disease frequency when studying low frequency events, ie cases of MRONJ. Consistently, as the sample size increases, MRONJ disease frequency estimates get smaller. Therefore when reviewing the literature cited below, the reader should weight more heavily studies with large sample sizes than a comparable study with a smaller sample size (ie disease estimates of a study with a sample size of 10,000 should be weighted more heavily than a study with 500 subjects).

1. MRONJ risk among cancer patients

To measure the risk for ONJ among patients exposed to a medication, we must know the risk for ONJ in patients *not exposed* to antiresorptive or antiangiogenic medications. **The risk for ONJ among cancer patients enrolled in clinical trials and assigned to *placebo* groups ranges from 0% to 0.019% (0-1.9 cases per 10,000 cancer patients).**⁸¹⁻⁸³

Among cancer patients exposed to zoledronate, the cumulative incidence of MRONJ is in the low single digits (range = 0.7% - 6.7%).^{82,84} When limited to studies with Level 1 evidence, ie systematic reviews or RCTs, the risk of MRONJ in subjects exposed to zoledronate approximates 1% (100 cases per 10,000 patients).^{81-83,85} **The risk of ONJ among cancer patients exposed to zoledronate ranges between 50-100 times higher than cancer patients treated with placebo.**

Among cancer patients exposed to denosumab, a RANK L inhibitor, the risk of MRONJ ranges from 0.7% - 1.9% (70-90 cases per 10,000 patients).^{81,85}

The risk for ONJ among cancer patient exposed to denosumab is comparable to the risk of ONJ in patients exposed to zoledronate.^{22,23,86}

The risk for ONJ among cancer patients exposed to bevacizumab, an antiangiogenic agent, is 0.2%. (20 cases per 10,000).⁸⁷ The risk may be higher among patients exposed to both bevacizumab and zoledronate, 0.9% (90 cases per 10,000).⁸⁷

There are several case reports describing jaw necrosis in cancer patients receiving targeted therapies, specifically tyrosine kinase inhibitors (TKIs) and monoclonal antibody targeting VEGF.⁸⁸⁻⁹⁰ In 2009 Brunello and colleagues reported consecutive episodes of ONJ, characterized by cutaneous fistula and bone sequestration, in a patient with renal cell carcinoma treated with bisphosphonates and the tyrosine kinase inhibitor (TKI) sunitinib.⁹¹ Disease improved after discontinuation of sunitinib and then rapidly worsened with resumption of sunitinib. The investigators hypothesized “that the antiangiogenic activity of sunitinib may amplify the inhibition of bone remodeling exerted by amino bisphosphonates entrapped within the osteonecrotic matrix, antagonize mucosal healing and expose to infections during treatment.” Subsequent reports have highlighted the potential additive toxic effect of antiangiogenic drugs (TKIs and monoclonal antibody targeting VEGF) in patients receiving or having a history of bisphosphonate medication use.^{87,92-98} Beuselink, et al, reported an overall incidence of ONJ to be 10% in renal cell carcinoma patients with bone metastasis treated with oral TKIs and concomitant bisphosphonates.⁹⁷ They concluded that the combined use of bisphosphonates and TKIs in renal cell carcinoma patients with bone involvement probably improves treatment efficacy but is associated with a high incidence of ONJ. Smidt-Hansen, et al, in a retrospective study of renal cell carcinoma patients who received zoledronic acid and sirolimus found that patients who developed ONJ had a significantly improved median survival of 31.6 months compared to 14.5 months in patients without ONJ.⁹⁸

Moreover, there have been multiple case reports detailing the development of ONJ in patients receiving these targeted antiangiogenic therapies who are bisphosphonate naïve.⁸⁸⁻⁹⁰ These case reports underscore the potential for novel medications such

as TKIs and VEGF inhibitors being implicated in the development of ONJ in the absence of concomitant antiresorptive medication use.

This preliminary level of evidence supporting the association of antiangiogenic medications with the development of jaw necrosis is primarily based on case reports (Level V evidence). While the FDA has issued an ONJ advisory only for bevacizumab and sunitinib^{99,100} the committee remains concerned about a similar potential risk associated with several other medications within the same drug class which have a similar mechanism of action. Further controlled, prospective studies will be required to characterize the risk of jaw necrosis associated with these agents.

2. MRONJ risk among osteoporosis patients

Most dentists and oral and maxillofacial surgeons see patients in their practices who have been exposed to antiresorptive therapy, eg oral BPs, for management of osteoporosis. When evaluated by age, 5.1 million patients over the age of 55 years received a prescription for a bisphosphonate in year 2008. A recent federal study estimated that the prevalence of BP exposure was 7 for every 100 US population receiving a prescription for a bisphosphonate in the outpatient setting for the treatment of osteoporosis.¹⁰¹ Ironically, the studies estimating MRONJ risk in this patient population have the weakest levels of evidence of the various study groups, eg survey or retrospective cohort studies with ascertainment of disease based on a combination of examination or review of medical records.¹⁰¹

2a. Risk for ONJ among osteoporotic patients exposed to oral BPs

In a survey study of over 13,000 Kaiser Permanent members, the prevalence of BRONJ in patients receiving long-term oral bisphosphonate therapy was reported at 0.1% (10 cases per 10,000) which increased to 0.21 (21 cases per 10,000) among patients with greater than 4 years of oral BP exposure.¹⁰² Felsenberg and Hoffmeister reported a prevalence of MRONJ among patients treated with



bisphosphonates for osteoporosis of 0.00038% (<1 case per 100,000 exposed), based on reports of 3 cases to the German Central Registry of Necrosis of the Jaw.¹⁰³ In a more recent report, Malden, et al, derived an incidence of 0.004% (0.4 cases per 10,000 patient-years of exposure to alendronate) from 11 cases of MRONJ reported in a population of 90,000 people living in southeast Scotland.¹⁰⁴

2b. MRONJ risk among osteoporotic patients exposed to IV BP or RANK-L inhibitors

Studies analyzing patients with osteoporosis exposed to yearly zoledronate therapy for 3 years reported a risk for MRONJ of 0.017% (1.7 cases per 10,000 subjects).¹⁰⁵ An extension of this study through 6 years did not demonstrate a change in frequency of MRONJ.¹⁰⁶ In recent reports studying patients exposed to denosumab, the risk for MRONJ is 0.04% (4 cases per 10,000 subjects).²¹ Interestingly, among patients with osteoporosis exposed to placebo medications, the risk for ONJ ranges from 0% to 0.02% (0-2 cases per 10,000 subjects).^{21,105} **The risk for ONJ among patients treated with either zoledronate or denosumab (0.017 – 0.04%) approximates the risk for ONJ of patients enrolled in placebo groups (0%-0.02%).**

Based on this current review of data, the risk of developing ONJ among osteoporotic patients exposed to oral, IV BPs, or denosumab is real but remains very low. The frequency of cases reported in the population (albeit very small) is best explained by the large number of patients, 5.1 million over the age of 55, exposed to these drugs.¹⁰⁷

3. Duration of medication therapy as a risk factor for MRONJ

Regardless of indications for therapy, the *duration of BP or antiresorptive therapy* continues to be a risk factor for developing ONJ. Among cancer patients exposed to zoledronate or denosumab, the incidence of developing ONJ was, respectively, 0.6 and 0.5% at 1 year, 0.9 and 1.1% at 2 years, and 1.3 and 1.1% at 3 years with the risk for ONJ among denosumab-exposed subjects plateauing between years 2 and 3.⁸⁶ In a study by Saad, et al, the investigators combined three-blinded phase three trials and found similar results, including a plateau after 2-years for patients exposed to denosumab.¹⁰⁸ Among cancer patients exposed to zoledronate or denosumab (n=5723), the incidence of developing

ONJ was, respectively, 0.5 and 0.8% at 1 year, 1.0 and 1.8% at 2 years, and 1.3 and 1.8% at 3 years.⁸⁶

For patients receiving oral bisphosphonate therapy to manage osteoporosis, the prevalence of ONJ increases over time from near 0 at baseline to 0.21% after four or more years of BP exposure (see Figure 1). The median duration of BP exposure for patients with ONJ and ONJ-like features was 4.4 years. For patients without ONJ, the median exposure to oral BPs was 3.5 years.^{101,102}

When compared to cancer patients receiving antiresorptive treatment, the risk of ONJ for patients with osteoporosis exposed to antiresorptive medications is about 100 times smaller.

B. Local factors

1. Operative treatment

Dentoalveolar surgery is considered a major risk factor for developing MRONJ. Several studies report that among patients with MRONJ, tooth extraction is a common predisposing event ranging from 52 to 61% of patients reporting tooth extraction as the precipitating event.^{84,108,109} In a case-control study among cancer patients exposed to zoledronate, tooth extraction was associated with a 16-fold increased risk for ONJ when compared to cancer patients without ONJ (odds ratio [OR] = 16.4; 95% confidence interval [CI], 3.4 – 79.6).¹¹⁰ In a longitudinal cohort study in a sample of cancer patients exposed to intravenous BPs (predominately zoledronate), tooth extraction was associated with a 33-fold increased risk for ONJ.⁸⁴

The above information, while important, is not what most patients or clinicians want to know. Most clinicians and patients want to know: “Among patients exposed to antiresorptive medications, what is the risk for developing ONJ following tooth extraction (or other dentoalveolar procedures such as implant placement or periodontal procedures)?” The best current estimate for the risk of ONJ among patients exposed to oral bisphosphonates following tooth extraction is 0.5%.¹¹¹ The estimate was derived from a prospective evaluation of 194 patients exposed to



oral BPs that underwent extraction of > 1 tooth. In this sample, one patient developed ONJ after tooth extraction.

Estimates for developing ONJ after tooth extraction among cancer patients exposed to intravenous BPs ranges from 1.6 to 14.8%. In a retrospective cohort study composed of a sample of cancer patients exposed to zoledronate (n=27), 4 (14.8%) subjects develop ONJ after tooth extraction.¹¹² In a prospective cohort study composed of 176 subjects with cancer who were exposed to zoledronate, 5 (2.8%) developed ONJ.¹¹³ In a prospective cohort study of 63 subjects with a history of cancer and intravenous BP exposure who underwent extraction of > 1 tooth, one subject (1.6%) developed ONJ.¹¹⁴ Among the studies reported above, the prospective studies should be weighted more heavily due to the larger sample sizes and the prospective, not retrospective, study designs.

The risk of developing ONJ among patients who have been exposed to antiresorptive medications for other dentoalveolar operations such as dental implant placement and endodontic or periodontal procedures is unknown. Absent data, the committee considers the risk for ONJ after dental implant placement and endodontic or periodontal procedures that require exposure and manipulation of bone to comparable to the risk associated with tooth extraction.

2. Anatomic factors

Limited new information regarding anatomic risk factors for MRONJ is available. MRONJ is more likely to appear in the mandible (73%) than the maxilla (22.5%) but can appear in both jaws (4.5%).¹⁰⁸ Denture use was associated with an increased risk for ONJ among cancer patients exposed to zoledronate (OR = 4.9; 95% CI = 1.2 – 20.1).¹¹⁰ In a study by Vahtsevanos, et al, a sample of 1,621 cancer patients treated with intravenous zoledronate, ibandronate, or pamidronate, there was a 2-fold increased risk for ONJ among denture wearers.⁸⁴

3. Concomitant oral disease

Pre-existing inflammatory dental disease such as periodontal disease or periapical pathology is a well-recognized risk factor.^{112,115} Among cancer patients with MRONJ, pre-existing inflammatory dental disease was a risk factor among 50% of the cases.^{108,112} Given that a common treatment of

inflammatory dental disease is tooth extraction, pre-existing dental disease may confound the relationship between tooth extraction and risk for MRONJ noted above. It would be valuable to see an estimate of the association between tooth extraction and MRONJ adjusted for pre-existing inflammatory dental disease.

C. Demographic and systemic factors and other medication factors

Age and sex are variably reported as risk factors for MRONJ.^{84,108,110,112,115} The higher prevalence of this complication in the female population is likely a reflection of the underlying disease for which the agents are being prescribed (ie osteoporosis, breast cancer). There are very limited data describing the occurrence of MRONJ in the pediatric population. In an observational study, Brown, et al, reviewed a total of 42 pediatric patients who had received IV bisphosphonate therapy (mean duration of therapy 6.5 years) for a variety of metabolic bone diseases. No cases of ONJ were reported despite invasive dental treatment in 11 patients.¹¹⁶ The risk of developing MRONJ in the pediatric population certainly requires more complete investigation.

Corticosteroids are associated with an increased risk for MRONJ.^{108,115} Antiangiogenic agents, when given in addition to antiresorptive medications, are associated with an increased risk of ONJ.^{87,108}

Co-morbid conditions among cancer patients that are inconsistently reported to be associated with an increased risk for MRONJ include anemia (hemoglobin < 10g/dL) and diabetes.^{108,115} Cancer type is also variably reported as a risk factor.^{81,84}

Tobacco use has been inconsistently reported as a risk factor for MRONJ. In a case-control study, tobacco use approached statistical significance as a risk factor for ONJ in cancer patients (OR=3.0; 95% CI= 0.8 - 10.4).¹¹⁰ In a more recent case-controlled study, tobacco use was not associated with ONJ in a sample of cancer patients exposed to zoledronate.¹¹⁵ Vahtsevanos did not report an association between tobacco use and MRONJ.⁸⁴

D. Genetic factors

Since the previous position paper there have been several reports describing single nucleotide polymorphisms (SNPs) that were associated with the development MRONJ. Most of these SNPs were located within regions of the gene associated with either bone turnover, collagen formation, or certain metabolic bone diseases. Katz reported an ONJ event rate of 57% when SNPs were present in 5 candidate genes that were responsible for bone turnover.¹¹⁷ In a genome wide study, Nicoletti reported that patients with an SNP in the RBMS3 gene (associated with bone density and collagen formation) were 5.8 times more likely to develop ONJ.¹¹⁸ In a study that analyzed polymorphisms related to farnesyl diphosphate synthase activity (the enzyme specifically inhibited by bisphosphonates) a positive correlation was established with the carrier status and ONJ.¹¹⁹ Collectively, these studies suggest that a germ line sensitivity to bisphosphonates may exist.

In summary, the current literature reaffirms that the risk of MRONJ is significantly greater in cancer patients receiving antiresorptive therapy as compared to treatment regimens for osteoporosis. Moreover, the risk of MRONJ in osteoporosis patients receiving antiresorptive therapy continues to be very low regardless of drug type (bisphosphonates, denosumab) or dosing schedule. Targeted cancer therapies (VEGF and tyrosine kinase inhibitors) are also associated jaw necrosis but further studies with these medications are warranted.

Management Strategies for Patients Treated with Antiresorptives or Antiangiogenics

1. Prevention of MRONJ

The AAOMS Special Committee on MRONJ supports a multi-disciplinary approach to the treatment of patients who benefit from antiresorptive or antiangiogenic medications. This approach would include consultation with an appropriate dental professional when it is determined a patient would benefit from an antiresorptive or antiangiogenic drug. There is considerable support for early screening and initiation of appropriate dental care, which not only decreases the incidence of ONJ but would also accrue the benefits that all patients enjoy with optimum oral health.^{32,87,98,109,110,120-136}

The implementation of dental screening and appropriate dental measures before initiating antiresorptive therapy reduced the risk of ONJ in several prospective studies when compared in a

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retrospective fashion to patients who did not undergo dental preventive measures.^{53,55,108,137,138}

Dimopoulos found a statistically significant, almost threefold reduction in the incidence of osteonecrosis in patients when preventive measures were applied.⁵³ Bonacina did not report any new cases of ONJ in patients who received dental screening and necessary dental treatment before initiating IV bisphosphonate treatment.¹³⁷ Vandone found the incidence rate of developing ONJ was reduced by 50% in patients who were screened and received preventive dental care before initiating drug therapy.¹³⁸

Treatment planning for patients who may be prescribed antiresorptive or antiangiogenic therapy should include thorough examination of the oral cavity and a radiographic assessment when indicated. It is important to identify both acute infection and sites of potential infection to prevent future sequelae that could be exacerbated once drug therapies begin. Considerations during the clinical and radiographic assessment include: patient motivation, patient education regarding dental care, fluoride application, chlorhexidine rinses, tooth mobility, periodontal disease, presence of root fragments, caries, periapical pathology, edentulism, and denture stability.¹³⁹

An additional benefit of early dental consultation when the use of antiresorptive or antiangiogenic therapy is being considered is that the patient is being informed of the low risk associated with these drug therapies and the risk incurred by not undergoing recommended dental preventive measures before consenting to treatment.

2. Cessation of at-risk medication therapy prior to tooth extraction or other procedures, which involve osseous injury (eg dental implant placement, periodontal or apical endodontic treatment)
 - a. Antiresorptive Therapy for Osteoporosis/Osteopenia

The concept of a drug holiday in individuals receiving oral bisphosphonates or denosumab who require tooth extractions has been an ongoing area of controversy with little data to support current recommendations. The *AAOMS Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw*,

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revised in 2009, recommended discontinuing oral bisphosphonates for 3 months prior to and 3 months following invasive dental surgery – systemic conditions permitting.¹ However there is currently no evidence that interrupting bisphosphonate therapy alters the risk of ONJ in patients following tooth extraction. In 2011 the ADA Council on Scientific Affairs revised their prior recommendation of a drug holiday and suggested that patients receiving lower cumulative doses of bisphosphonate (<2 years) or denosumab may continue antiresorptive therapy during invasive dental treatment.¹²⁶ An International ONJ Task Force recommended a drug holiday in patients at higher risk for developing ONJ, including those with greater cumulative bisphosphonate exposure (>4 years), and those with comorbid risk factors such as rheumatoid arthritis, prior or current glucocorticoid exposure, diabetes and smoking until the site has healed.¹⁴⁰ In a 2011 summary document on the long term safety of bisphosphonate therapy for osteoporosis, the FDA determined that there was “no substantial data available to guide decisions regarding the initiation or duration of a drug holiday.”¹⁰¹

Damm and Jones proposed several alternatives to a drug holiday in BP-exposed patients who require invasive dental treatment.¹⁴¹ While there are no studies to support these recommendations their approach is based on bone physiology and pharmacokinetics of the antiresorptive medications and merit consideration (Level 5 evidence). They note that since 50% of serum BP undergoes renal excretion the major reservoir of BP is the osteoclast whose life span is 2 weeks. Thus the majority of free BP within the serum would be extremely low 2 months following the last dose of an oral bisphosphonate and a 2-month drug free period should be adequate prior to an invasive dental procedure.

This committee recognized that there are limited data to support or refute the benefits of a drug holiday for osteoporosis patients receiving antiresorptive therapy. However, a theoretical benefit may still apply for those patients with extended exposure histories (>4 yrs). Therefore the committee considers the modified drug holiday strategy as described by Damm and Jones to be a prudent approach for those patients at risk.¹⁴¹

b. Oncology Patients Receiving Monthly Antiresorptive Therapy

Individuals receiving monthly intravenous bisphosphonates or denosumab for treatment of oncologic disease have an increased risk of developing ONJ following tooth extraction and thus these procedures should be avoided if possible. Increased awareness, preventive dental care and early recognition of the signs and symptoms of ONJ have resulted in earlier detection. Data are scant regarding the effect of discontinuing intravenous bisphosphonates prior to invasive dental treatments should these be necessary. However, if ONJ develops the oncologist may consider discontinuing antiresorptive therapy until soft tissue closure has occurred, depending on disease status.

As a fully humanized antibody, denosumab blocks the receptor-mediated activation of osteoclasts and has no binding affinity for bone matrix. Therefore, unlike bisphosphonates, the antiresorptive effects of denosumab should be mostly dissipated within 6 months of stopping the drug. However, there are no studies to support or refute the strategy of stopping denosumab therapy in the prevention or treatment of MRONJ.

There are no data to support or refute the cessation of antiangiogenic therapy in the prevention or management of MRONJ and therefore continued research in the area is indicated.

Treatment Goals

The major goals of treatment for patients at risk of developing or who have MRONJ are:

- Prioritization and support of continued oncologic treatment in patients receiving IV antiresorptive and antiangiogenic therapy.
 - o Oncology patients can benefit greatly from the therapeutic effect of antiresorptive therapy by controlling bone pain and reducing the incidence of other skeletal complications
 - o The antiangiogenic class of chemotherapy agents have demonstrated efficacy in the treatment of a variety of malignancies with proven survival benefits

- Preservation of quality of life through:
 - o Patient education and reassurance
 - o Control of pain
 - o Control of secondary infection
 - o Prevention of extension of lesion and development of new areas of necrosis

Management Strategies

A. *Patients about to initiate intravenous antiresorptive or antiangiogenic treatment for cancer therapy*

The treatment objective for this group of patients is to minimize the risk of developing MRONJ. Although a small percentage of patients receiving antiresorptives develop osteonecrosis of the jaw spontaneously, the majority of affected patients experience this complication following dentoalveolar surgery.^{108,112,142-144} Therefore if systemic conditions permit, initiation of antiresorptive therapy should be delayed until dental health is optimized.^{53,55,145} This decision must be made in conjunction with the treating physician and dentist and other specialists involved in the care of the patient.

Non-restorable teeth and those with a poor prognosis should be extracted. Other necessary elective dentoalveolar surgery should also be completed at this time. Based on experience with osteoradionecrosis, it appears advisable that antiresorptive or antiangiogenic therapy should be delayed, if systemic conditions permit, until the extraction site has mucosalized (14-21 days) or until there is adequate osseous healing. Dental prophylaxis, caries control and conservative restorative dentistry are critical to maintaining functionally sound teeth. This level of care must be continued indefinitely.

Patients with full or partial dentures should be examined for areas of mucosal trauma, especially along the lingual flange region. It is critical that patients be educated as to the importance of dental hygiene and regular dental evaluations, and specifically instructed to report any pain, swelling or exposed bone.

Medical oncologists should evaluate and manage patients scheduled to receive IV antiresorptive or antiangiogenic therapy similar to those patients scheduled to initiate radiation therapy to the head and neck. The osteoradionecrosis prevention protocols are guidelines that are familiar to most oncologists and general dentists.

B. *Patients about to initiate antiresorptive treatment for osteoporosis*

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At the initiation of treatment, patients should be educated as to the potential risks of MRONJ as the antiresorptive therapy is likely to exceed beyond 4 years treatment. The importance of optimizing dental health throughout this treatment period and beyond should be stressed.

C. *Asymptomatic patients receiving intravenous bisphosphonates or antiangiogenic drugs for cancer*

Maintaining good oral hygiene and dental care is of paramount importance in preventing dental disease that may require dentoalveolar surgery. Procedures that involve direct osseous injury should be avoided. Non-restorable teeth may be treated by removal of the crown and endodontic treatment of the remaining roots.¹⁴⁶ Placement of dental implants should be avoided in the oncology patient receiving intravenous antiresorptive therapy or antiangiogenic medications. There is no data regarding the risk of ONJ associated with implant placement in patients receiving antiangiogenic medications.

D. *Asymptomatic patients receiving antiresorptive therapy for osteoporosis*

Sound recommendations based on strong clinical research designs are still lacking for patients taking oral bisphosphonates. The committee strategies outlined below have been updated from those in the original *Position Paper* and are based on clinical studies that demonstrate a low prevalence of disease. The risk of developing MRONJ associated with oral bisphosphonates increased when duration of therapy exceeded four years.¹⁰² Although the current level of evidence is not strong, the committee continues to consider these strategies for patients receiving oral bisphosphonates as a prudent set of guidelines that will not compromise the long-term management of their osteoporosis. As more data become available and a better level of evidence is obtained, these strategies will be updated and modified as necessary.

Patients receiving antiresorptive therapy for osteoporosis are also at risk for developing MRONJ, but to a much lesser degree than those treated with intravenous antiresorptive therapy.^{101,102} MRONJ can develop



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spontaneously or after minor trauma. In general, these patients seem to have less severe manifestations of necrosis and respond more readily to stage specific treatment regimens.^{147,148} Elective dentoalveolar surgery does not appear to be contraindicated in this group. It is recommended that patients be adequately informed of the very small risk (<1%) of compromised bone healing. The risk of developing MRONJ associated with oral bisphosphonates, while exceedingly small, appears to increase when the duration of therapy exceeds 4 years.¹⁰¹ This time frame may be shortened in the presence of certain comorbidities, such as chronic corticosteroid or antiangiogenic use.^{87,108,115} If systemic conditions permit, the clinician may consider discontinuation of oral bisphosphonates for a period of two months prior to and three months following elective invasive dental surgery in order to lower the risk of MRONJ. The rationale for this approach is based on extrapolated data that demonstrate fluctuations of osteoclast function, which is related to bisphosphonate therapy, and recent outcomes studies that show improved outcome of MRONJ treatment with drug cessation.¹⁴¹

The efficacy of utilizing a systemic marker of bone turnover to assess the risk of developing jaw necrosis in patients at risk has not been validated.^{111,149-153} Therefore the use of systemic markers of bone turnover as a measure of MRONJ risk is not recommended although the Committee supports continued research in this area.^{53,55,145,154}

1. *For individuals who have taken an oral bisphosphonate for less than four years and have no clinical risk factors*, no alteration or delay in the planned surgery is necessary. This includes any and all procedures common to oral and maxillofacial surgeons, periodontists and other dental providers.

It is suggested that if dental implants are placed, informed consent should be provided related to possible long-term implant failure and the low risk of developing osteonecrosis of the jaws if the patient continues to take an antiresorptive agent. These concerns are based on recent animal studies that have demonstrated impaired long-term implant healing.¹⁵⁵ Such patients should be placed on a regular recall schedule. It is also advisable to contact the provider who originally prescribed the oral bisphosphonate and suggest monitoring such patients and considering either alternate dosing of the bisphosphonate, drug holidays, or an alternative to the bisphosphonate therapy.

2. *For those patients who have taken an oral bisphosphonate for less than four years and have also taken corticosteroids or antiangiogenic medications concomitantly*, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least two months prior to oral surgery, if systemic conditions permit. The antiresorptive should not be restarted until osseous healing has occurred. These strategies are based on reports that corticosteroid and antiangiogenic agents, in combination with antiresorptive therapy, may increase the risk of developing MRONJ and that a drug holiday may mitigate this risk. Long-term, prospective studies however are still required to establish the efficacy of drug holidays in reducing the risk of MRONJ for these patients.
3. *For those patients who have taken an oral bisphosphonate for more than four years with or without any concomitant medical therapy*, the prescribing provider should be contacted to consider discontinuation of the antiresorptive for two months prior to oral surgery, if systemic conditions permit. The bisphosphonate should not be restarted until osseous healing has occurred. The risk of long-term oral bisphosphonate therapy requires continued analysis and research.

E. Patients with established MRONJ

Treatment objectives for patients with an established diagnosis of MRONJ are to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone necrosis. Patients with established MRONJ should avoid elective dentoalveolar surgical procedures, since these surgical sites may result in additional areas of exposed necrotic bone.

Since the publication of the 2009 guidelines there have been several reports of successful treatment outcomes for all stages of MRONJ following operative therapy (sequestrectomy, resection)^{148,156-160} and non-operative therapy.¹⁶¹⁻¹⁶⁵ Except for the more advanced cases of Stage 3 disease or in those cases with a well-defined



sequestrum, it appears that a more prudent approach would be to consider operative therapies when non-operative strategies have failed.^{161,163} Regardless of the stage of disease, areas of necrotic bone that are a constant source of soft tissue irritation and loose bony sequestra should be removed or recontoured so that soft tissue healing can be optimized.¹⁶⁶ The extraction of symptomatic teeth within exposed, necrotic bone should be considered, since it appears unlikely that the extraction will exacerbate the established necrotic process.

A randomized controlled trial of hyperbaric oxygen therapy (HBO) as an adjunct to non-surgical and surgical treatment of MRONJ demonstrated some improvement in wound healing, long-term pain scores and quality of life scores.^{167,168} However given the small sample size, there was no statistically significant difference between the control and HBO group with regard to complete gingival coverage which was a major study endpoint. Therefore the use of HBO as the sole treatment modality for MRONJ cannot be supported at this time.

Case reports with small sample sizes have documented the use of other non-surgical treatment strategies, such as platelet rich plasma,^{169,170} low-level laser irradiation,^{128,171,172} parathyroid hormone¹⁷³, and bone morphogenic protein.^{169,174} The efficacy of these treatment modalities needs to be established through additional research and controlled studies.

Staging and Treatment Strategies (See Table 1)

1. Staging

Modifications in the staging system are necessary to ensure that it remains an accurate reflection of disease presentation and to assist in the appropriate stratification of patients. A Stage 0 category was added in 2009 to include patients with non-specific symptoms, or clinical and radiographic abnormalities that may be due to exposure to an antiresorptive agent. At that time the risk of a patient with Stage 0 disease advancing to a higher disease stage was unknown. Since then several case studies have reported that up to 50% of patients with Stage 0 have progressed to Stage 1, 2 or 3.^{175,176} Therefore, it appears that Stage 0 may be a valid disease category that captures patients with prodromal disease (non-exposed variant). Also, the definition of exposed bone was broadened (see above) to include the presence of cutaneous or mucosal fistulae that probe to bone for Stage 1, 2 and 3 categories. Other research groups have proposed including radiographic signs alone, eg scler-

rosis, persistent extraction sockets, etc, to define a case of MRONJ.^{177,178} The Special Committee members recognize the potential benefits and risks of diagnosing MRONJ based on radiographic signs alone. The Special Committee elected to not use radiographic signs alone in the case definition. The committee members accepted the consequence that the current case definition may underestimate the true frequency of the disease. Revising the definition to include cases with radiographic signs alone may overestimate the true disease frequency by including false positives in the numerator, eg cases with radiographic findings suggestive of MRONJ, but are not MRONJ.

In order to direct rational treatment guidelines and collect data to assess the prognosis in patients who have used either IV or oral antiresorptive and antiangiogenic agents, the Committee proposes use of the following revised staging system:

Patients at risk

No apparent necrotic bone in asymptomatic patients who have been treated with IV or oral antiresorptive or antiangiogenic therapy

Stage 0 (Non-exposed bone variant)

Patients with no clinical evidence of necrotic bone, but present with non-specific symptoms or clinical *and* radiographic findings, such as,

Symptoms

- odontalgia not explained by an odontogenic cause
- dull, aching bone pain in the body of the mandible, which may radiate to the temporomandibular joint region
- sinus pain, which may be associated with inflammation and thickening of the maxillary sinus wall
- altered neurosensory function

Clinical Findings

- loosening of teeth not explained by chronic periodontal disease
- periapical/periodontal fistula that is not associated with pulpal necrosis due to caries



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Radiographic Findings

- alveolar bone loss or resorption not attributable to chronic periodontal disease
- changes to trabecular pattern—dense woven bone and persistence of unremodeled bone in extraction sockets
- regions of osteosclerosis involving the alveolar bone and/or the surrounding basilar bone
- thickening/obscuring of periodontal ligament (thickening of the lamina dura and decreased size of the periodontal ligament space)¹⁵³

These non-specific findings, which characterize this non-exposed variant of ONJ, may occur in patients with a prior history of Stage 1, 2, or 3 disease who have healed and have no clinical evidence of exposed bone.

Stage 1

Exposed and necrotic bone, or fistulae that probe to bone, in patients who are asymptomatic and have no evidence of infection. These patients may also present with radiographic findings mentioned for Stage 0 which are localized to the alveolar bone region.

Stage 2

Exposed and necrotic bone, or fistulae that probe to bone, with evidence of infection. These patients are typically symptomatic. These patients may also present with radiographic findings mentioned for Stage 0 which are localized to the alveolar bone region.

Stage 3

Exposed and necrotic bone, or fistulae that probe to bone, with evidence of infection, and one or more of the following:

- exposed necrotic bone extending beyond the region of alveolar bone, ie, inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla
- pathologic fracture
- extra-oral fistula
- oral antral/oral nasal communication
- osteolysis extending to the inferior border of the mandible or sinus floor

2. Stage-Specific Treatment Strategies

At risk – Patients who are at risk of developing MRONJ due to an exposure history with an antiresorptive or an antiangiogenic drug. They do not have exposed bone nor do they require any treatment. However, these patients should be informed of the risks of developing MRONJ, as well as the signs and symptoms of this disease process.

Stage 0 – Provide symptomatic treatment, and conservatively manage other local factors, such as caries and periodontal disease. Systemic management may include the use of medication for chronic pain and control of infection with antibiotics, when indicated. These patients will require close monitoring given the potential for progression to a higher stage of disease. Among patients with radiographic signs alone suggesting Stage 0, (see above), the committee recommends close monitoring for progression to a higher stage of disease. Other diagnoses, eg fibro-osseous disease, chronic sclerosing osteomyelitis should also be considered.

Stage 1 – These patients benefit from medical management including the use of oral antimicrobial rinses, such as chlorhexidine 0.12%. No immediate operative treatment is required.

Stage 2 – These patients benefit from the use of oral antimicrobial rinses in combination with antibiotic therapy. Although local bone and soft tissue infection is not considered the primary etiology for this process, the colonization of the exposed bone is a very common occurrence. Most of the isolated microbes have been sensitive to the penicillin group of antibiotics. Quinolones, metronidazole, clindamycin, doxycycline and erythromycin have been used with success in those patients who are allergic to penicillin. Microbial cultures should also be analyzed and the antibiotic regimen should be adjusted accordingly. Biofilm formation on the surface of the exposed bone has been reported in several reports and may be responsible for the failure of systemic antibiotic therapies that are described in some refractory cases.^{66,70,179} In such cases, operative therapy directed at reducing the volume of colonized, necrotic bone may serve as a beneficial adjunct to antibiotic therapy.



Stage 3 – These patients benefit from debridement, including resection, in combination with antibiotic therapy, which may offer long-term palliation with resolution of acute infection and pain. Symptomatic patients with stage 3 disease may require resection and immediate reconstruction with a reconstruction plate or an obturator. The potential for failure of the reconstruction plate because of the generalized effects of the bisphosphonate exposure needs to be recognized by the clinician and patient. Case reports with small sample sizes describe successful immediate reconstruction with vascularized bone.¹⁸⁰⁻¹⁸²

Regardless of the disease stage, mobile bony sequestra should be removed to facilitate soft tissue healing. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process. A thorough histologic analysis is indicated for all resected bone specimens (especially for patients with a history a malignant disease) since metastatic cancer has been reported in such specimens.¹⁸³

Table 1 Staging and Treatment Strategies

MRONJ† Staging	Treatment Strategies‡
At risk category No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	<ul style="list-style-type: none"> • No treatment indicated • Patient education
Stage 0 No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms	<ul style="list-style-type: none"> • Systemic management, including the use of pain medication and antibiotics
Stage 1 Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2 Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	<ul style="list-style-type: none"> • Symptomatic treatment with oral antibiotics • Oral antibacterial mouth rinse • Pain control • Debridement to relieve soft tissue irritation and infection control
Stage 3 Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone,(i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer term palliation of infection and pain

† Exposed or probable bone in the maxillofacial region without resolution for greater than 8 weeks in patients treated with an antiresorptive and/or an antiangiogenic agent who have not received radiation therapy to the jaws.

‡ Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.

Future Research

The National Institutes of Health have provided funding opportunities for research on the pathophysiology of bisphosphonate-associated osteonecrosis of the jaw.¹⁸⁴ This has resulted in multiple research efforts focusing on several facets of this disease entity that have occurred since the last position paper. These studies are responsible for many of the new data and information that was presented in this paper. Areas of continued investigation include, but are not limited to: 1) analysis of alveolar bone hemostasis and the response to antiresorptive therapies; 2) the role of novel antiangiogenic medications and their effects on jaw bone healing; 3) pharmacogenetic research; 4) development of valid MRONJ risk assessment tools; 5) animal studies to validate existing and proposed treatment and prevention strategies.

Continued governmental and institutional support is required in order to further elucidate the underlying pathophysiological mechanisms of MRONJ at the cellular and molecular level. Moreover, improved strategies for the prevention, risk reduction, and treatment of MRONJ need to be developed further so that more accurate judgments about risk, prognosis, treatment selection, and outcome can be established for patients with MRONJ.

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DISCLAIMER

The American Association of Oral and Maxillofacial Surgeons (AAOMS) is providing this position paper on Medication Related Osteonecrosis of the Jaw (MRONJ) to inform practitioners, patients and other interested parties. The position paper is based on a review of the existing literature and the clinical observations of a Special Committee composed of oral and maxillofacial surgeons, oral pathologists, and oncologists experienced in the diagnosis, surgical and adjunctive treatment of diseases, injuries and defects involving both the functional and esthetic aspects of the hard and soft tissues of the oral and maxillofacial regions, epidemiologists, and basic researchers.

The position paper is informational in nature and is not intended to set any standards of care. AAOMS cautions all readers that the strategies described in the position paper are NOT practice parameters or guidelines and may NOT be suitable for every, or any, purpose or application. This position paper cannot substitute for the individual judgment brought to each clinical situation by the patient's oral and maxillofacial surgeon. As with all clinical materials, the position paper reflects the science related to MRONJ at the time of the paper's development, and it should be used with the clear understanding that continued research and practice may result in new knowledge or recommendations. AAOMS makes no express or implied warranty regarding the accuracy, content, completeness, reliability, operability, or legality of information contained within the position paper, including, without limitation, the warranties of merchantability, fitness for a particular purpose, and non-infringement of proprietary rights. In no event shall the AAOMS be liable to the user of the position paper or anyone else for any decision made or action taken by him or her in reliance on such information.

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Appendix I: Antiresorptive Preparations Commonly Used in the U.S.

	Primary Indication	Nitrogen Containing	Dose	Route
Alendronate (Fosamax [®])	Osteoporosis	Yes	10 mg/day 70 mg/week	Oral
Risedronate (Actonel [®])	Osteoporosis	Yes	5 mg/day 35 mg/week	Oral
Ibandronate (Boniva [®])	Osteoporosis	Yes	2.5 mg/day 150 mg/month	Oral
			3 mg every 3 months	IV
Pamidronate (Aredia [®])	Bone Metastases	Yes	90 mg/3 weeks	IV
Zoledronate (Zometa [®])	Bone Metastases	Yes	4 mg/3 weeks	IV
(Reclast [®])	Osteoporosis		5 mg/year	IV
Denosumab (Xgeva [®])	Bone metastases	No	120 mg/4 weeks	SQ
(Prolia [®])	Osteoporosis	Humanized monoclonal antibody	60 mg/6 months	SQ



Appendix II: Medications Used in the Treatment of Various Cancers that are Antiangiogenic or Targets of the Vascular Endothelial Growth Factor (VEGF) Pathway that have been Associated with Jaw Necrosis*.

Drug	Mechanism of action	Primary indication
Sunitinib (Sutent®)	Tyrosine kinase inhibitor	GIST, RCC, pNET
Sorafenib (Nexavar®)	Tyrosine kinase inhibitor	HCC, RCC
Bevacizumab (Avastin®)	Humanized monoclonal antibody	mCRC, NSCLC, Glio, mRCC
Sirolimus (Rapamune®)	Mammalian target of rapamycin pathway	Organ rejection in renal transplant

Abbreviations: GIST gastrointestinal stromal tumor; RCC renal cell carcinoma; pNET pancreatic neuroendocrine tumor, HCC hepatocellular carcinoma; mCRC metastatic colorectal carcinoma; NSCLC non-squamous non-small cell lung carcinoma; Glio Glioblastoma; mRCC metastatic renal cell carcinoma

* While the FDA has issued an ONJ advisory only for bevacizumab and sunitinib,^{99,100} the committee remains concerned about a similar potential risk associated with several other medications within the same drug class which have a similar mechanism of action. Therefore further controlled, prospective studies will be required to more fully characterize the risk of jaw necrosis associated with these agents.



Figure 1 – Frequency of ONJ Over Time¹⁰⁷

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drug/DrugSafetyandRiskManagementAdvisoryCommittee/UCM270958.pdf> (last accessed 4/7/2014) page 19.

Prevalence of ONJ by BP Duration

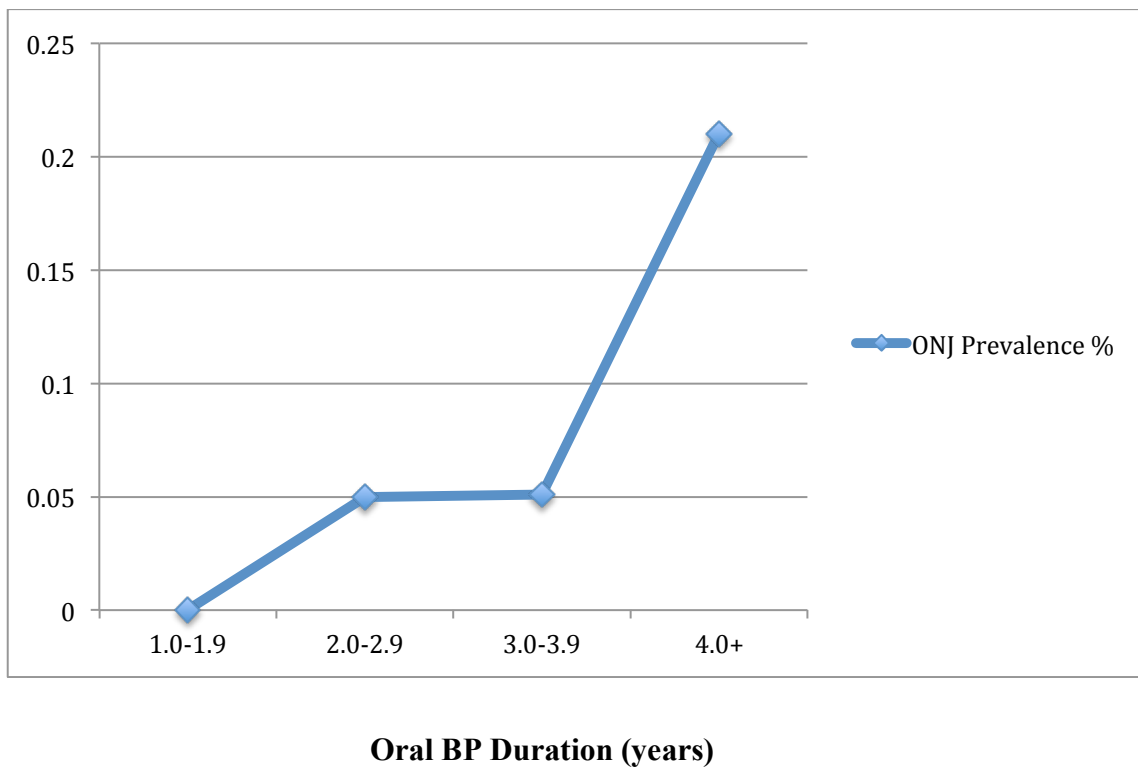




Figure 2 –

MRONJ Disease Frequency Grouped by Disease Status vs Medication Status

Medications

Indications for Treatment	Placebo	Zol²	Oral BP	Denosumab	Bevacizumab	Bevacizumab and Zolendronate	Study Design
Malignancy							
Guarneri, et al (2010)					0.2% (1076) ¹	0.9% (233)	Systematic Review
Qi, et al (2013)	0% (1450)	1.1% (2928)		1.9% (4585)			Systematic Review
Scagliotti, et al (2012)		0.8% (400)		0.7% (411)			RCT
Coleman, et al (2011)	0% (1675)	0.7% (1665)					RCT
Vahtsevanos, et al (2009)		6.7% (1163)					Prospective cohort study
Mauri, et al (2009)	0.019% (5382)	0.33% (3987)					Systematic Review
Osteoporosis							
Papapoulos, et al (2012)	0% (3383)			0.04% (4549)			RCT
Grbic, et al (2010)	0.020% (4945)	0.017% (5864)					Systematic Review
Malden, 2012			0.004% (90,000)				Prospective cohort study
Lo, 2010			0.1% ³ (8572)				Cross-sectional

¹Sample size in parentheses

²Zolendronate

³Prevalence estimate. All other frequencies reported in the figure are incidences.

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Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis

Executive summary of recommendations from the American Dental Association Council on Scientific Affairs

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This executive summary is based on a report developed by an advisory committee of the American Dental Association Council on Scientific Affairs following an appraisal of the literature identified by means of a systematic search.¹

The purpose of this report is to help dentists make treatment decisions based on the current best evidence when available, and on expert opinion when necessary, for patients being treated with antiresorptive agents (Table 1²). In an effort to improve the quality and efficiency of oral health care, the advisory committee compiled this report as an educational tool to assist dentists when discussing oral health with patients receiving antiresorptive therapy, as well as when treating these patients. This executive summary focuses on patients receiving antiresorptive therapy for low bone mass rather than on patients receiving antiresorptive therapy for cancer treatment. The committee chose this focus because patients with low bone mass are seen routinely by

ABSTRACT

Background. This narrative review of osteonecrosis of the jaw in patients with low bone mass receiving treatment with antiresorptive agents is based on an appraisal of the literature by an advisory committee of the American Dental Association Council on Scientific Affairs. It updates the committee's 2008 advisory statement.

Methods. The authors searched MEDLINE for literature published between May 2008 (the end date of the last search) and February 2011.

Results. This report contains recommendations based on the findings of the literature search and on expert opinion that relate to general dentistry; periodontal disease management; implant placement and maintenance; oral and maxillofacial surgery; endodontics; restorative dentistry and prosthodontics; orthodontics; and C-terminal telopeptide testing and drug holidays.

Conclusions. The highest reliable estimate of antiresorptive agent-induced osteonecrosis of the jaw (ARONJ) prevalence is approximately 0.10 percent. Osteoporosis is responsible for considerable morbidity and mortality. Therefore, the benefit provided by antiresorptive therapy outweighs the low risk of developing osteonecrosis of the jaw.

Clinical Implications. An oral health program consisting of sound hygiene practices and regular dental care may be the optimal approach for lowering ARONJ risk. No validated diagnostic technique exists to determine which patients are at increased risk of developing ARONJ. Discontinuing bisphosphonate therapy may not lower the risk but may have a negative effect on low-bone-mass-treatment outcomes.

Key Words. Oral and maxillofacial pathology; alveolar bone; antiresorptive agent-induced osteonecrosis of the jaw; bisphosphonate-associated osteonecrosis; jaw; oral and mandibular diseases; oral pathology.

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TABLE 1

Antiresorptive agents.					
BRAND NAME	GENERIC NAME	DOSAGE	MANUFACTURER	APPROVED (DATE)	INDICATIONS ^{††}
Oral Formulations					
Actonel	Risedronate sodium	5-, 35-, 75- and 150-milligram tablets	Warner Chilcott, Dublin	Worldwide (1998)	To prevent and treat osteoporosis in postmenopausal women; to increase bone mass in men with osteoporosis; to prevent and treat osteoporosis in men and women that is caused by treatment with steroid medicines such as prednisone; to treat Paget disease of bone in men and women
Atelvia	Risedronate sodium	35-mg tablet (once weekly)	Warner Chilcott	Worldwide (2010)	To treat osteoporosis in post-menopausal women
Bonefos	Clodronate disodium (not commercially available in United States)	400-mg capsules (Canada), 800-mg tablets (Europe)	Bayer, Toronto; Bayer Schering, Berlin	Canada (1992), Europe (1985)	To treat and prevent osteoporosis in women after menopause; to treat hypercalcemia and osteolysis due to malignancy; to reduce occurrence of bone metastases in primary breast cancer
Boniva	Ibandronate sodium	2.5-mg tablet once daily, 150-mg tablet once monthly	Genentech (a member of the Roche Group), South San Francisco, Calif.	United States (2003)	To treat and prevent osteoporosis in women after menopause
Bonviva	Ibandronate sodium	150-mg tablet once monthly	Genentech	Europe (2004)	To treat and prevent osteoporosis in women after menopause
Didronel	Etidronate disodium	400-mg tablet	Warner Chilcott	United States (1983), Europe	To treat Paget disease of bone; to prevent and treat heterotopic ossification in people who have undergone total hip replacement surgery or in people who have had an injury to the spinal cord
Etidronate (generic)	Etidronate	200-, 400-mg tablet	Mylan Pharmaceuticals, Morgantown, W.V.	United States (2003), Europe	Note: off-label use to treat and prevent osteoporosis caused by corticosteroid therapy; in addition, this medication may be used to treat a high calcium level in the blood that may occur with some cancers
Fosamax	Alendronate sodium	5-, 10-, 35-, 40- and 70-mg tablets	Merck & Co., Whitehouse Station, N.J.	United States (1995), Europe (1995)	To treat or prevent osteoporosis in women after menopause; to increase bone mass in men with osteoporosis; to treat osteoporosis in men or women being treated with corticosteroid medicines; to treat Paget disease of bone
Fosamax Plus D	Alendronate sodium/cholecalciferol	70-mg tablet or 70-mg oral solution	Merck & Co.	United States (2005), Europe (2005)	To treat osteoporosis in post-menopausal women; to increase bone mass in men with osteoporosis
Generic alendronate	Alendronate sodium	5-, 10-, 35-, 40- and 70-mg tablets	Various	Worldwide (2008)	To treat or prevent osteoporosis in women after menopause; to increase bone mass in men with osteoporosis; to treat osteoporosis in men or women being treated with corticosteroid medicines; to treat Paget disease of bone
Skelid	Tiludronate disodium	240-mg tablets (equivalent to 200-mg base)	Sanofi-Aventis, Bridgewater, N.J.	United States (1997)	To treat Paget disease of bone
Aredia	Pamidronate disodium	30-, 90-mg vials	Novartis Pharmaceuticals, East Hanover, N.J.	Worldwide (2001)	To treat moderate or severe hypercalcemia with malignancy, with or without bone metastases; to treat osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma in conjunction with standard antineoplastic therapy; to treat Paget disease of bone

* According to manufacturers' product information.

† Because of the effect that therapeutics such as bisphosphonates have on bone remodeling, antiresorptive drugs now are being used off-label to treat patients with several pathological bone processes other than osteoporosis, such as giant cell lesions, giant cell tumor of bone, osteogenesis imperfecta, fibrous dysplasia, Gaucher disease and osteomyelitis. Source: Landesberg and colleagues.²

TABLE 1 (CONTINUED)

BRAND NAME	GENERIC NAME	DOSAGE	MANUFACTURER	APPROVED (DATE)	INDICATIONS**
Parenteral Formulations					
Bonefos	Clodronate disodium	60 mg/1 milliliter, 1,500-mg single dose	Bayer, Bayer Schering	Canada (1992), Europe (1985)	To treat Paget disease of bone; to treat hypercalcemia due to metastatic bone disease, multiple myeloma and parathyroid carcinoma
Boniva IV	Ibandronate sodium	3 mg/3 mL single use	Genentech	United States (2006), Europe (2006)	To treat osteoporosis in postmenopausal women
Prolia	Denosumab	60-mg subcutaneous injection every six months	Amgen, Thousand Oaks, Calif.	United States (2010), Europe (2010)	To treat postmenopausal women who have osteoporosis and are at high risk of experiencing fracture
XGEVA	Denosumab	120 mg in 1.7-mL subcutaneous injection every four weeks	Amgen	United States (2010)	To prevent skeletally related events in patients with bone metastases from solid tumors
Reclast (United States), Aclasta (Europe)	Zoledronic acid	5 mg in a 100-mL ready-to-infuse solution	Novartis Pharmaceuticals	United States (Reclast) (2007), worldwide (Aclasta) (2005)	To treat osteoporosis in postmenopausal women; to prevent osteoporosis in postmenopausal women; to increase bone mass in men with osteoporosis; to treat and prevent glucocorticoid-induced osteoporosis in patients expected to receive glucocorticoid therapy for at least 12 months; to treat Paget disease of bone in men and women
Zometa	Zoledronic acid	4 mg/5 mL single-dose vials	Novartis Pharmaceuticals	Worldwide (2001)	To treat hypercalcemia of malignancy; to reduce and delay bone complications due to multiple myeloma and bone metastases from solid tumors, in conjunction with anticancer medications

general dentists, and dosing, apparent risk and patient care are different for patients receiving antiresorptive therapy for cancer treatment. This report updates the 2008 advisory statement from the American Dental Association Council on Scientific Affairs.³

NOMENCLATURE

The 2008 advisory statement³ included use of the term “bisphosphonate-associated osteonecrosis of the jaw,” or BON. A nonbisphosphonate antiresorptive agent—denosumab (Prolia, Amgen, Thousand Oaks, Calif.)—now is available for treatment of women with postmenopausal osteoporosis. Aghaloo and colleagues⁴ reported a case of ONJ in a patient with cancer who received denosumab therapy. Other antiresorptive agents, including cathepsin K inhibitors, also could prove to be associated with ONJ. Therefore, the panel proposes that all cases of ONJ related to the administration of antiresorptive therapeutic agents be termed “antiresorptive agent–induced ONJ” (ARONJ). This term encompasses cases associated with bisphosphonates, as well as cases associated with the use of other antiresorptive agents. We use ARONJ throughout this report

unless it is important to denote ONJ associated with a specific antiresorptive agent.

METHODS

We searched MEDLINE for literature published between May 2008 (the end date of the last search) and February 2011 by using this search strategy: (“Osteonecrosis”[Medical Subject Headings (MeSH) terms] OR osteonecrosis) AND (“Diphosphonates”[MeSH] OR “bisphosphonate*” OR “denosumab”) AND (“Jaw”[MeSH] OR “jaw”) NOT “Addresses”[Publication Type] NOT “News”[Publication Type] NOT “Newspaper Article”[Publication Type] AND (English[lang]). The authors also searched the Cochrane Central Register of Controlled Trials by using the following strategy: (Osteonecrosis OR “avascular necrosis” OR chemonecrosis) AND (Diphosphonate* OR bisphosphonate* OR denosumab) AND (jaw).

ABBREVIATION KEY. ARONJ: Antiresorptive agent–induced osteonecrosis of the jaw. BON: Bisphosphonate-associated osteonecrosis of the jaw. CTX: C-terminal telopeptide. MeSH: Medical Subject Headings.

PANEL CONCLUSIONS

On the basis of a review of the available scientific literature and expert opinion, the panel reached the following conclusions.

The risk of developing ARONJ in a patient who does not have cancer appears to be low, with the highest prevalence estimate in a large sample of patients about 0.10 percent.⁵ At present, there are no published studies that adequately address incidence. The few studies published to date involved the use of a wide range of methods, all with potential shortcomings, and the incidence estimates reported varied. Without good information about the incidence of ARONJ, it is difficult to predict risk in general, and it is impossible to predict a specific patient's risk.

ARONJ can occur spontaneously but more commonly is associated with specific medical and dental conditions and procedures, including dental procedures and conditions that increase the risk of experiencing bone trauma. Most commonly, ARONJ is associated with invasive bone procedures such as tooth extractions.⁶⁻⁸ Age older than 65 years, periodontitis, prolonged use of bisphosphonates (for more than two years), smoking, denture wearing and diabetes have been associated with an increased risk of developing ARONJ.⁶⁻¹⁰ The results of several studies do not show consistently that corticosteroid use is a risk factor.¹¹⁻¹⁴ Investigators in one study (which they controlled for the effects of several known or potential confounders) found that smoking and obesity were risk factors for ARONJ in patients with cancer who were receiving intravenous zoledronic acid.¹⁵

If a physician prescribes or is planning to prescribe an antiresorptive agent, it is important for the patient and the patient's dentist to be informed. The panel advises that clinicians ask questions during the health history interview process about osteoporosis, osteopenia and the use of one of the various antiresorptive agents. Both medical and dental communities continue to study ways to prevent and treat ARONJ to ensure the safest possible result for dental patients being treated with antiresorptive agents.

The physician serves as the best source of information regarding the need for antiresorptive therapeutic agents. Given the significant skeletal and psychosocial complications of osteoporosis, a physician likely will recommend continued antiresorptive treatment during dental treatment despite the slight risk of the patient's developing ARONJ. Although neither the physician nor the dentist can eliminate the possibility

of ARONJ's developing, regular dental visits and maintaining excellent oral hygiene are essential components of risk management for the patient. Open communication regarding treatment options is a fundamental requirement for all members of the health care team, but it is particularly important for those whose patients have significant dental problems or active ARONJ.

PANEL RECOMMENDATIONS FOR DENTAL CARE OF PATIENTS WITHOUT CANCER RECEIVING ANTIRESORPTIVE THERAPY

These recommendations focus on conservative surgical procedures, proper infection control technique, appropriate use of oral antimicrobials and the principle of effective antibiotic therapy when indicated. Because of a paucity of clinical data regarding the dental care of patients receiving antiresorptive therapy, these recommendations are based primarily on expert opinion. They are intended to help dentists make clinical decisions and should be considered along with the practitioner's professional judgment and the patient's preferences. Dentists are encouraged to review the full report¹ before treating patients receiving antiresorptive therapy. As new information becomes available, these recommendations will be updated, as appropriate.

GENERAL TREATMENT RECOMMENDATIONS

Practitioners generally should not modify routine dental treatment solely because of the use of antiresorptive agents. All patients should receive routine dental examinations. Patients for whom antiresorptive agents have been prescribed and who are not receiving regular dental care likely would benefit from a comprehensive oral examination before or early in their treatment.

Informing patients before they undergo dental care. A discussion of the risks and benefits of dental care with patients receiving antiresorptive therapy is appropriate. When informing a patient about the risk of developing ARONJ, the dental care provider must keep in mind that the patient may not be aware of this risk.¹⁶ This may raise the patient's concerns about the continuation of dental treatment.

Points that dental care providers can discuss with patients when informing them about the risks of bisphosphonate therapy include the following.

- Antiresorptive therapy for low bone mass places them at low risk of developing ARONJ

(the highest prevalence estimate in a large sample is about 0.10 percent⁵).

- The low risk of developing ARONJ can be minimized but not eliminated.
- An oral health program consisting of sound oral hygiene practices and regular dental care may be the optimal approach for lowering the risk of developing ARONJ.
- No validated diagnostic technique currently is available to determine which patients are at increased risk of developing ARONJ.
- Discontinuing bisphosphonate therapy may not eliminate the risk of developing ARONJ. However, discontinuation of bisphosphonate therapy may have a negative impact on the outcomes of low-bone-mass treatment. Therefore, significant dental risks need to be present for clinicians to consider cessation of antiresorptive therapy for low bone mass, cancer or other off-label purposes. The advisory committee recommends that all members of the health care team discuss this before discontinuing bisphosphonate therapy.

The dental care provider should inform the patient of the dental treatment needed, alternative treatments, the way in which any treatment relates to the risk of ARONJ, other risks associated with various treatment options and the risk of forgoing dental treatment even temporarily. The clinician should encourage the patient to consult with his or her physician about health risks associated with discontinuation of antiresorptive therapy. All decisions with respect to use of drugs prescribed for medical conditions should be discussed with the prescribing physician. Misinformation and misunderstandings can lead to severe and preventable adverse events. Therefore, clinicians should present to the patient a balanced assessment of the current information.¹⁷ The dental office staff should instruct patients who receive treatment with antiresorptive agents to contact their dentist if any problem develops in the oral cavity.

Making treatment decisions. The dental care provider may have to decide whether to treat a patient who has been exposed to antiresorptive agents. As discussed earlier, the risk of developing ARONJ is lower for a patient who is not being treated with these drugs for cancer. The panel recommends that a patient with active dental or periodontal disease should be treated despite the risk of developing ARONJ, because the risks and consequences of no treatment likely outweigh the risks of developing ARONJ. Leaving active dental disease (caries, periodontal disease, extensive periapical abscesses or granulomas) untreated can lead to complications that may

require more extensive and risky treatments.

Before starting therapy, the dentist should inform the patient to the fullest extent possible. He or she should consider documenting the discussion of risks, benefits and treatment options with the patient (see earlier discussion) and obtaining the patient's written acknowledgment of that discussion and consent for the chosen course of treatment. The dentist should retain in the patient's dental record the acknowledgment of the discussion and consent for treatment.

Prevention and treatment planning.

Table 2^{4,8,18} describes strategies for managing the oral health of patients receiving antiresorptive therapy in an effort to prevent ARONJ. A major goal in the prevention of ARONJ is to limit the possibility of extensive or multifocal involvement. Despite the absence of supporting evidence, a localized clinical approach to dentoalveolar surgery in patients receiving antiresorptive therapy for low bone density may help the practitioner assess the risks on an individual basis and before putting multiple quadrants at risk. Common scenarios include, but are not limited to, a patient's needing full-mouth tooth extractions for dentures or a patient's needing full-mouth periodontal surgery. For example, the dentist could extract a single tooth or perform alveolar surgery in one sextant initially while treating the patient with chlorhexidine or another topical antiseptic.¹⁹ The dentist may assume that the patient's healing response is adequate once he or she observes normal healing of the surgical site or sites. Antiseptic agents may be used for a longer period if the area remains inflamed, irritated or erythematous. After establishing the patient's apparently adequate healing response, the clinician could consider a more accelerated surgical treatment plan involving multiple (or all) sextants at a single appointment.

Because periapical pathoses, sinus tracts, purulent periodontal pockets, severe periodontitis and active abscesses that already involve the medullary bone may exacerbate osteonecrosis and are themselves risk factors for ARONJ, the dentist should treat them expeditiously. When dental pathoses are not evident, the trial sextant approach may be applicable. The sextant-by-sextant approach does not apply to emergency cases, even if multiple quadrants are involved.

TREATMENT RECOMMENDATIONS FOR SPECIFIC CONDITIONS

Management of periodontal diseases.

Patients receiving antiresorptive therapy who have active chronic periodontal diseases gener-

TABLE 2

Prevention strategies for patients receiving antiresorptive therapy* (absent evidence of ARONJ†).

VARIABLE	CONSIDERATIONS FOR MANAGING PATIENTS' ORAL HEALTH
Duration of Antiresorptive Therapy	
Before therapy	<ul style="list-style-type: none"> ■ Optimal time to establish lifetime oral health awareness, as the long-term nature of antiresorptive therapy is associated with ever-increasing ARONJ risk ■ Optimal period to remove unsalvageable teeth and perform invasive dentoalveolar procedures, although a less stringent requirement than that for patients being treated with these drugs as part of cancer therapy ■ On assessment of the overall caries risk, periodontal disease risk and "dental intelligence quotient" of the patient, the dentist is best qualified to establish an appropriate treatment plan in coordination with the patient and the patient's physician
< 2 years	<ul style="list-style-type: none"> ■ Above discussions and assessments often are not performed or even possible before start of antiresorptive therapy, but all remain applicable after treatment has begun ■ Risk during this period is very low; however, a few cases of ARONJ have been reported‡ ■ Dentoalveolar procedures involving periosteal penetration or intramedullary bone exposure (for example, extractions, apicoectomies, periodontal surgeries, implants or biopsies) seem to carry a minimal risk of the patient's developing ARONJ ■ Chlorhexidine rinses are advised whenever periosteal or medullary bone exposure is anticipated or observed ■ In patients with multiple surgical needs, a trial segmental approach may be helpful in assessing a specific patient's risk of developing osteonecrosis and in reducing the likelihood of developing multifocal ARONJ
≥ 2 years	<ul style="list-style-type: none"> ■ Continue as above while advising the patient and physician who prescribes antiresorptive drugs that the risk of developing ARONJ continues to increase with extended drug use
Any length of therapy	<ul style="list-style-type: none"> ■ The dentist should discuss antiresorptive therapy with the patient's physician as it relates to the patient's oral health ■ Discontinuation of antiresorptive therapy should be a medical decision based primarily on the risk of experiencing skeletally related events (for example, fractures) secondary to low bone density, not the potential risk of developing ARONJ ■ No oral or maxillofacial surgical procedures are strictly contraindicated, although it is the opinion of the expert committee that treatment plans that minimize periosteal and/or intrabony exposure or disruption are preferred
Risk Assessment	<ul style="list-style-type: none"> ■ Serum C-terminal telopeptide levels have not shown reliability or accuracy in predicting risk of developing ARONJ; therefore, serum testing is not recommended to predict risk ■ Although the trial segmental or sextant approach to surgical procedures has not been studied in a prospective fashion, this approach should help limit the extent of ARONJ in a given patient
Emergency Dental Therapy	<ul style="list-style-type: none"> ■ All extractions or dentoalveolar surgeries required on the basis of dental or medical emergencies are appropriate, regardless of the number of extractions or surgeries and multifocality
Routine Dental Care	<ul style="list-style-type: none"> ■ Good oral health and routine dental care always are recommended
<p>* Limited data suggest similar levels of risk for patients treated with oral bisphosphonates, intravenous bisphosphonates and subcutaneous denosumab in the treatment of low bone density. Similar prevention strategies appear appropriate for each of these modalities, with comparable modification according to duration of drug therapy. This does not mean that no differences exist between these treatment modalities, and further studies are needed. Sources: Aghaloo and colleagues⁴; Grbic and colleagues.¹⁸</p> <p>† ARONJ: Antiresorptive agent-induced osteonecrosis of the jaw.</p> <p>‡ Source: Mavrokokki and colleagues.⁸</p>	

ally should receive appropriate forms of nonsurgical therapy, which should be combined with the commonly recommended reevaluation at four to six weeks. However, this is not to say that surgical procedures are contraindicated in these patients. Because tooth extractions constitute a risk factor for ARONJ, practitioners should monitor patients regularly and treat them with the goal of preventing progression of periodontal disease to the point at which tooth extractions are necessary. The goal of surgical periodontal treatment should be to obtain access to root surfaces, and, when possible, practitioners should use atraumatic techniques that minimize dentoalveolar manipulation.

There are no published studies, to our knowledge, in which investigators evaluated the risk of ARONJ or the success of implant treatment after periodontal procedures such as guided tissue regeneration or bone grafting. Use of such techniques should be considered judiciously on the basis of a patient's need. Primary soft-tissue closure after periodontal surgical procedures is desirable, when feasible, although extended periosteal bone exposure for the sake of primary closure may increase, rather than decrease, the risk of developing ARONJ. Patients who do not have periodontal disease should receive preventive therapy or instruction in prevention of periodontal disease.

Implant placement and maintenance.

Investigators in several relatively small, short-term studies examined the risk of ARONJ, implant failure or both in women with a history of bisphosphonate use.²⁰⁻²³ Although there are case reports of ARONJ at implant osteotomy sites, the relative scarcity of ARONJ and dental implant failure in patients treated with bisphosphonates, despite the large number of such patients receiving dental implants, is reassuring. Indeed, Fugazzotto and colleagues²⁰ noted no postoperative cases of ARONJ in 61 patients in whom the average duration of bisphosphonate use was 3.3 years. None of the implants failed in this population. In a population of 42 patients treated with bisphosphonates (range, six months to 11 years) who received 101 implants, Bell and Bell²¹ observed no ARONJ and a 95 percent implant success rate. Using telephone and e-mail surveys, Grant and colleagues²² noted no ARONJ associated with 468 implants placed in 115 patients receiving bisphosphonate treatment and a 99.6 percent success rate. Koka and colleagues²³ compared 121 implants placed in 55 patients treated with bisphosphonates (approximately one-third of whom had been treated for more than five years) with 166 implants placed in 82 patients who had not received bisphosphonate treatment. They did not observe ARONJ in either group, and the implants in the two groups exhibited similar profiles, with a 99.2 percent success rate in bisphosphonate users and a 98.2 percent success rate in nonusers.

Taken together, these data are encouraging. Dentists can inform patients that the risk of developing ARONJ as a result of antiresorptive therapy is low, and that the success rates for implants placed in patients receiving bisphosphonate treatment appear to be no different in the short term (that is, less than 10 years) from the success rates for implants placed in patients without a history of bisphosphonate treatment. Presently, antiresorptive therapy does not appear to be a contraindication for dental implant placement. However, larger and longer-term studies are needed to determine if implants placed in patients exposed to antiresorptive agents perform as well as those placed in patients who have not been exposed to these agents.

Oral and maxillofacial surgery. When treatment of dental diseases, periodontal diseases or both has failed, surgical intervention may be the best alternative. Practitioners should inform patients receiving antiresorptive therapy who are to undergo invasive surgical procedures that there is the risk, albeit small, of developing ARONJ. Although surgical pro-

cedures are not necessarily contraindicated, the practitioner, as part of the informed consent process, should discuss alternative treatment plans with the patient; these include endodontics (including endodontic treatment followed by removal of the clinical crown), allowing the roots to exfoliate (instead of extraction) and use of fixed and removable partial dentures.

If extractions or bone surgery is necessary, dentists should consider a conservative surgical technique with primary tissue closure, when feasible. Placement of semipermeable membranes over extraction sites also may be appropriate if primary closure is not possible. In addition, before and after any surgical procedures involving bone, the patient should rinse gently with a chlorhexidine-containing rinse until the extraction site has healed. The chlorhexidine regimen may be extended depending on the patient's healing progress, but twice-daily use for four to eight weeks is a common regimen. Some evidence exists that antibiotic prophylaxis starting one day before and extending three to seven days after dental procedures may be effective in preventing ARONJ.²⁴ In addition, Lodi and colleagues²⁵ reported that the use of chlorhexidine and systemic antibiotics before and after tooth extraction appeared to reduce the risk of ARONJ in a small study of 23 patients.

In patients who already have ARONJ, researchers have reported limited evidence that teriparatide, a recombinant form of parathyroid hormone, may be helpful in treatment of the disease.²⁶⁻²⁸

Endodontics. In patients with an elevated risk of developing ARONJ, endodontic treatment is preferable to surgical manipulation if a tooth is salvageable. Practitioners should use a routine endodontic technique; however, the panel does not recommend manipulation beyond the apex. Limited evidence shows that periapical healing after endodontic therapy is similar regardless of whether or not a patient has a history of bisphosphonate use.²⁹ Endodontic surgical procedures should be guided by the same recommendation as that given for any oral or maxillofacial surgical procedure described earlier.

Restorative dentistry and prosthodontics. No evidence exists that malocclusion or masticatory forces increase the risk of developing ARONJ. Practitioners should perform all routine restorative procedures with the goal of minimizing the impact on bone, so as not to increase the risk of infection. To avoid ulceration and possible bone exposure, practitioners should adjust prosthodontic appliances promptly for fit.

Orthodontics. There are no large published

studies in which investigators examined the effect of bisphosphonates on orthodontic treatment. Case reports have recounted inhibited tooth movement in patients receiving bisphosphonate therapy.^{30,31} Dentists should advise patients of this potential complication. However, clinicians also have performed orthodontic procedures successfully in patients receiving antiresorptive therapy, and it is not necessarily contraindicated.^{31,32}

Orthodontics is unique in the dental specialties in that its existence is based on the delicate balance between osteoclast function and osteoblast function. While orthodontic treatment occurs predominantly in children and in patients in early adolescence, one in five orthodontic patients in the United States is an adult.³³ The orthodontic literature concerning bisphosphonates concentrates primarily on the ability of these drugs to stabilize teeth after treatment or on topical application to a localized area during orthodontic therapy.³⁴ However, with the advent of antiresorptive bone agents, there potentially are 44 million Americans in whom orthodontic movement may be compromised by the medication. Orthodontists need to recognize the potential problem of ARONJ and the alteration in bone physiology caused by antiresorptive therapy.^{31,32,35} The duration of orthodontic treatment may be longer, and predictable, uniform tooth movement may be compromised with use of antiresorptive agents. Orthognathic surgery and tooth extractions result in more extensive bone healing and remodeling. The orthodontic considerations related to such cases should include the potential risks of surgery, as well as the potential postsurgical delayed tooth movement. Treatment planning in these cases may require increased vigilance.

C-TERMINAL TELEPEPTIDE TESTING AND DRUG HOLIDAYS

Serum-based bone turnover markers are biochemical markers of bone remodeling. Two such markers are C-terminal telopeptide (CTX) and N-terminal telopeptide. These markers together represent each end of the three strands of type I collagen, and each is used in tests that monitor bone turnover. Investigators in some studies have advocated the use of serum CTX to predict the risk of developing ARONJ,³⁶⁻⁴¹ while others have questioned its utility.⁴²⁻⁴⁶

Although a few studies have been conducted regarding the suspension of antiresorptive drug therapy during treatment of ARONJ, no study results to date have confirmed that drug holidays are effective in prevention of ARONJ without increasing the skeletally related risks of

low bone mass. At present, there is insufficient evidence to recommend the use of serum tests, such as serum CTX, as a predictor of ARONJ risk. In addition, there is insufficient evidence to recommend a holiday from antiresorptive drug therapy or waiting periods before performing dental treatment for prevention of ARONJ. For a complete discussion of the rationale behind this recommendation regarding use of serum CTX and drug holidays, refer to the full report.¹

CONCLUSIONS

The clinical recommendations in this report, which are based on a critical evaluation of the relevant scientific evidence, do not represent a standard of care. The clinical recommendations should be integrated with the practitioner's professional judgment and the patient's needs and preferences. Treatments and procedures appropriate to a specific patient rely on communication between the patient, the dentist and other health care practitioners. This report focuses on prevention of ARONJ in patients being treated with antiresorptive agents for osteoporosis. The significant therapeutic benefit of antiresorptive agents in these patients far outweighs the small risk of developing ARONJ. ■

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Diagnosis and Management of Osteonecrosis of the Jaw: A Systematic Review and International Consensus

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ABSTRACT

This work provides a systematic review of the literature from January 2003 to April 2014 pertaining to the incidence, pathophysiology, diagnosis, and treatment of osteonecrosis of the jaw (ONJ), and offers recommendations for its management based on multidisciplinary international consensus. ONJ is associated with oncology-dose parenteral antiresorptive therapy of bisphosphonates (BP) and denosumab (Dmab). The incidence of ONJ is greatest in the oncology patient population (1% to 15%), where high doses of these medications are used at frequent intervals. In the osteoporosis patient population, the incidence of ONJ is estimated at 0.001% to 0.01%, marginally higher than the incidence in the general population (<0.001%). New insights into the pathophysiology of ONJ include antiresorptive effects of BPs and Dmab, effects of BPs on gamma delta T-cells and on monocyte and macrophage function, as well as the role of local bacterial infection, inflammation, and necrosis. Advances in imaging include the use of cone beam computerized tomography assessing cortical and cancellous architecture with lower radiation exposure, magnetic resonance imaging, bone scanning, and positron emission tomography, although plain films often suffice. Other risk factors for ONJ include glucocorticoid use, maxillary or mandibular bone surgery, poor oral hygiene, chronic inflammation, diabetes mellitus, ill-fitting dentures, as well as other drugs, including antiangiogenic agents. Prevention strategies for ONJ include elimination or stabilization of oral disease prior to initiation of antiresorptive agents, as well as maintenance of good oral hygiene. In those patients at high risk for the development of ONJ, including cancer patients receiving high-dose BP or Dmab therapy, consideration should be given to withholding antiresorptive therapy following extensive oral surgery until the surgical site heals with mature mucosal coverage. Management of ONJ is based on the stage of the disease, size of the lesions, and the presence of contributing drug therapy and comorbidity. Conservative therapy includes topical antibiotic oral rinses and systemic antibiotic therapy. Localized surgical debridement is indicated in advanced nonresponsive disease and has been successful. Early data have suggested enhanced osseous wound healing with teriparatide in those without contraindications for its use. Experimental therapy includes bone marrow stem cell intraliesional transplantation, low-level laser therapy, local platelet-derived growth factor application, hyperbaric oxygen, and tissue grafting. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: OSTEONECROSIS OF THE JAW; BISPHOSPHONATES; DENOSUMAB; IMAGING; RISK FACTORS; DIAGNOSIS; TREATMENT; MANAGEMENT

Introduction

This work provides a systematic review of the literature and international consensus on the classification, incidence, pathophysiology, diagnosis, and management of osteonecrosis of the jaw (ONJ) in both oncology and osteoporosis patient populations. Resulting recommendations for the diagnosis and

management of ONJ are also presented. This review updates previous systematic reviews and consensus statements regarding the management of ONJ.^(1,2)

Bisphosphonate (BP)-associated ONJ is defined by the American Society for Bone and Mineral Research (ASBMR) as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care

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provider, in a patient who was receiving or had been exposed to a BP and who has not received radiation therapy to the craniofacial region.⁽³⁾ The American Association of Oral and Maxillofacial Surgeons (AAOMS) has recently (2014) updated their definition of medication-related ONJ to (1) current or previous treatment with antiresorptive or antiangiogenic agents; (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks; and (3) no history of radiation therapy to the jaws or obvious metastatic disease to the jaws.⁽⁴⁾

The International Task Force on Osteonecrosis of the Jaw (hereafter, this Task Force or the Task Force) defines ONJ as: (1) exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider; (2) exposure to an antiresorptive agent; and (3) no history of radiation therapy to the craniofacial region. Early data suggest that antiangiogenic agents may contribute to the development of ONJ in the absence of concomitant BP therapy; the Task Force plans to address this in more detail in a subsequent document as more evidence emerges.

Oral ulceration with bone sequestration

The Task Force is also of the view that bone necrosis may occur in the absence of antiresorptive therapy, with attendant oral ulceration and bone sequestration (OUBS). However, such occurrences, typically associated with significant morbidity, are uncommon. OUBS was initially described as “lingual mandibular sequestration and ulceration” because of the predilection for involvement of the posterior lingual mandibular bone, but this terminology has been replaced by OUBS. The sequestrum can slough spontaneously, resulting in rapid resolution. However, in some cases, conservative surgical removal of the dead bone is indicated to permit efficient healing.⁽⁵⁻⁷⁾ The incidence of OUBS in the general population is not well defined. It is possible that cases of OUBS may be captured in incidence data pertaining to drug-related ONJ. Currently, it is not known what proportion of the spontaneous sequestration cases persist beyond 8 weeks and there are no studies identifying the prevalence or incidence of OUBS. OUBS was not included in the main systematic review, which pertains to drug-related ONJ; however, this Task Force conducted a separate literature search on OUBS and, at the end of this document, has provided a summary of that search as well as current recommendations pertaining to diagnosis and management based on international consensus.

Methods

In January 2012, an International ONJ Task Force was formed with expertise from basic science and from multiple medical, dental, and surgical specialties. There was representation from 14 national and international societies addressing bone health (The sponsoring societies are the American Society of Bone and Mineral Research, American Association of Oral and Maxillofacial Surgeons, Canadian Association of Oral and Maxillofacial Surgeons, Canadian Academy of Oral and Maxillofacial Pathology and Oral Medicine, European Calcified Tissue Society, International Bone and Mineral Society, International Society of Clinical Densitometry, International Osteoporosis Foundation,

International Association of Oral and Maxillofacial Surgeons, International Society of Oral Oncology, Japanese Society for Bone and Mineral Research, Osteoporosis Canada, Pan Arab Osteoporosis Society and The Endocrine Society). The Task Force formalized nine key questions to be addressed relevant to the diagnosis and management of ONJ in oncology and osteoporosis patient populations (Supporting Table S1). A systematic review of published literature was completed based on these key questions. A search strategy was developed by combining medical subject headings and/or text words from four categories: interventions (BPs and denosumab); population (oncology and osteoporosis); areas of interest for the review (classification, diagnosis, incidence, risk factors, treatment); and outcome (osteonecrosis of the jaw). All searches were limited to human studies published in the English language and excluded reviews, editorials, and letters. The electronic search was conducted in Medline (January 1, 2003 to April 10, 2014) and EMBASE (January 1, 2003 to April 10, 2014) using OVID (see Supporting Table S2 for search strategies). The results from both databases were combined and duplicates excluded. The Cochrane Database of systematic reviews was also searched for applicable references. A manual search of the bibliography of identified published articles was also performed. In order to obtain additional unpublished data, personal communication with relevant experts was conducted and pharmaceutical companies were invited to submit relevant information. A total of 46 records were included from manual searches and expert communication. The total number of references were reviewed was 933 and from these, 599 papers were reviewed in full (see Supporting Fig. S1 for articles reviewed and retained for each of the nine questions).

The published literature was critically appraised and graded based on quality of evidence (see Supporting Table S3 for Level of Evidence scales and Supporting Tables S4 and S5 for Evidence Grades, respectively). All assessments were made in duplicate with disagreements discussed between reviewers until consensus was achieved. If no consensus was possible, a third reviewer would have provided the final decision. However, adjudication by a third reviewer was not necessary in any instance.

The key questions and a summary of the current evidence were reviewed in detail by the ONJ Task Force at an in-person meeting in October 2012. The panel members were divided into subgroups, with each subgroup being responsible for responding to a specific question, each represented in a section of this systematic review. Each subgroup communicated electronically, and regularly scheduled conference calls were implemented in order to address points of controversy in order to arrive at consensus. The co-chairs reviewed the sections from each of the subgroups and completed the manuscript. The manuscript was circulated to the Task Force and was modified until consensus was achieved on each of the sections; there were a total of 21 circulations and manuscript revisions. A second in-person meeting occurred in October 2013, followed by teleconferences to ensure that all recommendations had consensus agreement. Consensus was not achieved regarding appropriate terminology for staging of ONJ because of limited available prospective data. After approval by each of the supporting societies, the manuscript was finalized. Funding and in-kind support for the ONJ Task Force has been received solely from the sponsoring societies; industry support was not requested nor received.

This guideline will be updated every 5 years or as required using the same criteria outlined above.

Results and Discussion

Supporting Table S6 provides the key recommendations with their supporting levels of evidence.

1. How is ONJ defined, and staged?

As noted in the Introduction, this Task Force defined ONJ as (1) exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider; (2) exposure to an antiresorptive agent; and (3) no history of radiation therapy to the craniofacial region.

The first report describing ONJ was published in 2003,⁽⁸⁾ and the first peer-reviewed article describing ONJ was published by Ruggiero and colleagues⁽⁹⁾ in 2004. In 2007, the definition of ONJ was formalized by AAOMS⁽¹⁰⁾ and further clarified by the ASBMR⁽³⁾ as “area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to a BP and had not had radiation therapy to the craniofacial region.”

Recently, ONJ has been identified in BP-naïve patients receiving denosumab (Dmab),^(11–14) which necessitated accommodation of Dmab in the definition. Emerging data has also suggested an association between antiangiogenic agents and the development of ONJ and a subsequent paper is planned to address this as more data emerge.

Diagnosis

The differential diagnosis of ONJ includes other previously-defined clinical conditions such as alveolar osteitis, sinusitis, gingivitis/periodontitis, periapical pathosis, and some forms of cement-osseous dysplasia showing secondary sequestration. Bone inflammation and infection are usually present in patients with advanced ONJ, and appear to be secondary events.

In a Beagle model with increasing doses of BPs, regions of matrix necrosis increased in size and number with no evidence of infection or microbial colonization initially, but after time, exposed bone and surrounding soft tissue became secondarily infected resulting in a clinical picture similar to osteomyelitis.⁽¹⁵⁾ However, the histologic analyses of these bone specimens rarely demonstrated the criteria required to establish a diagnosis of acute or chronic osteomyelitis (typical histologic findings include regions of nonviable bone with surrounding bacterial debris and inflammatory cell infiltration). Analyses of the physical properties of resected necrotic bone from ONJ patients have also failed to demonstrate any unique features that would serve as a reliable biomarker for ONJ.^(16,17)

Patient history and clinical examination remain the most sensitive diagnostic tools for ONJ. A clinical finding of exposed bone in the oral cavity for 8 weeks or longer in the absence of response to appropriate therapy is the consistent diagnostic hallmark of ONJ.

Areas of exposed and necrotic bone may remain asymptomatic for prolonged periods of weeks, months, or even years.⁽¹⁷⁾ These lesions most frequently become symptomatic with inflammation of surrounding tissues. Signs and symptoms may occur before the development of clinically detectable

osteonecrosis and include pain, tooth mobility, mucosal swelling, erythema, ulceration, paresthesia, or even anesthesia of the associated branch of the trigeminal nerve.^(18,19) Some patients may also present with symptoms of altered sensation in the affected area because the neurovascular bundle may become compressed from the surrounding inflammation.^(20,21) These features may occur spontaneously or, more commonly following, dentoalveolar surgery. The vast majority of case series have described ONJ occurring at sites of prior oral surgery, particularly at extraction sites.^(22–29) Exposed bone has also been reported as occurring spontaneously in the absence of prior trauma or in edentulous regions of the jaw or at sites of exostoses in oncology patients. Intraoral and extraoral fistulae may develop when necrotic mandible or maxilla becomes secondarily infected.⁽³⁰⁾ Chronic maxillary sinusitis secondary to osteonecrosis with or without an oral-antral fistula may be the presenting feature in patients with maxillary bone involvement.⁽³¹⁾

Staging

Evidence identified for the staging of osteonecrosis of the jaw is reviewed in Supporting Table A1. Because there was so little evidence reviewed for the staging section, recommendations from this section should be considered consensus statements rather than evidence-based statements.

The clinical staging system currently being used was developed by Ruggiero and colleagues⁽³²⁾ and has been adopted by AAOMS.^(10,33) This system is of value in identifying the stage characteristics of the condition and providing appropriate terminology for diagnosis and management (Supporting Table S7). Patients with Stage 1 disease have exposed bone and are asymptomatic with no evidence of significant adjacent or regional soft tissue inflammation or infection. Stage 2 disease is characterized by exposed bone with associated pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection. Stage 3 disease is characterized by exposed bone associated with pain, adjacent or regional soft tissue inflammatory swelling, or secondary infection, in addition to a pathologic fracture, an extraoral fistula or oral-antral fistula, or radiographic evidence of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus.

Nonspecific oral signs or symptoms not explained by common periapical or periodontal disease in the absence of clinically exposed bone may develop in patients in the presence or absence of antiresorptive therapy. These symptoms include bone pain, fistula track formation, abscess formation, altered sensory function, or abnormal radiographic findings extending beyond the confines of the alveolar bone. The term “Stage 0” ONJ is used by AAOMS⁽²⁾ to refer to any or all of these symptoms or signs in patients on antiresorptive therapy. Members of this Task Force, however, expressed concern that the use of such Stage 0 terminology may lead to overdiagnosis of ONJ because these same presenting symptoms may ultimately lead to an alternative diagnosis. A recent study by Schiodt and colleagues⁽³⁴⁾ concluded that the non-exposed variant of ONJ is the same disease as exposed ONJ and further recommended that the non-exposed disease could be classified as either Stage 1, 2, or 3, dependent on the underlying characteristics of the disease. The demographics of patients on antiresorptive medications overlap those of patients with chronic periodontal and periapical disease. Thus, many patients on antiresorptive

therapy will present to the dentist's office for common dental care. Overdiagnosing patients with ONJ could lead to detrimental effects in their skeletal health, especially if modification or discontinuation of the antiresorptive medication is entertained.

Odontalgia is caused by a number of conditions, necessitating careful exclusion. Radiographic findings of altered bone morphology, increased bone density, sequestration, or periosteal bone formation in a patient with odontalgia may be early radiographic features suggestive of a prodromal phase of ONJ and such patients require close follow-up and monitoring by the oral health care provider (see Supporting Table S8). It appears from the limited data available that up to 50% of such patients may progress to the development of clinical ONJ with bone exposure.⁽¹⁹⁾ Several members of the Task Force felt that this condition could be referred to as "preclinical ONJ." However, because at least 50% of these lesions do not progress to overt ONJ, the Task Force felt unable to unanimously support the designation "preclinical ONJ" as appropriate for this particular clinical manifestation until further prospective data become available.

ONJ lesions occur more commonly in the mandible than the maxilla (65% mandible, 28.4% maxilla, 6.5% both mandible and maxilla, and 0.1% other locations; see Supporting Table A2) and are also more prevalent in areas with thin mucosa overlying bone prominences such as tori, exostoses, and the mylohyoid ridge.^(9,32,35) The extent of lesions can vary and range from a nonhealing extraction site to exposure and necrosis of large sections of the mandible or maxilla.⁽¹⁸⁾ The exposed bone is typically surrounded by inflamed erythematous soft tissue. Purulent discharge at the site of the exposed bone is evident in the presence of secondary infection.^(36,37) Microbial cultures from areas of exposed bone usually isolate normal oral microbes.^(38,39) However, in the presence of extensive soft tissue involvement, microbial cultures may identify coexisting oral pathogens and enable the selection of an appropriate antibiotic regimen. Interestingly, although ONJ is exclusive to the jaws by definition, it should be noted that osteonecrosis of the external auditory canal in patients on BP therapy has also been reported.⁽⁴⁰⁻⁴⁶⁾

2. How common is ONJ?

For the full review of evidence regarding the prevalence and incidence of ONJ in osteoporotic and oncology populations, please refer to Supporting Tables A3 and A4, respectively.

2a. Osteoporosis

There are very limited prospective cohort data evaluating the frequency of ONJ in the osteoporosis patient population, making it difficult to accurately evaluate its incidence. The published data evaluating the incidence of ONJ have largely been obtained from case-series, retrospective observational studies, or retrospective cohort studies, typically from pooled data from insurance or healthcare databases. Pooled data can be problematic in that search terms may not be specific to ONJ.

Prevalence

The prevalence of ONJ in patients prescribed oral BPs for the treatment of osteoporosis ranges from 0% to 0.04%, with the majority being below 0.001%.⁽⁴⁷⁻⁵⁷⁾ The prevalence of ONJ in those prescribed high dose intravenous (i.v.) BPs is significantly higher than that seen with low dose i.v. or oral BPs, with

prevalence rates of 0% to 0.348% and the majority being under 0.005%.^(47,48,58-60) Felsenberg⁽⁶¹⁾ noted a prevalence of ONJ in patients treated with BPs for osteoporosis of <1/100,000. Lo and colleagues⁽⁵²⁾ evaluated the Kaiser Permanente database and found the prevalence of ONJ in those receiving BPs for more than 2 years to range from 0.05% to 0.21% and appeared to be related to duration of exposure. In Canada, Khan and colleagues⁽⁶²⁾ completed a survey of oral surgeons in Ontario and found the prevalence of ONJ in those on BPs to be approximately 0.001%.

Barasch and colleagues⁽²⁴⁾ completed a case-control study and noted an association between oral BPs and ONJ with an odds ratio (OR) of 12.2 (95% confidence interval [CI], 4.3 to 35). This study, however, included patients with cancer on oncologic doses of BPs, which likely increased the incidence of ONJ. Vestergaard and colleagues⁽⁶³⁾ evaluated jaw-related events in BP users with nonusers in a historical cohort study and noted a hazard ratio (HR) of 3.15 (95% CI, 1.44 to 6.87) with alendronate use.

Incidence

The incidence of ONJ in patients prescribed oral BPs for the treatment of osteoporosis ranges from 1.04 to 69 per 100,000 patient-years.^(62,64-66) The incidence of ONJ in patients prescribed i.v. BPs for the treatment of ONJ ranges from 0 to 90 per 100,000 patient-years.^(58,59,65,67,68) Last, the incidence of ONJ in patients who are prescribed Dmab ranges from 0 to 30.2 per 100,000 patient-years.⁽⁶⁹⁻⁷²⁾ In Australia, Mavrokki and colleagues⁽⁵⁴⁾ conducted a national survey and found the incidence of ONJ in osteoporotic patients receiving BPs to be 0.01% to 0.04%. However, in Sweden, Ulmner and colleagues⁽⁶⁶⁾ surveyed oral surgery and dental clinics and estimated an incidence of 0.067%. Zavras and Zhu⁽⁷³⁾ evaluated medical claims in the United States and found no association between oral BP use and the risk of minor jaw surgery. However, in those receiving i.v. BPs there was a fourfold increased risk of minor jaw surgery, possibly reflecting an increased risk of ONJ. Similar findings were noted by Pazianas and colleagues.⁽⁷⁴⁾

In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial involving 7765 patients receiving either zoledronic acid 5 mg or placebo over 3 years, a single adjudicated case of ONJ was identified in each arm. Both patients had additional risk factors for ONJ (prednisone use in the patient receiving placebo and diabetes with dental abscess in the patient receiving zoledronic acid) and both resolved with antibiotics and debridement.⁽⁶⁷⁾ The data from four additional randomized controlled trials (RCTs) evaluating 5 mg zoledronic acid were combined with the data from the HORIZON Pivotal Fracture Trial and the overall incidence of ONJ was reviewed.⁽⁷⁵⁾ The additional trials included: the HORIZON Recurrent Fracture Trial with 2127 subjects after a recent low-trauma hip fracture followed for 1.9 years⁽⁵⁸⁾; the Glucocorticoid-Induced Osteoporosis Trial involved 833 subjects and compared zoledronic acid 5 mg or risedronate 5 mg over 1 year⁽⁷⁶⁾; the Male Osteoporosis Trial involved 302 subjects followed over 2 years receiving either zoledronic acid 5 mg annually or alendronate 70 mg orally weekly⁽⁷⁷⁾; and the Prevention of Osteoporosis Trial evaluated 581 subjects over 2 years randomized to either zoledronic acid 5 mg annually versus placebo.⁽⁷⁸⁾ The combined adverse event database was searched for possible cases of ONJ using preferred Medical Dictionary for Regulatory Activities terms and no additional

cases of ONJ were identified in these four additional RCTs. In all, the incidence of adjudicated ONJ was <1 in 14,200 patient treatment years with zoledronic acid 5 mg.

In the completed Phase II and III clinical trials evaluating Dmab in the treatment of postmenopausal osteoporosis, no cases of ONJ were positively adjudicated in placebo-treated or Dmab-treated subjects after more than 16,000 patient-years of follow-up.^(71,79–82)

In the extension of the Phase III clinical trial evaluating Dmab in postmenopausal women with osteoporosis (FREEDOM extension), eight cases of ONJ were identified.⁽⁶⁹⁾ Four cases developed in the long-term treatment group with patients receiving 5 to 6 years of Dmab. Two of the four patients continued on Dmab, while two discontinued drug therapy. All cases that developed ONJ healed following treatment. ONJ developed in two patients receiving Dmab in the crossover extension study at 1.5 years and 2 years of exposure; one patient continued on Dmab, while the other discontinued therapy with both healing thereafter. In the seventh year of the FREEDOM extension trial, one additional case of ONJ was observed in the long-term study and one in the crossover study. All cases healed with conservative therapy (normal soft tissue covering previously exposed bone). Three of these individuals stopped treatment, but one continued Dmab therapy without recurrence of ONJ.

From the currently available data, the incidence of ONJ in the osteoporosis patient population appears to be very low, ranging from 0.15% to less than 0.001% person-years of exposure and may be only slightly higher than the frequency observed in the general population. It will, however, be important to quantify this, identify those at a greater risk of ONJ, implement measures to further decrease the likelihood of ONJ developing in patients taking BP or Dmab therapy for osteoporosis.

2b. Oncology

In general, the oncology patient with bone metastases is exposed to more intensive osteoclast inhibition than those with osteoporosis and the incidence of ONJ is much higher. The majority of the cases of ONJ have occurred with the use of high-dose i.v. BPs in the oncology patient population.

Data evaluating the incidence of ONJ in those with cancer include limited prospective studies as well as retrospective studies and case-series.

Prevalence

The prevalence of ONJ in oncology patients treated with i.v. BPs ranges from 0% to 0.186%.^(47,83–107)

Incidence

The incidence of ONJ in oncology patients treated with i.v. BPs ranges from 0 to 12,222 per 100,000 patient-years,^(14,23,62,65,108–148) and the incidence of ONJ in oncology patients treated with Dmab ranges from 0 to 2,316 per 100,000 patient-years.^(14,120,123,136,140–142,149)

The Phase III, randomized placebo-controlled studies comparing zoledronic acid 4 mg with Dmab 120 mg dosed monthly for the management of bone metastases have been pooled and analyzed for ONJ adverse events. In these studies, where counseling on oral health was provided, the incidence of ONJ was approximately 1% to 2%. In these pooled studies of Dmab,

in comparison to BPs, a similar or slightly higher numerical incidence of ONJ was seen with Dmab, but was not statistically significant.⁽²⁰⁾ Additional details of this study are outlined below, and similar results have been noted in other studies.^(14,26,28,120,123,139,149–153)

In patients with cancer, the incidence of ONJ appears to be related to dose and duration of BP or Dmab exposure.^(50,105,106,125) There is considerable variability in the reported incidence and prevalence of ONJ occurrence in association with monthly administration of i.v. BPs.^(26,28,29,65,83,85,99,103,105–107,109,113,119,122,125,132,139,150,154–161)

The incidence of ONJ in the oncology patient population may be affected by the type of malignancy being treated.^(28,65,85,99,107,119,132,150,154–156,159,162) Confounding variables also include the use of other drugs that may also impact bone health, such as glucocorticoids, or antiangiogenic drugs, such as bevacizumab. Christodoulou and colleagues⁽¹¹³⁾ retrospectively evaluated the incidence of ONJ among 116 patients receiving i.v. BPs. The prevalence of ONJ was 1.1% for those on i.v. BPs alone; however, this increased to a prevalence of 16% in those on BPs in addition to antiangiogenic agents (bevacizumab and sunitinib).

In a placebo-controlled trial in 1432 men with prostate cancer receiving androgen deprivation therapy (716 Dmab, 716 placebo), there were 33 cases of ONJ in the Dmab arm (cumulative incidence 5%), and none in the placebo arm.⁽¹⁴⁹⁾ This was a time-to-event (discovery of bone metastasis) study with some subjects followed up to 42 months.

The incidence of ONJ has been reviewed in an integrated analysis of three clinical trials comparing Dmab 120 mg monthly to zoledronic acid 4 mg monthly in the prevention of skeletal-related events (SREs): pathological fracture; radiation therapy to bone; surgery to bone; and spinal cord compression.⁽²⁶⁾ These trials were in patients with breast cancer, prostate cancer, multiple myeloma, or solid tumors with bone metastases. Dmab use was associated with significantly fewer SREs in the breast and prostate cancer trials. Overall, in 5723 patients studied over approximately 30 months, there were 89 ONJ cases: 52 in the Dmab arms (1.8%) versus 37 in the zoledronic acid-treated arm (1.3%). Although there were more ONJ cases in the Dmab-treated subjects, the difference was not statistically significant—the combined three trials had only sufficient power to detect a difference in relative risk of 76% between treatment arms.⁽¹⁵²⁾

In a recent meta-analysis of seven randomized controlled trials, Dmab was associated with an overall 1.7% risk of ONJ and an increased risk of developing ONJ in comparison to a combination of BP-treatment or placebo-treatment groups. However, the increased risk of ONJ with BP therapy alone was not statistically significant. At this time there are not enough data to determine if there is a difference in the risk of ONJ with high-dose Dmab therapy versus high-dose intravenous BP therapy.⁽¹⁶³⁾ Cessation of Dmab therapy may be associated with more rapid rate of resolution of ONJ than occurs with BPs; however, this requires further prospective study.

3. Who develops ONJ? What are the risk factors and comorbidity?

For a complete listing of the evidence reviewed for this topic, please refer to Supporting Table A5. A summary table of risk factors can be found in Supporting Table S9.

Epidemiological data on the prevalence and incidence of ONJ are limited and, when available, typically not based on prospective studies or population-based surveys.

Significant risk factors for the development of ONJ in the oncology population, in declining order of importance, include: i.v. BPs (both dose of BP and duration of exposure impact ONJ risk)⁽²⁴⁾; zoledronic acid^(83,105,112,150,164); pamidronate⁽¹⁵⁰⁾; Dmab (from incidence and prevalence data); radiation therapy⁽²⁴⁾; dental extraction^(24,105,150,161,165); chemotherapy⁽⁸⁴⁾; periodontal disease⁽¹⁶⁶⁾; oral BP use⁽²⁴⁾; osteoporosis⁽¹⁰⁵⁾; local suppuration⁽²⁴⁾; glucocorticoid therapy⁽¹⁰⁶⁾; diabetes⁽²⁸⁾; denture use^(150,165,167); erythropoietin therapy⁽¹⁰⁶⁾; tobacco use⁽²⁸⁾; hyperthyroidism⁽²⁸⁾; renal dialysis⁽¹⁰⁶⁾; cyclophosphamide therapy⁽¹⁰⁶⁾; etidronate⁽¹⁶⁸⁾; and increasing age.^(106,161)

Significant risk factors for the development of ONJ in the osteoporosis patient population, in declining order of importance, include: suppuration⁽²⁴⁾; BP use⁽²⁴⁾; dental extraction⁽²⁴⁾; and anemia.⁽²⁴⁾

Although Dmab was not identified as a risk factor in any of the searches, the data presented in the incidence and prevalence section would suggest that it is an additional risk factor, similar to BPs. It should be noted that both the BPs and Dmab are essentially included in the definition of drug-associated ONJ, so defining either as a risk factor for drug-related ONJ is methodologically perilous. However, it is clear that both of these drugs increase the incidence and prevalence of ONJ in both osteoporotic and oncology populations, as described in section 2 (How common is ONJ?), and are thus strongly implicated as being risk factors for ONJ.

4. Why does ONJ develop?

The pathophysiology of ONJ is not well understood. Until recently, most studies addressed the potential role of BPs, but the knowledge that Dmab therapy also increases the risk of ONJ^(13,69) emphasizes the need to explore mechanisms common to both interventions. All of the evidence reviewed regarding the pathophysiology/etiology of ONJ is provided in Supporting Table A6. A summary of these data is provided in Supporting Table S10.

Infection

The sequence of events leading to the development of ONJ is unclear; in particular, it is unknown whether necrosis precedes or follows infection. Dental disease is a well-established risk factor for ONJ,⁽³⁵⁾ implicating infection and inflammation in the pathogenetic process. Aggregates of bacteria and polymorphonuclear leukocytes are commonly seen in ONJ tissue and the presence of bacterial microfilms has been described in close association with active osteoclastic resorption on the bone surface.^(38,166) Bacteria are known to stimulate bone resorption^(169,170); hence, the microorganisms present may directly contribute to bone necrosis. In addition to preexisting dental trauma and disease, inhibitory effects of BPs on the proliferation and viability of oral keratinocytes^(171–176) may further damage the integrity of the oral mucosa and increase the risk of infection. Activation by BPs of gamma delta T cells may stimulate the production of proinflammatory cytokines and later depletion of these T cells may impair the immune response to infection.^(177–179)

Bone turnover

Suppression of bone turnover may also play a role in the development of ONJ.^(180,181) The association of ONJ with potent antiresorptive drugs^(62,69) and the increased risk with higher doses of BPs and Dmab would be consistent with this contention.^(14,62,120) In Beagle dogs treated with high doses of BPs, areas of necrosis in the mandible sometimes develop, with nonviable osteocytes in the affected bone.⁽¹⁵⁾ However, low bone turnover is not characteristically seen in affected tissue from ONJ patients⁽¹⁶⁶⁾; furthermore, ONJ has not been reported in other conditions associated with low bone turnover.

Vascularity

BPs are known to have antiangiogenic properties^(177–179) and it has been suggested that these may also contribute to the development of ONJ. ONJ has been described in several patients treated for cancer with antiangiogenic agents, in particular sunitinib⁽¹⁸²⁾ and bevacizumab,⁽¹⁵⁷⁾ although in these patients other risk factors were also present. Dmab is not known to have antiangiogenic effects, and normal vasculature has been reported in most histological studies of ONJ tissue.^(166,183) Animal studies with BPs do not support any diminution of vascular volume with BP administration.⁽¹⁸⁴⁾

Genetic predisposition

Not all patients with similar comorbidities and similar medical management develop ONJ; hence, pharmacogenomics may influence the risk of developing ONJ. It has been suggested that polymorphisms in the farnesyl pyrophosphate synthase⁽¹⁸⁵⁾ or cytochrome P450 CYP2C8 genes^(186,187) might predispose some individuals to develop ONJ. Genomewide association case-control studies have been performed in oncology patients and this is an area undergoing further exploration.^(188,189)

5. What is the role of imaging in diagnosis and management?

The evidence reviewed for the imaging of ONJ can be found in Supporting Table A7.

ONJ is a clinical diagnosis based on history and physical exam. Radiographic features of ONJ remain relatively nonspecific. Plain film radiography is usually unremarkable in the early stages of the disease because decalcification is limited.⁽¹⁹⁰⁾ The presence of localized or diffuse osteosclerosis or a thickening of the lamina dura on plain film imaging may predict future sites of exposed necrotic bone.⁽¹⁹⁰⁾ Poor ossification at a previous extraction site may also be an early radiographic feature of ONJ. Findings on computed tomography (CT) are nonspecific and may include areas of focal sclerosis, thickened lamina dura, early sequestrum formation, and reactive periosteal bone.^(191–194) CT imaging is of value in delineating the extent of disease and is helpful in planning surgical intervention.^(192,195) Features noted on bone scanning include increased tracer uptake at sites that subsequently develop necrosis.⁽¹⁹⁶⁾ The utility of nuclear bone scanning in patients at risk of ONJ requires further study.^(196,197)

Imaging modalities used as adjunctive assessment in the evaluation of the ONJ patient may include plain radiographs, CT, magnetic resonance imaging (MRI), and functional imaging with bone scintigraphy and positron emission tomography (PET).

Each one of these approaches has advantages and limitations. Supporting Figs. S2 and S3 provide clinical and radiographic images of patients with Stage 1 and 2 ONJ, respectively. Plain radiographs are often sufficient to support the diagnosis of ONJ for reasons described below, thus precluding the need for additional, more costly imaging procedures. However, advanced imaging may become necessary if the diagnostic information obtained via plain films is incomplete.

Radiographs—intraoral and panoramic radiographs

Intraoral (periapical and bitewing) radiographs are easy to acquire, inexpensive, and deliver a low radiation dose. Images are of high resolution and are useful in assessing early features of ONJ, including thickening of the lamina dura, increased trabecular density of the alveolar bone, and widening of the periodontal ligament space.⁽¹⁹⁸⁾ In addition, they provide useful information regarding the presence of carious lesions, periodontal disease, or periapical disease, which are all important risk factors for ONJ.⁽¹⁹⁹⁾

Panoramic radiographs are also of value and provide assessment of both arches, as well as adjacent anatomic structures including the maxillary sinus, nasal cavity, mental foramen, and mandibular canal. The typical radiographic findings of ONJ on intraoral and panoramic radiographs are increased trabecular density, incomplete healing of extraction sockets, sequestrum formation, thickening of the mandibular canal or sinus floor cortication, and periosteal bone formation.^(30,192,195,200,201)

Intraoral and panoramic projections are useful screening tools for assessing the presence of dental disease and the severity and extent of osteonecrotic changes, as well as for follow-up of patients with ONJ. However, if the diagnostic information is ambiguous or more detailed investigation of the dental and osseous health is required, more advanced imaging is necessary as described in the following sections.

CT and cone beam CT

CT has clear advantages over 2D imaging in characterizing the features of ONJ. The cortical and trabecular architecture of the maxilla and mandible can be evaluated as well as the presence of periosteal bone reaction, presence of sequestrum, and integrity of adjacent vital structures, allowing for earlier detection of ONJ lesions.^(193,200)

Common CT findings in ONJ patients include diffuse osteosclerosis, areas of osteolysis, cortical erosion, increased periosteal bone formation, and sequestration. Potential fistula track formation and incomplete extraction socket healing may be seen.^(30,200–203) Typically, these radiographic changes extend beyond the clinically exposed bone areas. In early stages of ONJ, increased trabecular density may not be detected on panoramic radiographs but may be seen on CT.⁽²⁰⁴⁾ CT radiographic findings may underestimate the extent of bony changes as assessed during surgery.⁽¹⁹³⁾ CT may demonstrate radiographic evidence of altered bone architecture at the symptomatic site and aid in disease diagnosis.^(190,205) Radiographic features of osteosclerosis can be seen in the absence of clinically exposed bone,⁽³⁸⁾ and in individuals with symptoms of bone pain careful evaluation is advised because these radiographic features may be a reflection of an early prodromal phase of ONJ.

Cone beam CT (CBCT) offers similar advantages to CT in evaluating the osseous structures of the face, while delivering

significantly less radiation. CBCT allows improved detection of periodontal and periapical disease in comparison to dental radiographs, particularly if a small field of view (FOV) is used.^(206,207) There are no conclusive definitive studies regarding the use of CBCT use and the diagnosis of ONJ. Data are limited to preliminary investigations.

A major disadvantage of CBCT is the low contrast resolution and poor soft tissue detail. However, the ability of CBCT to image bony structures is similar to that of CT.⁽²⁰⁷⁾ Because of the high-resolution volumetric imaging, CBCT shows improved diagnostic ability for periodontal and periapical disease in comparison to conventional radiographs.⁽²⁰⁶⁾ CBCT imaging findings of the osteonecrotic areas are similar to those with CT, and include increased bone density, osteolysis, cortical erosions, sequestration, and periosteal bone reaction.^(192,208,209)

MRI

MRI offers similar advantages to CT in evaluating the osseous ONJ changes, while it appears to be superior in assessing bone marrow change at the early stage of ONJ, as well as the soft tissue changes surrounding the osteonecrotic area.

One of the most consistent and earliest MRI findings is a decrease of bone marrow signal intensity on T1-weighted images that can be present prior to clinical features of ONJ.^(193,197,201,210) T2-weighted and short T1 inversion recovery (STIR) sequences may show increased signal intensity because of high water content,⁽²⁰⁴⁾ while irregular gadolinium enhancement of bone marrow and soft tissues around osteolytic areas is observed.^(197,201,210) In advanced disease the bone marrow signal intensity on T2-weighted and STIR images can be variable: the exposed bone shows decreased signal intensity, and the unexposed diseased bone shows increased signal intensity.^(201,211) Sequestra display a low-signal-intensity center with a high-signal-intensity rim on the T2-weighted image.^(197,212) Soft tissue thickening and edema and lymph node enlargement can also be observed.^(36,210) Similar to CT, MRI shows increased ability to detect osseous ONJ changes compared to panoramic radiographs; however, it may also fail to demonstrate the full extent of bony changes seen on surgical exploration.⁽¹⁹³⁾

Nuclear imaging with scintigraphy and PET

Bone scintigraphy using Tc99m methylene diphosphonate (MDP) or hydroxymethylene diphosphonate (HDP) has a high sensitivity for detecting early disease. Bone scintigraphy shows increased radionuclide uptake with increased perfusion and increased blood pool. Single-photon emission CT (SPECT) and fusion SPECT/CT provide more precise localization of osteonecrotic areas with surrounding areas of increased radionuclide uptake.^(191,213) In 67.5% of patients with ONJ, increased Tc99m-MDP or HDP was observed in areas that later developed clinical osteonecrosis; thus, bone scans may be useful in early identification of ONJ.^(196,214) However, it is not uncommon for conditions other than ONJ to produce increased uptake in the jaw, including tumor or periodontal disease.^(215,216)

PET alone or in combination with CT has also been used for the assessment of ONJ patients, using both F-18 fluoride (NaF) and F-18 fluorodeoxyglucose (FDG) tracers.^(214,217,218) Interestingly, FDG-PET uptake appears to increase with ONJ severity, although a clear relationship has not been established, which is possibly due to the small number of patients in the study.⁽²¹⁷⁾

In summary, imaging is of value in diagnosing ONJ. This is particularly the case in those individuals on antiresorptive therapy with ONJ-like symptoms, but without obvious bone exposure. Because periapical and periodontal disease is an important risk factor for ONJ, identifying early dental disease with imaging and proceeding with dental preventive measures may decrease the risk of ONJ and minimize the need for dental extractions.^(118,219) In addition, imaging enables exclusion of other conditions that may contribute to necrosis, such as metastatic disease.^(220,221) There are no pathognomonic features of ONJ on imaging that definitively differentiate ONJ from other conditions.⁽²²²⁾ However, imaging can assist in identifying the extent of bone and soft tissue disease as well as providing information on dental, periodontal, and periapical health. A summary of imaging findings with ONJ is presented in Supporting Table S11.

Recommendations for imaging

A. Individuals on low-dose antiresorptive treatment without signs or symptoms of ONJ do not require any additional imaging over and above routine dental evaluation.^(223–225)

B. Patients on high-dose antiresorptive treatment without ONJ are at significant risk of developing ONJ and early identification of dental disease is important.^(118,219) Following a complete examination of the oral cavity, high-risk patients should ideally receive bitewing and periapical intraoral radiographs of all existing teeth as well as panoramic radiographs. When available, CBCT 3D imaging using high-resolution protocols could also be performed, given the superior ability of CBCT (compared to conventional radiographs) in diagnosing periapical and periodontal disease. Following a baseline evaluation of oral health, additional conventional and CBCT radiographs are performed only if necessary in the presence of oral complaints or signs or symptoms of ONJ.⁽²²⁶⁾

C. In patients in whom ONJ is a clinical consideration on low-dose or high-dose antiresorptive therapy presenting with oral symptoms, CBCT or CT imaging may aid in evaluating early changes in the cortical and trabecular architecture of the maxilla and mandible. Imaging also allows assessment of possible sequestrum or fistula track formation and evaluation of the status of any involved teeth. If both CBCT and CT are available, small-FOV, high-resolution CBCT is preferred because it delivers less radiation and provides similar diagnostic information as CT. CBCT may be performed in conjunction with bitewing, periapical, and panoramic radiographs. If clinically indicated, MRI may provide additional information of the presence and extent of osteonecrosis.

D. In patients with clinical ONJ under conservative management (Stage 1 and 2), the nature and extent of osseous changes around the area of clinical bone exposure can be evaluated with CT or small-FOV high-resolution CBCT imaging. Dental disease in all existing teeth should also be determined with bitewing, periapical, and panoramic radiographs.

E. In patients with clinical ONJ where surgical intervention is considered (Stage 2 and 3), CBCT or CT may be complemented with MRI, bone scan, or PET for a more thorough evaluation of involved bone and soft tissues.

6. Are biomarkers useful in identifying ONJ?

Please refer to Supporting Table A8 for a full description of all the papers reviewed in this section.

ONJ is a complication associated with the use of the antiresorptive therapies, either with BPs and/or Dmab. Marx and colleagues⁽²²⁷⁾ suggested that quantification of bone resorption may be useful for prognosis. They reported data on 30 women treated with oral BPs for low bone density who had subsequently presented with ONJ. Seventeen of these women were still taking oral BP at the time of presentation, and had C-terminal telopeptide (CTX) values of 30 to 102 pg/mL (mean 73 pg/mL). After 6 months off BPs, CTX values were 162 to 343 pg/mL (mean 228 pg/mL), a mean rise of 26 pg/mL/month. ONJ healed in all patients over the following 18 months, and the authors concluded that this was causally associated with the higher bone turnover. Although this is possible, the hypothesis was not formally tested because none of the patients were assessed while continuing BP therapy. At presentation, there was no correlation between CTX and clinical severity in this cohort, nor in 60 other ONJ patients receiving i.v. BPs. They concluded that if CTX is >150 pg/mL in patients receiving oral BPs then invasive oral surgical procedures can be completed with minimal risk of osteonecrosis, although no data supporting this statement are presented (Marx criteria: CTX <100 pg/mL = high risk, 100 to 150 pg/mL = moderate risk, and >150 pg/mL = minimal risk).

Cross-sectional studies in patients with ONJ have evaluated the association between CTX levels and disease severity. Although Bagan and colleagues⁽²²⁸⁾ found no relationship in 15 oncology patients, Kwon and colleagues⁽²²⁹⁾ found that CTX levels were related ($r = 0.47$) to the number of the ONJ lesions and their stage in 18 patients receiving oral BP therapy, although CTX levels were not different from those in BP-treated osteoporosis patients without ONJ.⁽²³⁰⁾

The utility of CTX has been evaluated in its ability to predict outcomes in patients with ONJ. In each of these studies, many patients were “at risk” by the Marx criteria. Atalay and colleagues⁽²³¹⁾ found that CTX did not predict treatment prognosis in 20 cancer patients, despite a wide range of baseline CTX values. CTX levels in BP-treated subjects have been assessed as a predictor of ONJ risk after oral surgery. Kunchur and colleagues⁽²³²⁾ measured CTX in 222 BP users undergoing extractions. Only one patient developed ONJ and had a moderate level of CTX (126 pg/mL). Lee and Suzuki⁽²³³⁾ assessed CTX levels in 54 patients on oral BPs undergoing oral surgery and despite a very wide range of CTX values prior to surgery (39 to 330 pg/mL; mean of 161 pg/mL), no patient developed ONJ. Similarly, O’Connell and colleagues⁽²³⁴⁾ measured CTX values in 23 patients on BPs, 21 with osteoporosis and two with cancer, prior to oral surgery (CTX range, 50 to 370 pg/mL; mean 180 pg/mL). After 5 months of observation, no patient had developed ONJ. In the HORIZON trial, one case of ONJ developed in 5903 patients given zoledronic acid, and a second case developed in the 5140 placebo-treated subjects.⁽⁷⁵⁾ In this trial, 43% of patients had serum CTX <100 ng/mL 6 months after zoledronic acid and would be considered at “high risk” by the Marx criteria, yet ONJ risk was no higher than in the placebo group. The very low incidence of ONJ in osteoporosis subjects indicates that even very large studies are underpowered to answer this question.

Few other biomarkers of bone turnover have been assessed with respect to ONJ management or to their utility in making decisions regarding the individual patient’s risk for ONJ. One study found that neither N-terminal telopeptide (NTX) nor bone alkaline phosphatase was associated with the development of ONJ.⁽²³⁵⁾ Lehrer and colleagues^(236,237) performed two studies

with neither finding an association of ONJ with CTX, NTX, bone alkaline phosphatase, or osteocalcin.

Thus, although low CTX is a reflection of recent antiresorptive treatment, current data do not establish it as having a useful role in managing patients with or at risk of ONJ.

7. Can ONJ be prevented and what is the role of drug interruption?

Supporting Table A9 presents all the data with respect to prevention of ONJ.

Recommendations to reduce the risk of ONJ include completion of necessary oral surgery prior to initiation of antiresorptive therapy,^(154,219,238,239) the use of antibiotics before and/or after the procedure,^(22,25,239–242) antimicrobial mouth rinsing,^(22,25,241) appropriate closure of the wound following tooth extraction,^(240–242) and maintenance of good oral hygiene.^(103,238,240,241,243,244)

The etiology of ONJ continues to be further investigated. Poor oral health, minor oral surgery, and use of potent antiresorptive agents appear to be associated with the condition. In an attempt to prevent ONJ, optimizing oral health prior to the initiation of BP and Dmab therapy is emphasized. Indeed, this simple intervention appears to be efficacious in reducing the risk of ONJ as noted by Ripamonti and colleagues⁽²¹⁹⁾ and Dimopoulos and colleagues,⁽¹¹⁸⁾ and Montefusco and colleagues⁽²³⁹⁾ retrospectively assessed the role of prophylactic antibiotics prior to dental procedures for the prevention of ONJ in a group of patients with multiple myeloma. Interestingly, of the 178 patients assessed, eight cases of ONJ developed, but all cases occurred in the group not provided with prophylactic antibiotics. It was concluded that a course of antibiotics prior to dental procedures may prevent the occurrence of subsequent ONJ.

Following the initial reports of ONJ in association with BP use in 2003, the vast majority of cases (>90%) have occurred in cancer patients receiving sixfold to 10-fold higher doses of BPs than those used to treat osteoporosis. Invasive oral surgery procedures have been identified as an important risk factor for ONJ. Therefore, it is recommended by the Task Force that patients who undergo invasive oral surgery have their antiresorptive therapy withheld following the procedure until soft tissue healing has occurred. However, it is acknowledged that there is little evidence to support this recommendation in terms of changing the outcome of the dental procedure because BPs remain in bone for many years. In patients taking lower-dose BPs for osteoporosis, the risk of ONJ is recognized to be extremely low (1 in 10,000 to 1 in 100,000 patients, compared with ~1% to 2% per year for cancer patients receiving higher doses of BPs). In 2011, the American Dental Association Guidelines recognized the lower risk in osteoporosis patients, and stated that discontinuation of oral BP was not necessary prior to dental procedures.⁽²⁴⁵⁾

In determining the best approach for each individual patient with respect to ongoing antiresorptive therapy it is necessary to stratify risk and weigh the risks of ONJ with the risk of fracture in osteoporosis patients and the risk of SREs in oncology patients. The ONJ risk will be impacted by comorbidity as well as the extent of the planned surgery.

Clinical judgment is always essential, and in patients who may require extensive invasive oral surgery, as well as those with multiple risk factors for ONJ (diabetes, periodontal disease, glucocorticoid treatment, immune deficiencies, smoking, etc.), it may be advisable to stop antiresorptive therapy if it is possible to

do so without adverse consequences for bone health. In such circumstances the Task Force recommends stopping antiresorptive therapy.

For cancer patients requiring oncology doses of i.v. BPs or Dmab, a thorough dental examination with dental radiographs should be ideally completed prior to the initiation of oncology-dose antiresorptive therapy in order to identify dental disease before drug therapy is initiated. Any necessary invasive dental procedure including dental extractions or implants should ideally be completed prior to initiation of BP or Dmab therapy. Non-urgent procedures should be assessed for optimal timing because it may be appropriate to complete the non-urgent procedure prior to osteoclast inhibition, delay it until it is necessary, or perhaps plan for it during a drug holiday; however, there are no compelling data to guide these decisions.

Injudicious discontinuation of osteoporosis therapy can lead to increased risk of fractures, including hip and vertebral fractures. The decision to discontinue therapy with bone active agents must also consider the risk of fracture and implications for skeletal health.

In the presence of ONJ in a patient receiving BP or Dmab, it is recommended that oncology-dose antiresorptive drug therapy be withheld until soft tissue closure with well-epithelialized mucosa is achieved.

8. How should ONJ be managed?

A review of all the evidence for the treatment of ONJ is found in Supporting Table A10.

There are no universally accepted treatment protocols for ONJ. In the absence of a defined treatment algorithm for ONJ, there is a generally accepted approach of palliation of symptoms and controlling associated infection. Treatment strategies range from conservative nonsurgical therapy to early surgical intervention. The extent of surgery also varies and is dependent upon the stage of disease.

Treatment

Many variables may contribute to the treatment decision-making tree, including age, sex, disease status (osteoporosis, metastatic disease versus multiple myeloma, for example), ONJ stage and lesion size, medication exposure, and medical and pharmacological comorbidities. The specifics of how these factors influence the course of ONJ and its treatment response are largely unknown and, as such, clinical judgment should guide individual treatment approach.

Other important factors to consider in this group of patients are prognosis and life expectancy, quality of life, and an individual's ability to cope with their ONJ lesion(s). A similar-sized lesion may be asymptomatic in one patient, but pose considerable difficulties in another.

Conservative management

The majority of patients with ONJ have been managed conservatively. Conservative therapy includes maintaining optimal oral hygiene (diligent home self-care and regular professional dental care), elimination of active dental and periodontal disease, topical antibiotic mouth rinses, and systemic antibiotic therapy, as indicated. This is consistent with the previous recommendations of the Canadian Association of Oral and Maxillofacial Surgeons (CAOMS), AAOMS, and

the American Dental Association,^(1,2,33,245) and is supported by many practitioners.^(132,246) Conservative therapy is the mainstay of care and although it may not necessarily lead to complete resolution of lesions, it may symptomatically provide long-term relief.^(26,247) Among patients with breast cancer and multiple myeloma, Fortuna and colleagues⁽²⁴⁸⁾ reported a more rapid response to conservative therapy in the breast cancer group compared to those with multiple myeloma.

Recent case reports of successful treatment of ONJ with teriparatide are encouraging^(249,250) and this may become a conservative treatment choice for those with osteoporosis and without cancer or prior radiation therapy to bone. Because teriparatide has been reported to facilitate osseous wound healing in the oral cavity,⁽²⁴⁹⁾ it may be a viable approach for patients on antiresorptive therapy for the treatment of osteoporosis. Considering the low risk of ONJ in patients with osteoporosis being treated with osteoporosis doses of anti-resorptive agents and the absence of evidence that changing to teriparatide would alter the outcome of an invasive dental procedure in someone who does not have ONJ, it is not recommended at this time to switch to teriparatide in those at a low risk of ONJ or fracture. However, in an osteoporotic patient with established ONJ, treatment with teriparatide may be of value as observed in published case reports.^(251–256)

The same approach should not be used in patients with cancer, a history of skeletal radiation, or with active bone metastases, because these patients are at risk for the development or advancement of bone malignancies and teriparatide should be avoided unless prospective studies demonstrate a favorable benefit-to-risk ratio for its use.

Other experimental treatment approaches found in the literature awaiting further substantiation include topically applied ozone,⁽²⁵⁷⁾ bone marrow stem cell intralesional transplantation,⁽²⁵⁸⁾ and addition of pentoxifylline and tocopherol to the standard antibiotic regimen.⁽²⁵⁹⁾ The latter reportedly reduced both ONJ symptoms and the amount of exposed bone. One in vitro study suggested that geranylgeraniol might potentially prevent BP-induced predisposition to ONJ.⁽²⁶⁰⁾ Favorable outcomes have been reported with low-level laser therapy, in conjunction with conservative and/or surgical debridement, but further confirmation is needed.^(261,262)

Conservative therapy should be continued as long as there is not: (1) obvious progression of disease; (2) pain that is not being controlled by conservative means; or (3) a patient who has had antiresorptive therapy discontinued by their oncologist because of ONJ.

Surgical management

Early treatment recommendations for ONJ discouraged surgical intervention with conservative therapy continuing indefinitely or until there was progression of disease. However, there are now many reports demonstrating success with surgical management of these lesions. With surgery, a full-thickness mucoperiosteal flap should be elevated and extended to reveal the entire area of exposed bone and beyond to disease-free margins. Resection of the affected bone should be extended horizontally and inferiorly to reach healthy-appearing, bleeding bone. Sharp edges should be smoothed and primary soft tissue closure achieved in a tension-free fashion with sutures that resorb after 1 week.⁽²⁶³⁾ Several authors have reported better outcomes with larger resections compared to limited debridement and/or conservative therapy.^(264,265)

We propose that if surgery is indicated, resection with tension-free closure affords the most positive results.

Adjunctive treatments, in combination with surgery, have been also described in the literature. Vescovi and colleagues⁽²⁶²⁾ achieved good results treating ONJ lesions with laser-assisted surgical debridement; in contrast, Atalay and colleagues⁽²³¹⁾ found no statistically significant benefit of this approach in comparison to conventional surgery. Martins and colleagues⁽²⁶⁶⁾ conducted a preliminary retrospective survey of patients undergoing antibiotic therapy plus surgery followed by low-level laser therapy and platelet-rich plasma applied to the surgical wound, and observed improved healing.

Promising results have also been reported with surgical debridement in combination with platelet-derived growth factor (PDGF) applied to the site in Stage 2 ONJ cases.⁽²⁴²⁾ Pautke and colleagues⁽²⁶⁷⁾ reported that intraoperative fluorescence guidance was helpful in identifying surgical resection margins in Stage 2 ONJ cases. Hoefert and Eufinger⁽²⁶⁸⁾ suggested that longer-term preoperative antibiotics (23 to 54 days) resulted in improved surgical outcomes versus short-term antibiotic therapy (1 to 8 days). Surgical success rates have been higher in patients with multiple myeloma or in those with osteoporosis receiving low-dose BP therapy in comparison to patients with solid tumors.⁽²⁶⁹⁾

Adjunctive therapy with hyperbaric oxygen (HBO) in combination with surgery has been investigated^(270,271) with encouraging results. Further research is required with these innovative combination therapies prior to formalizing treatment recommendations.

In summary, in the absence of debilitating ONJ lesions, conservative therapy with optimal oral hygiene, topical antibiotic rinses, and systemic antibiotics are advised as needed for pain or infection.⁽²³⁸⁾

For nonresponsive ONJ lesions, surgery is an option and includes ostectomy of the affected area with resection margins that extend into adjacent normal-appearing bone. Soft tissue closure should be tension-free with no underlying sharp edges of bone that could lead to mucosal breakdown.

In the presence of a pathologic fracture or ONJ extending to the sinus or inferior border of the mandible, or if the ostectomy to healthy tissue leads to a discontinuity defect, consideration should be given to microvascular composite tissue grafting at the time of surgical resection in the mandible and the same or obturator construction for the maxilla.

At present, other adjunctive procedures as discussed in this section may be considered, but all require further research to define their value.

9. Research and future directions

It has been 10 years since the original case descriptions of ONJ were reported. The insights gained during this past decade into the pathophysiology of ONJ as well as mechanisms involved that could be targeted for therapeutic approaches have increased, but are not at a sufficient level to enable the development of optimal care strategies for our patients.⁽²⁷²⁾ Over these 10 years, the paucity of scientifically sound information has often led to confusion among patients and healthcare providers. We need to do better and must rely on the scientific community, supported by governmental agencies, pharmaceutical companies, and foundations, to expand our knowledge and improve patient care.

The pathophysiology of ONJ needs to be more clearly delineated using well-characterized animal models that lend themselves to better understanding the human condition. Several ONJ animal models have been described in mice, rats, minipigs, and dogs treated with high doses of bisphosphonates.^(15,273–289) Most of these models use tooth extraction,^(275,280–286,288) while others stimulate experimental periodontal or periapical disease^(273,274,279,287) to induce ONJ-like lesions. Recently, ONJ was described in mice treated with RANKL inhibitors without BPs, indicating the central role of osteoclast inhibition in ONJ pathogenesis.⁽²⁸⁹⁾ These animal models capture several of the clinical, radiographic, and histologic features of ONJ. However, differences in bone composition, bone remodeling, and overall metabolism between animals and humans have been problematic. None have effectively captured the full picture of the human condition such that interventional approaches can be reliably tested.

ONJ appears to occur most commonly in those with metastatic bone disease receiving high doses of osteoclast inhibitors concurrently with anticancer therapy. In this patient population, the risk-benefit profile associated with the osteoclast inhibitors is unique from other indications for an antiresorptive therapy, in that their risk of skeletal complications of malignancy is estimated as one event occurring every 3 to 4 months in the absence of osteoclast inhibition.⁽²⁹⁰⁾ These SREs may be catastrophic, for example spinal cord compression resulting in paralysis, or hypercalcemia of malignancy, which is often a life-threatening event. When administered at U.S. Food and Drug Administration (FDA)-recommended dosing, the use of potent osteoclast inhibitors reduces the risk of skeletal-related events by approximately 20% to 50%.⁽²⁹¹⁾ Hence, the oncology patient with metastatic bone disease, and their clinical care team, may view the risk of ONJ as the lesser of two evils. However, the risk of ONJ is much lower than the risk of SRE for the vast majority of cancer patients.

As advances in osteoclast inhibition and anticancer therapies are made, it is critical that treatment regimens be assessed for both short-term and long-term adverse events, including ONJ. This is the case for both early-stage and late-stage cancers. In early-stage breast cancer, there are evolving data that the potent osteoclast inhibitors may have an anticancer effect in postmenopausal women. Therefore, it is possible that the BPs may be used in a larger patient population including those who may not have low bone mass. In one adjuvant zoledronic acid Phase III study, approximately 2% of the patients with breast cancer treated with zoledronic acid developed ONJ,⁽¹³³⁾ although other studies have reported a lower incidence.

Further research will provide effective strategies to prevent ONJ as well as define the risk of SRE and ONJ in individuals with metastatic bone disease. A greater understanding of these risks will enable clinicians to more effectively tailor drug therapy with respect to dose and frequency of administration of the osteoclast inhibitor in order to minimize both the risk of SRE and ONJ. The management of these individuals requires a multidisciplinary approach to develop evidence-based clinical practice algorithms. The panel will provide guidance through expert opinion and best evidence currently available for the oncology patient in a subsequent document.

Ongoing registries of ONJ include independent international studies and a study funded by Amgen. There is an ongoing

biomarkers study as well as ongoing case-control ONJ studies and correlative investigations incorporated into BP and Dmab clinical trials. The results of these studies will add prospective epidemiologic information on risk factors associated with the development of ONJ. In addition, basic science studies of the mechanism of ONJ include investigation of the effect of antiresorptive therapy on wound healing, the oral mucosal barrier, and identification of biomarkers predictive of the development of ONJ.

There is considerable room for clinical, translational, and basic science research because the cellular mechanisms involved in oral wound healing and the influences of antiresorptive medications need to be clarified. Much of the hope for progress resides in the field of osteoimmunology. Although osteoclasts have been the focus of studies in the mineralized tissue field for decades, the dependence of oral wound healing on osteoclasts is understudied. The temporal nature of osteoclastic activity in oral wounding and the role of osteoclasts as phagocytic cells in the wound environment are of interest. For example, are the signaling molecules different in activated osteoclasts depending on the mineral surface they are associated with? Do osteoclasts associate differently with bacterial toxin-contaminated surfaces? What is the impact of antiresorptives in the inflammatory lesion? The role of osteocytes in osseous necrosis, remodeling, and antiresorptive drug actions requires further investigation. The impact of antiresorptive drugs on non-osteoclast bone marrow cells such as macrophages is ill-defined. Do BPs or anti-RANKL antibodies alter the profile of classical M1 macrophages, M2 alternatively activated macrophages, or pro-resolving macrophages?

There is a clear need for improved diagnostic and prognostic factors for ONJ. Improved prospective studies in patients at risk for ONJ could provide better insight into predictors of the condition as well as optimizing preventive approaches. What is the impact of inhibiting osteoclasts early during wound healing (eg, immediately postextraction) when osteoclasts are responsible for recontouring the wound margins versus later (eg, when the immature woven bone is remodeled to form mature lamellar bone)?

Finally, current therapeutic options are inadequate for the prevention and treatment of ONJ. It is challenging to do large clinical trials with the patient population currently presenting with ONJ. However, we do not yet have in-depth studies of the effects of any drugs used for the treatment of osteoporosis and cancer on osseous tissues in the oral cavity. Such studies are necessary to clarify potential issues specific to craniofacial bones. A detailed trajectory of healing postextraction in patients on antiresorptives relative to patients on anabolic agents or normal healthy controls has not been performed and would provide valuable new insights into skeletal site specificity and oral wound healing.

Oral Ulceration and Benign Sequestration

A literature search was conducted specifically pertaining to oral ulceration and benign sequestration (OUBS) on June 25, 2014 (<http://www.ncbi.nlm.nih.gov/pubmed/?term=oral+ulceration+and+sequestration>). The literature search yielded 11 total citations, three of which were not related and were discarded. The remaining eight papers were case reports or case series.^(5,292–298) Two additional investigations were added through expert review.^(6,7)

Diagnosis

This condition presents as a variably painful ulceration, usually involving the posterior lingual mandible at the level of the mylohyoid ridge.^(5–7,292) There is a hard insensitive base formed by exposed non-vital bone. The ulcer can persist for periods that vary between a few days to several months. Occlusal radiographs show a localized radiopacity, representing the necrotic bone, superficial to the lingual cortical plate. Similar lesions can occur over oral exostoses. Histopathologic exam of the necrotic bone base shows irregular zones of resorption, microbial colonization, and often, adherent fragments of acutely inflamed granulation tissue. The condition occurs in the absence of predisposing systemic disease or antiresorptive therapy.

Pathophysiology

The pathogenesis is not well understood. However, ulceration, either traumatic or in the form of an aphthous ulcer, is thought to be the initial pathologic event.^(5–7,292) Sequestration could occur following subsequent disruption of blood supply from the periosteal layer to the poorly vascularized superficial cortical bone and possible secondary infection. The devitalized and secondarily infected bone base then impedes resolution of the ulcer. The predilection of the condition for posterior lingual mandibular bone has resulted in suggestions that the anatomic site might be of etiologic importance. Of possible significance, many of these cases occur in patients who have lost posterior molars or have restorations, which do not recapitulate the normal lingual inclination of the molars. Thus, the protective lingual inclination of the molars over the mylohyoid ridge is lost and the nonkeratinized mucosal lining over the projecting mylohyoid ridge would not be shielded from chronic trauma during mastication. After the ulcer has formed, it would be further susceptible to secondary infection because it is located in a relatively stagnant oral region. The suggestion that an aphthous ulcer, rather than a traumatic ulcer, might be the primary lesion could result in the same sequence of pathologic events, and these are not mutually exclusionary suggestions.

Management

This is usually a self-limited condition that heals with conservative measures.^(5–7,292) The necrotic bone may undergo spontaneous exfoliation. If the sequestrum is mobile, the process can be expedited with gentle manipulation of the sequestrum through the ulcer base. If the dead bone is adherent to the underlying cortex, surgical removal might be required. However, often a patient approach with supportive management involving antimicrobial rinses, such as chlorhexidine or tetracycline, will result in detachment of the sequestrum from underlying vital bone and eventually permit spontaneous exfoliation. Once the necrotic bone has been removed, efficient healing occurs.⁽²⁹⁹⁾

Future research directives

There is a need for further research on OUBS. Studies are required to evaluate the incidence and prevalence of this condition. The proportion of OUBS conditions that can result in significant morbidity in terms of size, duration, and pain should be assessed. Development of a staging system would be of value, particularly with respect to optimization of treatment strategies. The role of this condition as an initiating event for the significant drug-associated ONJs should be evaluated.

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