American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw—2014 Update

Salvatore L. Ruggiero, DMD, MD, Thomas B. Dodson, DMD, MPH,† John Fantasia, DDS,‡ Reginald Goodday, DDS, MSc,§ Tara Aghaloo, DDS, MD, PhD,‖ Bhoomi Mehrotra, MD,¶ and Felice O'Ryan, DDS#*

Strategies for management of patients with, or at risk for, medication-related osteonecrosis of the jaw (MRONJ) were set forth in the American Association of Oral and Maxillofacial Surgeons (AAOMS) position papers in 2007 and 2009. The position papers were 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. The AAOMS considers it vitally important that this information be disseminated to other relevant health care professionals and organizations.

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The special committee recommends changing the nomenclature of *bisphosphonate-related osteonecrosis of the jaw*. 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 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,

*Clinical Professor, Division of Oral and Maxillofacial Surgery, Stony Brook School of Dental Medicine, Hofstra North Shore-LIJ School of Medicine, New York Center for Orthognathic and Maxillofacial Surgery, Lake Success, NY.

†Professor and Chair, Associate Dean for Hospital Affairs, Department of Oral and Maxillofacial Surgery, University of Washington School of Dentistry, Seattle, WA.

‡Chief, Division of Oral Pathology, Department of Dental Medicine, Hofstra North Shore-LIJ School of Medicine, New Hyde Park, NY.

§Professor, Department of Oral and Maxillofacial Sciences, Dalhousie University, Halifax, NS, Canada.

‖Associate Professor, Oral and Maxillofacial Surgery, Assistant Dean for Clinical Research, UCLA School of Dentistry, Los Angeles, CA.

¶Director, Cancer Institute at St Francis Hospital, Roslyn, NY.

#Director, Division of Maxillofacial Surgery, Kaiser Permanente Oakland Medical Center, Oakland, CA.

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Address correspondence and reprint requests to Dr Ruggiero: New York Center for Orthognathic and Maxillofacial Surgery, 2001 Marcus Avenue, Suite N10, Lake Success, NY 11042; e-mail: sruggie@optonline.net

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Purpose

The purpose of this updated position paper is to provide:

- Risk estimates of developing MRONJ
- Comparisons of the risks and benefits of medications related to osteonecrosis of the jaw (ONJ) to facilitate medical decision making for the treating physician, dentist, dental specialist, and patients
- Guidance to clinicians regarding:
  - The differential diagnosis of MRONJ in patients with a history of exposure to antiresorptive or antiangiogenic agents
  - MRONJ prevention measures and management strategies for patients with MRONJ based on 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 (SREs) associated with bone metastases in the context of solid tumors such as breast, prostate, and lung cancers, and for management of lytic lesions in the setting of multiple myeloma.[2-13] Although the potential for BPs 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, such as once yearly infusion of zoledronate (Reclast; Novartis Pharmaceuticals Corporation, East Hanover, NJ) and a parenteral formulation of ibandronate (Boniva; Genentech, South San Francisco, CA) administered every 3 months, have US Food and Drug Administration (FDA) approval for management of osteoporosis.[14]

Oral BPs are approved for treatment of osteoporosis and osteopenia.[15] They have been used in less common conditions, such as Paget disease of bone and osteogenesis imperfecta.[16,17] The most common use is for osteopenia and osteoporosis.[18,19]

The receptor activator of nuclear factor κB ligand (RANKL) inhibitor (denosumab) is an antiresorptive agent that exists as a fully humanized antibody against RANKL and inhibits osteoclast function and associated bone resorption. When denosumab (Prolia; Amgen, Thousand Oaks, CA) is administered subcutaneously every 6 months, there is a decrease in the risk of vertebral, nonvertebral, and hip fractures in osteoporotic patients.[20,21] Denosumab (Xgeva; Amgen) also is effective in decreasing SREs 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 BPs, RANKL 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 molecules, thus disrupting the angiogenesis-signaling cascade. These novel medications have shown efficacy in the treatment of gastrointestinal tumors, renal cell carcinomas, neuroendocrine tumors, and other malignancies.

Risks of Jaw Necrosis Related to Antiresorptive Therapy

Oral and maxillofacial surgeons first recognized and reported cases of nonhealing exposed bone in the maxillofacial region in patients treated with IV BPs.[24,25] In September 2004, Novartis (Basel, Switzerland), the manufacturer of the IV BPs pamidronate (Aredia) and zoledronic acid (Zometa), notified health care professionals of additions to the labeling of these products, which provided cautionary language related to the development of ONJ.[26] This was followed in 2005 by a broader drug class warning of this complication for all BPs, including the oral preparations.[27,28] More recently, other antiresorptive agents and novel anticancer drugs have been linked to the development of ONJ (Appendices I, II).

MRONJ Case Definition

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 the following characteristics are present:

- Current or previous treatment with antiresorptive or antiangiogenic agents
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- 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 also can present with other common clinical conditions not to be confused with MRONJ. Commonly misdiagnosed conditions can include, but are not limited to, alveolar osteitis, sinusitis, gingivitis and periodontitis, caries, periapical pathology, odontalgia, atypical neuralgias, fibro-osseous lesions, sarcoma, chronic sclerosing osteomyelitis, and temporomandibular joint disorders. Moreover, it is important to remember that exposed bone or sequestra can occur 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 concerns 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]

INHIBITION OF OSTEOCLASTIC BONE RESORPTION AND REMODELING

BPs and other antiresorptive drugs, 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 play a vital role in bone healing and remodeling in all skeletal sites, but ONJ occurs only 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 to occur in the jaws compared with other bones in the axial or appendicular skeleton. Long-term studies in a large animal model have shown decreased intracortical bone turnover with dynamic histomorphometry.[30,47] The central role of bone remodeling inhibition has been further corroborated by a similar incidence of ONJ observed with other antiresorptive medications, such as denosumab.[48-50] Preliminary evidence has shown improved extraction socket healing in animals receiving systemic zoledronic acid when treated with parathyroid hormone. This might be due to its positive effect on osteoclasts to increase bone remodeling.[51,52]

INFLAMMATION AND INFECTION

Systemic and local oral risk factors have been implicated in ONJ pathogenesis, in which several human studies have implicated dental disease or bacterial infection.[53-55] Although tooth extraction was performed in most 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 show that inflammation or bacterial infection and systemic antiresorptive drugs 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 from 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 multi-organism ONJ-associated biofilm.[67-70]

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 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; therefore, it is not surprising that inhibition of angiogenesis is a leading hypothesis in ONJ pathophysiology.[30-32,71] In vitro experiments have consistently shown a decrease in angiogenesis in response to zoledronic acid.[40,72] Studies in patients with cancer treated with zoledronic acid have supported these data by reporting decreased circulating VEGF levels.[73] Moreover, there is a growing body of literature linking ONJ and osteonecrosis of other bones in patients receiving novel antiangiogenic drugs (tyrosine kinase inhibitors [TKIs] and monoclonal antibody–targeting VEGF). However,

inhibition of angiogenesis has not been reported with denosumab.

OTHER HYPOTHESES

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 have exhibited increased apoptosis or decreased proliferation after exposure to BPs in vitro, including cervical, prostate, and oral epithelial cells.[75-77] Because BPs are excreted renally after only a few hours in the circulation, their concentration in tissues outside bone is minimal.[78] In contrast to BPs, no soft tissue toxicity has been reported with denosumab.

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 have shown 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 earlier, many hypotheses exist, and many of the animal models cited have produced 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 bone exposure or stage 0 disease.

Risk Factors for MRONJ

MEDICATION-RELATED RISK FACTORS

To interpret MRONJ disease frequency estimates, 2 parameters need to be considered: therapeutic indications and types of medication (Table 1).[21,81-89] The therapeutic indications are grouped into 2 categories: osteoporosis and osteopenia or malignancy. Medications are grouped into 2 categories, BP and non-BP (other antiresorptive or antiangiogenic medications). Disease frequency is reported as incidence (number of new cases per sample [or population] per unit of 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 tried 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 controlled [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 relied on medical record review or insurance-claim data were excluded from analyses.

Owing to the low frequency of disease, studies with small samples (<500 patients) 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 decrease. Therefore, when reviewing the literature cited below, the reader should weight more heavily studies with large samples than a comparable study with a smaller sample (ie, disease estimates of a study with a sample size of 10,000 should be weighted more heavily than a study with 500 patients).

MRONJ Risk in Patients With Cancer

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

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

In patients with cancer exposed to denosumab, a RANKL inhibitor, the risk of MRONJ ranges from 0.7 to 1.9% (70 to 90 cases per 10,000 patients).[81,85] The risk for ONJ in patients with cancer exposed to denosumab is comparable to the risk of ONJ in patients exposed to zoledronate.[22,23,90]

The risk for ONJ in patients with cancer exposed to bevacizumab, an antiangiogenic agent, is 0.2% (20 cases per 10,000).[86] The risk may be higher in patients exposed to bevacizumab and zoledronate (0.9%; 90 cases per 10,000).[86]

There are several case reports describing jaw necrosis in patients with cancer receiving targeted therapies, specifically TKIs and monoclonal antibody–targeting VEGF.[91-93] In 2009 Brunello et al[94] reported consecutive episodes of ONJ, characterized

Table 1. DISEASE FREQUENCY OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW GROUPED BY DISEASE STATUS VERSUS MEDICATION STATUS

Indications for Treatment	Medications						Study Design
	Placebo	Zoledronate	Oral BP	Denosumab	Bevacizumab	Bevacizumab and Zoledronate	
Malignancy							
Guarneri et al[86] (2010)					0.2% (1,076)	0.9% (233)	systematic review
Qi et al[81] (2013)	0% (1,450)	1.1% (2,928)		1.9% (4,585)			systematic review
Scagliotti et al[85] (2012)		0.8% (400)		0.7% (411)			RCT
Coleman et al[82] (2011)	0% (1,675)	0.7% (1,665)					RCT
Vahtsevanos et al[84] (2009)		6.7% (1,163)					prospective cohort study
Mauri et al[83] (2009)	0.019% (5,382)	0.33% (3,987)					systematic review
Osteoporosis							
Papapoulos et al[21] (2012)	0% (3,383)			0.04% (4,549)			RCT
Grbic et al[89] (2010)	0.020% (4,945)	0.017% (5,864)					systematic review
Malden and Lopes[88] (2012)			0.004% (90,000)				prospective cohort study
Lo et al[87] (2010)			0.1%* (8,572)				cross-sectional

Note: Sample size is presented within parentheses.
Abbreviations: BP, bisphosphonate; RCT, randomized controlled trial.
* Prevalence estimate. All other frequencies reported in the table are incidences.
Ruggiero et al. Medication-Related Osteonecrosis of the Jaw. J Oral Maxillofac Surg 2014.

by cutaneous fistula and bone sequestration, in a patient with renal cell carcinoma treated with BPs and the TKI sunitinib. Disease was alleviated 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 BP medication use.[86,95-101] Beuselinck et al[100] reported an overall incidence of 10% for ONJ in patients with renal cell carcinoma and bone metastasis treated with oral TKIs and concomitant BPs. They concluded that the combined use of BPs and TKIs in patients with renal cell carcinoma and bone involvement probably improves treatment efficacy, but is associated with a high incidence of ONJ. Smidt-Hansen et al[101] in a retrospective study of patients with renal cell carcinoma who received zoledronic acid and sirolimus found that patients who developed ONJ had a significantly improved median survival of 31.6 months compared with 14.5 months in patients without ONJ.

Moreover, there have been multiple case reports detailing the development of ONJ in patients receiving these targeted antiangiogenic therapies who are BP naive.[91-93] 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 based primarily on case reports (Level V evidence). Although the FDA has issued an ONJ advisory only for bevacizumab and sunitinib,[102,103] the committee remains concerned about a similar potential risk associated with several other medications within the same drug class that have a similar mechanism of action. Further controlled prospective studies will be required to characterize the risk of jaw necrosis associated with these agents.

MRONJ Risk in Patients With Osteoporosis

In their practices, most dentists and oral and maxillofacial surgeons have seen patients who have been exposed to antiresorptive therapy (eg oral BPs) for management of osteoporosis. When evaluated by age, 5.1 million patients older than 55 years received a prescription for a BP in 2008. A recent federal study has estimated that the prevalence of BP exposure is 7

for every 100 US patients receiving a prescription for a BP in the outpatient setting for the treatment of osteoporosis.[104] 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.[104]

Risk for ONJ in osteoporotic patients exposed to oral BPs. In a survey study of more than 13,000 Kaiser Permanente members, the prevalence of MRONJ in patients receiving long-term oral BP therapy was reported at 0.1% (10 cases per 10,000), which increased to 0.21% (21 cases per 10,000) in patients with longer than 4 years of oral BP exposure.[87] Felsenberg and Hoffmeister[105] reported a prevalence of MRONJ in patients treated with BPs 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. In a more recent report, Malden and Lopes[88] 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 patients living in southeast Scotland.

MRONJ risk in osteoporotic patients exposed to IV BP or RANKL inhibitors. A study 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 patients).[89] An extension of this study through 6 years did not show a change in frequency of MRONJ.[106] In recent reports studying patients exposed to denosumab, the risk for MRONJ was 0.04% (4 cases per 10,000 patients).[21] Interestingly, in patients with osteoporosis exposed to placebo medications, the risk for ONJ ranged from 0 to 0.02% (0 to 2 cases per 10,000 patients).[21,89] The risk for ONJ in patients treated with yearly zoledronate or denosumab (0.017 to 0.04%) approximated the risk for ONJ of patients enrolled in placebo groups (0 to 0.02%).

Based on this current review of data, the risk of developing ONJ in osteoporotic patients exposed to oral or 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 >55 yr old) exposed to these drugs.[107]

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. In patients with cancer exposed to zoledronate or denosumab, the incidence of developing ONJ was, respectively, 0.6% or 0.5% at 1 year, 0.9% or 1.1% at 2 years, and 1.3% or 1.1% at 3 years, with the risk for ONJ in denosumab-exposed patients plateauing between years 2 and 3.[90] In a study by Saad et al,[108] the investigators combined 3 blinded phase 3 trials and found similar results, including a plateau after 2 years for patients exposed to denosumab. In patients with cancer exposed to zoledronate or denosumab (n = 5,723), the incidence of developing ONJ was, respectively, 0.5% or 0.8% at 1 year, 1.0% or 1.8% at 2 years, and 1.3% or 1.8% at 3 years.[90]

For patients receiving oral BP therapy to manage osteoporosis, the prevalence of ONJ increases over time, from nearly 0% at baseline to 0.21% after at least 4 years of BP exposure (Fig 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.[87,104]

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

LOCAL FACTORS

Operative Treatment

Dentoalveolar surgery is considered a major risk factor for developing MRONJ. Several studies have reported that in patients with MRONJ, tooth extraction is a common predisposing event, with 52 to 61% of patients reporting tooth extraction as the precipitating event.[84,108,109] In a case-control study of patients with cancer exposed to zoledronate, tooth extraction was associated with a 16-fold increased risk for ONJ

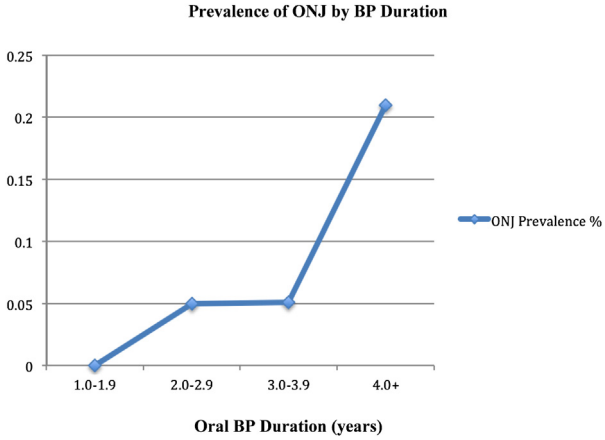

FIGURE 1. Frequency of ONJ over time (US Food and Drug Administration: Background document for meeting of advisory committee for reproductive health drugs and drug safety and risk management advisory committee. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM270958.pdf, p 19. Accessed April 7, 2014). BP, bisphosphonate; ONJ, osteonecrosis of the jaws.

Ruggiero et al. Medication-Related Osteonecrosis of the Jaw. J Oral Maxillofac Surg 2014.

compared with those without ONJ (odds ratio [OR] = 16.4; 95% confidence interval [CI], 3.4-79.6).[110] In a longitudinal cohort study of a sample of patients with cancer exposed to IV BPs (predominately zoledronate), tooth extraction was associated with a 33-fold increased risk for ONJ.[84]

This information, although important, is not what most patients or clinicians want to know. Most clinicians and patients want to know the answer to this question: "In patients exposed to antiresorptive medications, what is the risk for developing ONJ after tooth extraction (or other dentoalveolar procedures, such as implant placement or periodontal procedures)?" The best current estimate for the risk of ONJ in patients exposed to oral BPs after tooth extraction is 0.5%.[111] The estimate was derived from a prospective evaluation of 194 patients exposed to oral BPs who underwent extraction of at least 1 tooth. In this sample, 1 patient developed ONJ after tooth extraction.

Estimates for developing ONJ after tooth extraction in patients with cancer exposed to IV BPs ranges from 1.6 to 14.8%. In a retrospective cohort study composed of a sample of patients with cancer exposed to zoledronate (n = 27), 4 patients (14.8%) developed ONJ after tooth extraction.[112] In a prospective cohort study composed of 176 patients with cancer who were exposed to zoledronate, 5 (2.8%) developed ONJ.[113] In a prospective cohort study of 63 patients with a history of cancer and IV BP exposure who underwent extraction of at least 1 tooth, 1 patient (1.6%) developed ONJ.[114] Among these studies, the prospective studies should be weighted more heavily owing to the larger samples and the prospective, not retrospective, study designs.

The risk of developing ONJ in 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 be comparable to the risk associated with tooth extraction.

Anatomic Factors

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

Concomitant Oral Disease

Pre-existing inflammatory dental disease, such as periodontal disease or periapical pathology, is a well-recognized risk factor.[112,115] In patients with cancer and MRONJ, pre-existing inflammatory dental disease was a risk factor in 50% of cases.[108,112] Given that a common treatment of inflammatory dental disease is tooth extraction, pre-existing dental disease may confound the relation between tooth extraction and the risk for MRONJ noted earlier. It would be valuable to see an estimate of the association between tooth extraction and MRONJ adjusted for pre-existing inflammatory dental disease.

DEMOGRAPHIC, SYSTEMIC, AND OTHER MEDICATION FACTORS

Age and gender 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[116] reviewed 42 pediatric patients who had received IV BP therapy (mean duration of therapy. 6.5 years) for different metabolic bone diseases. No cases of ONJ were reported despite invasive dental treatment in 11 patients. 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.[86,108]

Comorbid conditions in patients with cancer that are inconsistently reported to be associated with an increased risk for MRONJ include anemia (hemoglobin <10 g/dL) and diabetes.[108,115] Cancer type also is 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 patients with cancer (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 patients with cancer exposed to zoledronate.[115] Vahtsevanos et al[84] did not report an association between tobacco use and MRONJ.

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 bone

turnover, collagen formation, or certain metabolic bone diseases. Katz et al[117] reported an ONJ event rate of 57% when SNPs were present in 5 candidate genes that were responsible for bone turnover. In a genomewide study, Nicoletti et al[118] 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. In a study that analyzed polymorphisms related to farnesyl diphosphate synthase activity (the enzyme specifically inhibited by BPs), a positive correlation was established with the carrier status and ONJ.[119] Collectively, these studies suggest that a germline sensitivity to BPs may exist.

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

Management Strategies for Patients Treated With Antiresorptive or Antiangiogenic Medications

PREVENTION OF MRONJ

The AAOMS special committee on MRONJ supports a multidisciplinary 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 would not only decrease the incidence of ONJ, but also accrue the benefits that all patients enjoy with optimum oral health.[32,86,101,109,110,120-136]

The implementation of dental screening and appropriate dental measures before initiating antiresorptive therapy lowered the risk of ONJ in several prospective studies when compared in a retrospective fashion to patients who did not undergo dental preventive measures.[53,55,108,137,138]

Dimopoulos et al[53] found a statistically significant, almost 3-fold, decrease in the incidence of osteonecrosis in patients when preventive measures were applied. Bonacina et al[137] did not report any new cases of ONJ in patients who received dental screening and necessary dental treatment before initiating IV BP treatment. Vandone et al[138] found the incidence rate of developing ONJ was decreased by 50% in patients who were screened and received preventive dental care before initiating drug therapy.

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 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 assessments 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 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.

CESSATION OF AT-RISK MEDICATION THERAPY BEFORE TOOTH EXTRACTION OR OTHER PROCEDURES THAT INVOLVE OSSEOUS INJURY (EG, DENTAL IMPLANT PLACEMENT, PERIODONTAL OR APICAL ENDODONTIC TREATMENT)

Antiresorptive Therapy for Osteoporosis or Osteopenia

The concept of a drug holiday in patients receiving oral BPs or denosumab who require tooth extractions has been an ongoing area of controversy, with sparse data to support current recommendations. The AAOMS Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw, revised in 2009, recommended discontinuing oral BPs for 3 months before and 3 months after invasive dental surgery—*systemic conditions permitting*.[1] However, there is currently no evidence that interrupting BP therapy alters the risk of ONJ in patients after tooth extraction. In 2011 the American Dental Association Council on Scientific Affairs revised their prior recommendation of a drug holiday and suggested that patients receiving lower cumulative doses of BP (<2 yr) or denosumab could 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 BP exposure (>4 yr) 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 BP 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."[104]

Damm and Jones[141] proposed several alternatives to a drug holiday in BP-exposed patients who require invasive dental treatment. Although 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 noted that because 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 after the last dose of an oral BP and a 2-month drug-free period should be adequate before an invasive dental procedure.

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

Oncologic Patients Receiving Monthly Antiresorptive Therapy

Patients receiving monthly IV BPs or denosumab for treatment of oncologic disease have an increased risk of developing ONJ after 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 IV BPs before 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 BPs, 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; 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
  - Oncologic patients can benefit greatly from the therapeutic effect of antiresorptive therapy by controlling bone pain and lowering the incidence of other skeletal complications
  - The antiangiogenic class of chemotherapy agents have shown efficacy in the treatment of different malignancies with proven survival benefits
- Preservation of quality of life through:
  - Patient education and reassurance
  - Control of pain
  - Control of secondary infection
  - Prevention of extension of lesion and development of new areas of necrosis

Management Strategies

PATIENTS ABOUT TO INITIATE IV 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 antiresorptive medications develop ONJ spontaneously, most affected patients develop this complication after 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.

Nonrestorable teeth and those with a poor prognosis should be extracted. Other necessary elective dentoalveolar surgery also should 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 to 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 similarly 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.

PATIENTS ABOUT TO INITIATE ANTIRESORPTIVE TREATMENT FOR OSTEOPOROSIS

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

ASYMPTOMATIC PATIENTS RECEIVING IV BP 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. Nonrestorable 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 oncologic patient receiving IV antiresorptive therapy or antiangiogenic medications. There are no data regarding the risk of ONJ associated with implant placement in patients receiving antiangiogenic medications.

ASYMPTOMATIC PATIENTS RECEIVING ANTIRESORPTIVE THERAPY FOR OSTEOPOROSIS

Sound recommendations based on strong clinical research designs are still lacking for patients taking oral BPs. The committee strategies outlined below have been updated from those in the original position paper and are based on clinical studies that have shown a low prevalence of disease. The risk of developing MRONJ associated with oral BPs increases when duration of therapy exceeds 4 years.[87] Although the current level of evidence is not strong, the committee continues to consider these strategies for patients receiving oral BPs 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 also are at risk for developing MRONJ, but to a much lesser degree than those treated with IV antiresorptive therapy.[87,105] MRONJ can develop 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 BPs, although exceedingly small, appears to increase when the duration of therapy exceeds 4 years.[104] This time frame may be shortened in the presence of certain comorbidities, such as chronic corticosteroid or antiangiogenic use.[86,108,115] *If systemic conditions permit*, the clinician may consider discontinuation of oral BPs for a period of 2 months before and 3 months after elective invasive dental surgery to lower the risk of MRONJ. The rationale for this approach is based on extrapolated data that have shown fluctuations of osteoclast function, which is related to BP therapy, and recent outcomes studies that have shown improved outcome of MRONJ treatment with drug cessation.[141]

The efficacy of using 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 measurement of MRONJ risk is not recommended, although the committee supports continued research in this area.[53,55,145,154]

1. For patients who have taken an oral BP for less than 4 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 ONJ if the patient continues to take an antiresorptive agent. These concerns are based on recent animal studies that have shown impaired long-term implant healing.[155] Such patients should be placed on a regular recall schedule. In addition, it is advisable to contact the provider who originally prescribed the oral BP and suggest monitoring such patients and considering alternate dosing of the BP, drug holidays, or an alternative to the BP therapy.

2. For those patients who have taken an oral BP for less than 4 years and have taken corticosteroids or antiangiogenic medications concomitantly, the prescribing provider should be contacted to consider discontinuation of the oral BP (drug holiday) for at

least 2 months before 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 are still required to establish the efficacy of drug holidays in decreasing the risk of MRONJ for these patients.

3. For those patients who have taken an oral BP for longer than 4 years with or without any concomitant medical therapy, the prescribing provider should be contacted to consider discontinuation of the antiresorptive for 2 months before oral surgery, *if systemic conditions permit*. The BP should not be restarted until osseous healing has occurred. The risk of long-term oral BP therapy requires continued analysis and research.

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 tissues, and minimize the progression or occurrence of bone necrosis. Patients with established MRONJ should avoid elective dentoalveolar surgical procedures, because 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 after operative therapy (sequestrectomy, resection)[148,156-160] and nonoperative 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 nonoperative 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, because 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 nonsurgical and surgical treatment of MRONJ showed some improvement in wound healing, long-term pain scores, and quality-of-life scores.[167,168] However, given the small sample, there was no statistically significant difference between the control and HBO groups 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 samples have documented the use of other nonsurgical treatment strategies, such as platelet-rich plasma,[169,170] low-level laser irradiation,[128,171,172] parathyroid hormone,[173] 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

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 (Table 2). A stage 0 category was added in 2009 to include patients with nonspecific symptoms or clinical and radiographic abnormalities that might 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 cases studies have reported that up to 50% of patients with stage 0 have progressed to stage 1, 2, or 3.[175,176] Therefore, stage 0 seems to be a valid disease category that captures patients with prodromal disease (unexposed variant). Also, the definition of exposed bone was broadened (see above) to include the presence of cutaneous or mucosal fistulas that probe to bone for stage 1, 2, and 3 categories. Other research groups have proposed including radiographic signs alone (eg, sclerosis, persistent extraction sockets) 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 might 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-positive values in the numerator (eg, cases with radiographic findings suggestive of MRONJ, but are not MRONJ).

To direct rational treatment guidelines and collect data to assess the prognosis in patients who have used IV or oral antiresorptive and antiangiogenic agents, the committee proposes the use of the following revised staging system.

At Risk

There is no apparent necrotic bone in asymptomatic patients who have been treated with IV or oral antiresorptive or antiangiogenic therapy.

Table 2. STAGING AND TREATMENT STRATEGIES

Staging of Medication-Related Osteonecrosis of the Jaw*	Treatment Strategies†
At risk—no apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates	no treatment indicated patient education
Stage 0—no clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms	systemic management, including use of pain medication and antibiotics
Stage 1—exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection	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 fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage	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 ≥1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor	antibacterial mouth rinse antibiotic therapy and pain control surgical debridement or resection for longer-term palliation of infection and pain

* Exposed or probeable bone in the maxillofacial region without resolution for longer than 8 weeks in patients treated with an antiresorptive or an antiangiogenic agent who have not received radiation therapy to the jaws.

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

Ruggiero et al. Medication-Related Osteonecrosis of the Jaw. J Oral Maxillofac Surg 2014.

Stage 0 (Unexposed Bone Variant)

These patients have no clinical evidence of necrotic bone but present with nonspecific symptoms or clinical and radiographic findings, such as those listed below.

Symptoms.

- Odontalgia not explained by an odontogenic cause
- Dull, aching bone pain in the jaw, 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 or periodontal fistula that is not associated with pulpal necrosis caused by caries, trauma, or restorations

Radiographic findings

- Alveolar bone loss or resorption not attributable to chronic periodontal disease
- Changes to trabecular pattern—dense bone and no new bone in extraction sockets
- Regions of osteosclerosis involving the alveolar bone or surrounding basilar bone
- Thickening or obscuring of the periodontal ligament (thickening of the lamina dura, sclerosis, and decreased periodontal ligament space)[153]

These nonspecific findings, which characterize this unexposed variant of ONJ, can occur in patients with a history of stage 1, 2, or 3 disease who have healed and have no clinical evidence of exposed bone.

Stage 1

Stage 1 is defined as exposed and necrotic bone or a fistula that probes to bone in patients who are asymptomatic and have no evidence of infection. These patients also may present with radiographic findings mentioned for stage 0, which are localized to the alveolar bone region.

Stage 2

Stage 2 is defined as exposed and necrotic bone or a fistula that probes to bone with evidence of infection.

These patients are typically symptomatic. These patients also may present with radiographic findings mentioned for stage 0, which are localized to the alveolar bone region.

Stage 3

Stage 3 is defined as exposed and necrotic bone or fistulas that probe to bone with evidence of infection and at least 1 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
- Extraoral fistula
- Oral antral or oral nasal communication
- Osteolysis extending to the inferior border of the mandible or sinus floor

STAGE-SPECIFIC TREATMENT STRATEGIES

At Risk

These patients are at risk of developing MRONJ owing to an exposure history with an antiresorptive or an antiangiogenic drug. They do not have exposed bone and they do not require any treatment. However, these patients should be informed of the risks of developing MRONJ and of the signs and symptoms of this disease process.

Stage 0

These patients should receive symptomatic treatment and conservative management of other local factors, such as caries and periodontal disease. Systemic management can 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.

In 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) also should 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 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 also should 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 can 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 BP exposure needs to be recognized by the clinician and the patient. Case reports with small samples have described 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 because 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) because metastatic cancer has been reported in such specimens.[183]

Future Research

The National Institutes of Health has provided funding opportunities for research on the pathophysiology of BP-associated ONJ.[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 were presented in this report. 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, and *5)* animal studies to validate existing and proposed treatment and prevention strategies.

Continued governmental and institutional support is required to further elucidate the underlying pathophysiologic mechanisms of MRONJ at the cellular and molecular levels. 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.

Disclaimer

The AAOMS is providing this position paper on 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, and injuries and defects involving the functional and esthetic aspects of the hard and soft tissues of the oral and maxillofacial regions, epidemiologists, and basic researchers.

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Press Release

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Appendix I. ANTIRESORPTIVE PREPARATIONS COMMONLY USED IN THE UNITED STATES

Bisphosphonates	Primary Indication	Nitrogen Containing	Dose	Route
Alendronate (Fosamax)	osteoporosis	yes	10 mg/day, 70 mg/wk	oral
Risedronate (Actonel)	osteoporosis	yes	5 mg/day, 35 mg/wk	oral
Ibandronate (Boniva)	osteoporosis	yes	2.5 mg/day 150 mg/mo, 3 mg every 3 mo	oral IV
Pamidronate (Aredia)	bone metastases	yes	90 mg/3 wk	IV
Zoledronate				
Zometa	bone metastases	yes	4 mg/3 wk	IV
Reclast	osteoporosis		5 mg/yr	IV
Denosumab				
Xgeva	bone metastases		120 mg/4 wk	SQ
Prolia	osteoporosis	humanized monoclonal antibody	60 mg/6 mo	SQ

Abbreviations: IV, intravenous; SQ, subcutaneous.

Ruggiero et al. Medication-Related Osteonecrosis of the Jaw. J Oral Maxillofac Surg 2014.

Appendix II. MEDICATIONS USED IN TREATMENT OF VARIOUS CANCERS THAT ARE ANTIANGIOGENIC OR TARGETS OF THE VASCULAR ENDOTHELIAL GROWTH FACTOR 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 of renal transplant

Note: Although the Food and Drug Administration has issued an advisory only for bevacizumab and sunitinib for osteonecrosis of the jaw,[102,103] the committee remains concerned about a similar potential risk associated with several other medications within the same drug class that 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.

Abbreviations: GIST, gastrointestinal stromal tumor; Glio, glioblastoma; HCC, hepatocellular carcinoma; mCRC, metastatic colorectal carcinoma; mRCC, metastatic renal cell carcinoma; NSCLC, nonsquamous non–small cell lung carcinoma; pNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma.

Ruggiero et al. Medication-Related Osteonecrosis of the Jaw. J Oral Maxillofac Surg 2014.