

# American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws—2009 Update

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Bisphosphonate-related osteonecrosis of the jaw (BRONJ) adversely affects the quality of life, producing significant morbidity in afflicted patients. Strategies for the treatment of patients with, or at risk of, BRONJ were set forth in the American Association of Oral and Maxillofacial Surgeons (AAOMS) *Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws (Position Paper)* and approved by the Board of Trustees in September 2006.<sup>1</sup> The *Position Paper* was developed by a Task Force 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 BRONJ has expanded, necessitating modifications and refinements to the original *Position Paper*. The Task Force was reconvened in August 2008 to

review the 2006 recommendations, appraise the current published data, and revise the *Position Paper* and recommendations, where indicated. This update contains revisions to the diagnosis and staging and management strategies and highlights the status of basic science research. AAOMS considers it vitally important that this information be disseminated to other dental and medical specialties.

## Purpose

The purpose of this updated position paper is to provide:

1. Perspectives on the risk of developing BRONJ and the risks and benefits of bisphosphonates to facilitate medical decision-making of both the treating physician and the patient

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2. Guidance to clinicians regarding the differential diagnosis of BRONJ in patients with a history of treatment with intravenous (IV) or oral bisphosphonates
3. Guidance to clinicians on possible BRONJ prevention measures and treatment of patients with BRONJ according to the presenting stage of the disease

## Background

### INDICATIONS AND BENEFITS OF BIPHOSPHONATE THERAPY

#### *IV Bisphosphonates*

IV bisphosphonates are primarily used and effective in the treatment and management of cancer-related conditions, including hypercalcemia of malignancy, skeletal-related events associated with bone metastases in the context of solid tumors such as breast cancer, prostate cancer, and lung cancer, and management of lytic lesions in the setting of multiple myeloma.<sup>2-13</sup> Although bisphosphonates have not been shown to improve cancer-specific survival, they have had a significant positive effect on the quality of life for patients with advanced cancer involving the skeleton. Before 2001, pamidronate (Aredia; Novartis Pharmaceuticals, East Hanover, NJ) was the only drug approved in the United States for the treatment of metastatic bone disease. In 2002, zoledronic acid (Zometa; Novartis Pharmaceuticals) was approved for this indication by the US Food and Drug Administration (FDA).<sup>13</sup> More recently, a once-yearly infusion of zoledronate (Reclast; Novartis Pharmaceuticals) and a parenteral formulation of ibandronate (Boniva; Roche, Basel, Switzerland) administered every 3 months have been approved by the FDA for management of osteoporosis.<sup>14</sup>

#### *Oral Bisphosphonates*

Oral bisphosphonates are approved to treat osteoporosis and are frequently used to treat osteopenia as well.<sup>15</sup> They are also used for a variety of less common conditions such as Paget's disease of bone and osteogenesis imperfecta of childhood.<sup>16,17</sup> By far the most prevalent and common indication, however, is osteoporosis.<sup>18,19</sup> Osteoporosis can arise in the context of other diseases such as inflammatory bowel disease or primary biliary cirrhosis, as a result of medications, most commonly steroids, or as a consequence of postmenopausal aging.<sup>20-22</sup>

### RISKS OF BIPHOSPHONATE THERAPY

Oral and maxillofacial surgeons first recognized and reported cases of nonhealing exposed bone in the maxillofacial region in patients treated with IV bisphosphonates.<sup>23,24</sup> Since these initial reports, several case series and reviews have been published.<sup>25-32</sup> In September 2004, Novartis, the manufacturer of the IV bisphospho-

nates pamidronate (Aredia) and zoledronic acid (Zometa), notified healthcare professionals of additions to the labeling of these products that provided cautionary language related to the development of osteonecrosis of the jaws.<sup>33</sup> This was followed in 2005 by a broader drug class warning of this complication for all bisphosphonates, including the oral preparations.<sup>34,35</sup> See [Appendix 1](#) for a list of bisphosphonate medications currently available in the United States.

## Causality

Epidemiologic studies have established a compelling, albeit circumstantial, association between IV bisphosphonates and BRONJ in the setting of malignant disease. An association between IV bisphosphonate exposure and BRONJ can be hypothesized from the following observations: 1) a positive correlation between bisphosphonate potency and the risk of developing BRONJ; 2) a negative correlation between bisphosphonate potency and duration of bisphosphonate exposure before developing BRONJ; and 3) a positive correlation between the duration of bisphosphonate exposure and developing BRONJ. However, the current level of evidence does not fully support a cause-and-effect relationship between bisphosphonate exposure and necrosis of the jaws.<sup>36</sup> Although causality might never be proven, emerging experimental and epidemiologic studies have established a firm foundation for a strong association between monthly IV bisphosphonate therapy and the development of BRONJ. The causal association between oral or IV bisphosphonates for treating osteoporosis and BRONJ is much more difficult to establish.

## BRONJ Case Definition

To distinguish BRONJ from other delayed healing conditions, the following working definition of BRONJ has been adopted by the AAOMS and remains unchanged from the original *Position Paper*:<sup>1</sup>

*Patients may be considered to have BRONJ if all of the following 3 characteristics are present:*

1. Current or previous treatment with a bisphosphonate
2. Exposed bone in the maxillofacial region that has persisted for more than 8 weeks
3. No history of radiation therapy to the jaws

It is important to understand that patients at risk of, or with established, BRONJ can also present with other common clinical conditions not to be confused with BRONJ. Commonly misdiagnosed conditions can include, but are not limited to, alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathologic findings, and temporomandibular joint disorders.

## Estimated Incidence and Factors Associated With Development of BRONJ

### IV BISPHOSPHONATES AND INCIDENCE OF BRONJ

The clinical efficacy of IV bisphosphonates for the treatment of hypercalcemia and bone metastases is well established.<sup>2-5</sup> IV bisphosphonate exposure in the setting of managing malignancy remains the major risk factor for BRONJ. According to case series, case-controlled studies, and cohort studies, estimates of the cumulative incidence of BRONJ have ranged from 0.8% to 12%.<sup>37-45</sup>

Zoledronic acid (Reclast) administered once annually for the treatment of osteoporosis was approved by the FDA in August 2007.<sup>14</sup> A single, large, prospective placebo-controlled study established its efficacy for this indication through 3 years of treatment.<sup>46</sup> Two cases of osteonecrosis of the jaw were reported, one each in the treatment and control groups, suggesting a low risk of BRONJ with this treatment modality through 3 years.

### ORAL BISPHOSPHONATES AND INCIDENCE OF BRONJ

The clinical efficacy of oral bisphosphonates for the treatment of osteopenia/osteoporosis is well established and is reflected in the fact that more than 190 million oral bisphosphonate prescriptions have been dispensed worldwide.<sup>47</sup> The specialty's experiences have identified several BRONJ cases related to oral bisphosphonates.<sup>24,26</sup> Patients receiving oral bisphosphonate therapy are at a considerably lower risk of BRONJ than cancer patients treated with monthly IV bisphosphonates. According to the data from the manufacturer of alendronate (Merck, Whitehouse Station, NJ), the incidence of BRONJ was calculated to be 0.7/100,000 person-years of exposure.<sup>48</sup> This was derived from the number of reported (not confirmed) cases that were deemed to likely represent BRONJ divided by the number of alendronate pills prescribed since approval of the drug and converted to the number of patient-years. Although these are the best available data to date, serious underreporting could be present and, as noted, none were confirmed. Surveillance data from Australia estimated the incidence of BRONJ for patients treated weekly with alendronate as 0.01% to 0.04%.<sup>49</sup> In a survey study of more than 13,000 Kaiser-Permanente members, the prevalence of BRONJ in patients receiving long-term oral bisphosphonate therapy was reported at 0.06% (1:1,700).<sup>50</sup> Felsenberg and Hoffmeister<sup>51</sup> reported a prevalence of BRONJ among patients treated with bisphosphonates for osteoporosis of 0.00038%, according to reports of 3 cases to the German Central Registry of Necrosis of the Jaw.

From the available data, the risk of BRONJ for patients receiving IV bisphosphonates is significantly

greater than the risk of BRONJ for patients receiving oral bisphosphonates. Regardless, given the large number of patients receiving oral bisphosphonates for the treatment of osteoporosis/osteopenia, it is likely that most practitioners will encounter some patients with BRONJ. It is important to accurately determine the incidence of BRONJ in this population and to assess the risk associated with long-term use (ie, longer than 3 years) of oral bisphosphonates. The low prevalence of BRONJ in osteoporosis patients poses a significant challenge for future clinical trials aimed at establishing accurate incidence data.

### RISK FACTORS

In the original *Position Paper*, BRONJ risks were categorized as drug-related, local, and demographic or systemic factors.<sup>1</sup> Other medications, such as steroids and thalidomide, and other chemotherapeutic agents were thought to be risk factors, but no measurable associations were identified. Subsequently, 2 new sets of factors, genetic and preventative, are available to report.

#### I. Drug-related risk factors include

- A. Bisphosphonate potency: zoledronate (Zometa) is more potent than pamidronate (Aredia), and pamidronate (Aredia) is more potent than the oral bisphosphonates; the IV route of administration results in greater drug exposure than the oral route.<sup>37,38,45,52</sup> Using a number of different risk measures, the BRONJ risk among cancer patients given IV bisphosphonate exposure ranged from 2.7 to 4.2, suggesting that cancer patients receiving IV bisphosphonates have a 2.7- to 4.2-fold increased risk of BRONJ than cancer patients not exposed to IV bisphosphonates.<sup>37,53</sup>
- B. Duration of therapy: a longer duration appears to be associated with increased risk.<sup>38,45</sup>

#### II. Local risk factors include

- A. Dentoalveolar surgery, including, but not limited to<sup>37,45,52</sup>
  1. Extractions
  2. Dental implant placement
  3. Periapical surgery
  4. Periodontal surgery involving osseous injury

In the original *Position Paper*, local factors such as dentoalveolar procedures, local anatomic structures (eg, tori), and concomitant dental disease were hypothesized to increase the risk of BRONJ in the setting of IV bisphosphonate exposure.<sup>1</sup> Patients receiving IV bisphosphonates and undergoing dentoalveolar surgery are at least 7 times more likely to develop BRONJ than patients who are not undergoing dentoalveolar

surgery.<sup>45,52</sup> In the setting of IV bisphosphonate exposure, 4 studies reported that dentoalveolar procedures or concomitant dental disease increased the risk of BRONJ between 5.3 (odds ratio) and 21 (relative risk).<sup>37,52,54,55</sup> Thus, cancer patients treated with IV bisphosphonates who undergo dentoalveolar procedures have a 5- to 21-fold increased risk of BRONJ compared with cancer patients treated with IV bisphosphonates who do not undergo dentoalveolar procedures.

#### B. Local anatomy

##### 1. Mandible

- a. Lingual tori
- b. Mylohyoid ridge

##### 2. Maxilla

- a. Palatal tori

It has been observed that lesions are found more commonly in the mandible than the maxilla (2:1 ratio) and more commonly in areas with thin mucosa overlying bony prominences such as tori, bony exostoses, and the mylohyoid ridge.<sup>24,26,56</sup> No data are available to provide risk estimates for anatomic structures and BRONJ.

- C. Concomitant oral disease: cancer patients exposed to IV bisphosphonates with a history of inflammatory dental disease (eg, periodontal and dental abscesses) are at a 7-fold increased risk of developing BRONJ.<sup>45</sup>

#### III. Demographic and systemic factors

In the original *Position Paper*, age, race, and cancer diagnosis with or without osteoporosis were reported as risk factors for BRONJ.<sup>1</sup> Seven studies reported increasing age as consistently associated with BRONJ.<sup>38,39,52,54,55,57,58</sup> Sex was not significantly associated statistically with BRONJ.<sup>38,39,52,54,55,57</sup> Race was reported in 1 study to be a risk factor, with whites having an increased risk of BRONJ compared with blacks.<sup>52</sup>

Other systemic factors or conditions (ie, renal dialysis, low hemoglobin, obesity, and diabetes) were variably reported to increase the risk of BRONJ.<sup>53,54,59</sup> Malignancy type was not significantly associated statistically with an increased risk of BRONJ,<sup>38</sup> although the presence of metastatic disease reached near statistical significance ( $P = .051$ ) in the report by Wessel et al.<sup>53</sup>

In contrast to the original *Position Paper*, a few current studies have noted an increased risk of BRONJ among patients exposed to chemotherapeutic agents (ie, cyclophosphamide, erythropoietin, and steroids).<sup>54,57</sup> Others, however, have failed to confirm the association between chemothera-

peutic agents and BRONJ risk.<sup>37,39,52,53,58</sup> Wessel et al<sup>53</sup> reported an increased risk of BRONJ among tobacco users, but no increased risk was associated with alcohol exposure.

#### IV. Genetic factors

Sarasquete et al<sup>60</sup> demonstrated that genetic perturbations (ie, single nucleotide polymorphisms, in the cytochrome P450-2C gene [CYP2C8]) were associated with an increased risk of BRONJ among multiple myeloma patients treated with IV bisphosphonates.

#### V. Preventive factors

The AAOMS Taskforce on BRONJ recommended that patients undergo dental evaluations and receive necessary treatment before initiating IV bisphosphonate therapy.<sup>1</sup> In addition, given the long-term biologic activity of IV bisphosphonates, one could hypothesize that different dosing regimens might be equally effective and decrease the risk of BRONJ.

Using a retrospective cohort study design, Corso et al<sup>58</sup> evaluated the BRONJ- and skeletal-related events (eg, pathologic fracture) in multiple myeloma patients using different dosing schedules for zoledronate. These findings suggest that alternative dosing schedules that reduce IV bisphosphonate exposure have comparable outcomes in terms of preventing skeletal-related events and a decreased risk of BRONJ.

Since the original *Position Paper* on BRONJ, several studies have generated quantitative estimates of risk of BRONJ in the setting of IV bisphosphonates exposure. The 2 largest risk factors for BRONJ are IV bisphosphonate exposure and dentoalveolar procedures. Recent studies have suggested that manipulation of IV bisphosphonate dosing might be effective in reducing skeletal-related events and minimizing BRONJ risk.<sup>58</sup> In addition, preventive dental interventions before initiating IV bisphosphonate treatment can also effectively reduce, but not eliminate, the risk of BRONJ.

## Management Strategies for Patients Treated With Bisphosphonates

### PREVENTION OF BRONJ

Before treatment with monthly IV bisphosphonates, the patient should undergo a thorough oral examination, any unsalvageable teeth should be removed, all invasive dental procedures should be completed, and optimal periodontal health should be achieved.

Three studies have reported that preventive dental treatment decreased the BRONJ risk among patients

with malignancy treated with IV bisphosphonates.<sup>61-63</sup> These findings suggest that, although BRONJ is not eliminated, dental evaluations and treatment before initiating IV bisphosphonate therapy among cancer patients reduces the BRONJ risk.

The risk of developing BRONJ associated with oral bisphosphonates, although exceedingly small, appears to increase when the duration of therapy exceeds 3 years. This period can be shortened in the presence of certain comorbidities, such as chronic corticosteroid use. *If systemic conditions permit*, the clinician might consider discontinuation of oral bisphosphonates for a 3-month period before and 3-month period after elective invasive dental surgery to lower the risk of BRONJ. The rationale for this approach is based on extrapolated data demonstrating fluctuations in osteoclast function related to bisphosphonate therapy and recent outcomes studies that have shown improved outcomes of BRONJ treatment with drug cessation.<sup>61-64</sup> Long-term, prospective studies are required to establish the efficacy of drug “holidays” in reducing the risk of BRONJ for patients receiving oral bisphosphonates. The risk reduction could vary depending on the duration of bisphosphonate exposure. Modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

#### TREATMENT GOALS

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

Prioritization and support of continued oncologic treatment in patients receiving IV bisphosphonates. Oncology patients can benefit greatly from the therapeutic effect of bisphosphonates by controlling bone pain and reducing the incidence of other skeletal complications.

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

#### TREATMENT STRATEGIES

The treatment strategies have been determined from published studies.<sup>26,31,65-67</sup>

##### *Patients About to Initiate IV Bisphosphonate Treatment*

The treatment objective for this group of patients is to minimize the risk of developing BRONJ. Although a small percentage of patients receiving bisphosphonates develop osteonecrosis of the jaw spontane-

ously, most affected patients experience this complication after dentoalveolar surgery.<sup>37,45,52</sup> Therefore, *if systemic conditions permit*, initiation of bisphosphonate therapy should be delayed until the dental health has been optimized.<sup>61-63</sup> 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 teeth with a poor prognosis should be extracted. Other necessary elective dentoalveolar surgery should also be completed at this time. From the experience with osteoradionecrosis, it appears advisable that bisphosphonate therapy should be delayed, *if systemic conditions permit*, until the extraction site has mucosalized (14 to 21 days) or until adequate osseous healing has occurred. 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 treat patients scheduled to receive IV bisphosphonates similarly to those patients scheduled to initiate radiotherapy to the head and neck. The osteoradionecrosis prevention protocols are guidelines that are familiar to most oncologists and general dentists.

##### *Asymptomatic Patients Receiving IV Bisphosphonates*

Maintaining good oral hygiene and dental care is of paramount importance in preventing dental disease that might require dentoalveolar surgery. Procedures that involve direct osseous injury should be avoided. Nonrestorable teeth can be treated by removal of the crown and endodontic treatment of the remaining roots.<sup>67</sup> Placement of dental implants should be avoided in the oncology patient exposed to the more potent IV bisphosphonate medications (zoledronic acid and pamidronate) on a frequent dosing schedule (4 to 12 times annually).

Zoledronic acid (Reclast) administered once annually for the treatment of osteoporosis was approved by the FDA in August 2007.<sup>14</sup> A single, large, prospective placebo-controlled study established its efficacy for this indication through 3 years of treatment.<sup>46</sup> Two cases of osteonecrosis of the jaw were reported, one each in the treatment and control groups, suggesting a low risk of BRONJ with this treatment modality through 3 years. The efficacy of a drug holiday for patients receiving yearly zoledronic acid therapy and the appropriate tim-

ing of dentoalveolar surgery (if required) is unknown and requires additional study.

#### *Asymptomatic Patients Receiving Oral Bisphosphonate Therapy*

Patients receiving oral bisphosphonates are also at risk of developing BRONJ but to a much lesser degree than those treated with IV bisphosphonates.<sup>24,26,27,56</sup> BRONJ 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<sup>68,69</sup> (Table 1). Elective dentoalveolar surgery does not appear to be contraindicated in this group. It is recommended that patients be adequately informed of the small risk of compromised bone healing. The use of bone turnover marker levels, in conjunction with a drug holiday, has been reported as an additional tool to guide treatment decisions in patients exposed to oral bisphosphonates.<sup>68</sup> The efficacy of using a systemic marker of bone turn-

over to assess the risk of developing jaw necrosis in patients at risk requires additional research before it can be considered a valid risk assessment tool. Long-term, prospective studies are also required to establish the efficacy of drug holidays in reducing the risk of BRONJ for these patients.

The risk of BRONJ might be associated with an increased duration of treatment with oral bisphosphonates (ie, 3 or more years). No information is available to suggest that monthly dosing of oral bisphosphonates (ie, ibandronate [Boniva], risedronate [Actonel]) is associated with either an elevated or reduced risk of BRONJ compared with weekly dosing regimens. The risk of long-term oral bisphosphonate therapy clearly requires continued analysis and research.

Sound recommendations determined from strong clinical research designs are still lacking for patients taking oral bisphosphonates. The Task Force strate-

**Table 1. STAGING AND TREATMENT STRATEGIES**

BRONJ* Stage	Description	Treatment Strategies†‡§
At risk category	No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment indicated Patient education
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms	Systemic management, including use of pain medication and antibiotics
Stage 1	Exposed and necrotic bone in asymptomatic patients without evidence of infection	Antibacterial mouth rinse Clinical follow-up on quarterly basis Patient education and review of indications for continued bisphosphonate therapy
Stage 2	Exposed and necrotic bone associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent drainage	Symptomatic treatment with oral antibiotics Oral antibacterial mouth rinse Pain control Superficial debridement to relieve soft tissue irritation
Stage 3	Exposed and necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (ie, inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement/resection for longer term palliation of infection and pain

Abbreviations: BRONJ, bisphosphonate-related osteonecrosis of the jaw; IV, intravenous.

\*Exposed bone in maxillofacial region without resolution within 8-12 weeks in persons treated with bisphosphonate who have not undergone radiotherapy to 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 established necrotic process.

‡Discontinuation of IV bisphosphonates has shown no short-term benefit. However, *if systemic conditions permit*, long-term discontinuation might be beneficial in stabilizing established sites of BRONJ, reducing risk of new site development, and reducing clinical symptoms. Risks and benefits of continuing bisphosphonate therapy should be made only by treating oncologist in consultation with oral and maxillofacial surgeon and patient.

§Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease. Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution after debridement surgery. *If systemic conditions permit*, modification or cessation of oral bisphosphonate therapy should be done in consultation with treating physician and patient.

gies outlined below have remained essentially unchanged from those in the original *Position Paper* and are based on clinical experience of clinicians (expert opinion) involved in caring for these patients and from case series.<sup>63,65-68</sup> The risk of developing BRONJ associated with oral bisphosphonates increased when the duration of therapy exceeded 3 years. Although the current level of evidence is not strong, the Task Force considers 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.

*For individuals who have taken an oral bisphosphonate for fewer than 3 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, periodontitis, and other dental providers.

It is suggested that if dental implants are placed, informed consent should be provided related to possible future implant failure and possible osteonecrosis of the jaws if the patient continues to take an oral bisphosphonate. 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.

*For those patients who have taken an oral bisphosphonate for fewer than 3 years and have also taken corticosteroids concomitantly*, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least 3 months before oral surgery, *if systemic conditions permit*. The bisphosphonate should not be restarted until osseous healing has occurred. These strategies have been determined from the opinion of experts with significant clinical experience and the hypothesis that concomitant treatment with corticosteroids might increase the risk of developing BRONJ and that a drug holiday may mitigate this risk. Long-term, prospective studies are required to establish the efficacy of drug holidays in reducing the risk of BRONJ for these patients.

*For those patients who have taken an oral bisphosphonate for more than 3 years with or without any concomitant prednisone or other steroid medication*, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate for 3 months before oral surgery, *if systemic conditions permit*. The bisphosphonate should not be restarted until osseous healing has occurred. These

strategies have been determined from the opinion of experts and observational studies.<sup>68</sup>

#### *Patients With BRONJ*

The treatment objectives for patients with an established diagnosis of BRONJ are to eliminate pain, control infection of the soft and hard tissue, and minimize the progression or occurrence of bone necrosis.

These patients respond less predictably to the established surgical treatment algorithms for osteomyelitis or osteoradionecrosis. Surgical debridement has been variably effective in eradicating the necrotic bone.<sup>22-24,29</sup> It could be difficult to obtain a surgical margin with viable bleeding bone, because the entire jawbone has been exposed to the pharmacologic influence of the bisphosphonate. Therefore, surgical treatment should be delayed if possible and reserved for those patients with stage 3 disease or in those cases with well-defined sequestrum. Areas of necrotic bone that are a constant source of soft-tissue irritation should be removed or recontoured without exposure of additional bone. Loose segments of bony sequestrum should be removed without exposing uninvolved bone.<sup>70</sup> 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.

Patients with established BRONJ should avoid elective dentoalveolar surgical procedures, because these surgical sites could result in additional areas of exposed necrotic bone. Symptomatic patients with stage 3 disease might require resection and immediate reconstruction with a reconstruction plate or an obturator. Recent case series have described acceptable outcomes after surgical therapy for patients with stage 2 and stage 3 disease.<sup>69</sup> 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. Immediate reconstruction with nonvascularized or vascularized bone is still considered potentially problematic, because necrotic bone could be present at the resection margins or develop at the recipient site.

The effectiveness of hyperbaric oxygen therapy as an adjunct to nonoperative and operative treatment is under investigation at 2 institutions, where a randomized controlled trial is underway.<sup>71</sup> The preliminary results have shown some improvement in wound healing and long-term pain scores, but its use as the sole treatment modality for BRONJ cannot be supported at this time.

Case reports with small sample sizes have documented the use of other nonoperative treatment strategies, including platelet-rich plasma, parathyroid hormone, and bone morphogenic protein.<sup>72</sup> The efficacy

of these treatment modalities needs to be established through additional research and controlled studies.

## Staging and Treatment Strategies

### STAGING

Since the publication of the original *Position Paper*, changes in the staging system have become necessary so that patients could be more accurately stratified (Table 1). Specifically, a stage 0 category was added to include patients with nonspecific symptoms or clinical and radiographic abnormalities that might have been due to bisphosphonate exposure. The risk of a patient with stage 0 disease advancing to a higher disease stage is unknown at this time. The definition of stage 3 disease was also amended to include, and more appropriately categorize, advanced maxillary disease.

To direct rational treatment guidelines and collect data to assess the prognosis in patients who have used either IV or oral bisphosphonates, the AAOMS proposes the 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 bisphosphonates.

**Stage 0:** Patients with no clinical evidence of necrotic bone, but who present with nonspecific symptoms or clinical and radiographic findings, including Symptoms

- Odontalgia not explained by an odontogenic cause

- Dull, aching bone pain in the body of the mandible that may radiate to the temporomandibular joint region

- Sinus pain, which could 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

**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

- Thickening/obscuring of periodontal ligament (thickening of the lamina dura and decreased size of the periodontal ligament space)

- Inferior alveolar canal narrowing

These nonspecific findings, which characterize stage 0, 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: exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection.

Stage 2: exposed and necrotic bone in patients with pain and clinical evidence of infection.

Stage 3: exposed and necrotic bone in patients with pain, 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

- Extraoral fistula

- Oral antral/oral nasal communication

- Osteolysis extending to the inferior border of the mandible or sinus floor

### TREATMENT STRATEGIES

**At risk:** patients who are at risk of developing BRONJ because they have been exposed to a bisphosphonate do not require any treatment. However, these patients should be informed of the risks of developing BRONJ, 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 can include the use of medication for chronic pain and the control of infection with antibiotics, when indicated.

**Stage 1:** these patients benefit from the use of oral antimicrobial rinses, such as chlorhexidine 0.12%. No surgical treatment is indicated.

**Stage 2:** these patients benefit from the use of oral antimicrobial rinses combined with antibiotic therapy. It has been hypothesized that the pathogenesis of BRONJ might be related to factors adversely influencing bone remodeling. Additionally, BRONJ is not due to a primary infectious etiology. 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 allergic to penicillin. Microbial cultures should also be analyzed for the presence of *Actinomyces* species of bacteria. If this microbe is isolated, the antibiotic regimen should be adjusted accordingly. In some refractory cases, patients might require combination antibiotic therapy, long-term antibiotic maintenance, or a course of IV antibiotic therapy.

**Stage 3:** these patients benefit from debridement, including resection, combined with antibiotic therapy, which might offer long-term palliation, with resolution of acute infection and pain.

Regardless of the disease stage, mobile segments of bony sequestrum should be removed without expos-

ing 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.

#### DISCONTINUATION OF BISPHOSPHONATE THERAPY

##### *IV Bisphosphonates*

Oncology patients benefit greatly from the therapeutic effects of bisphosphonates because they control bone pain and the incidence of pathologic fractures. Discontinuation of IV bisphosphonates offers no short-term benefit. However, *if systemic conditions permit*, long-term discontinuation might be beneficial in stabilizing established sites of BRONJ, reducing the risk of new site development, and reducing clinical symptoms.<sup>61-63</sup> The risks and benefits of continuing bisphosphonate therapy should be determined only by the treating oncologist in consultation with the oral and maxillofacial surgeon and the patient.

##### *Oral Bisphosphonates*

Discontinuation of oral bisphosphonate therapy in patients with BRONJ has been associated with gradual improvement in clinical disease.<sup>68</sup> Discontinuation of oral bisphosphonates for 6 to 12 months can result in either spontaneous sequestration or resolution after debridement surgery. *If systemic conditions permit*, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

## Future Research

The National Institutes of Health have provided funding opportunities for research on the pathophysiology of bisphosphonate-associated osteonecrosis of the jaw.<sup>73</sup> This has resulted in multiple research efforts focusing on several facets of this disease entity. The areas of investigation include, but are not limited to, 1) the effect of bisphosphonates on intraoral soft-tissue wound healing; 2) analysis of alveolar bone hemostasis and the response to bisphosphonate therapy; 3) the antiangiogenic properties of bisphosphonates and their effects on jaw bone healing; 4) pharmacogenetic research; and 5) the development of valid BRONJ risk assessment tools.

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

## Disclaimer

The AAOMS has provided this *Position Paper* on BRONJ to inform practitioners, patients, and other interested parties. The *Position Paper* is based on a review of the existing data and the clinical observations of an expert Task Force composed of oral and maxillofacial surgeons and oncologists experienced in the diagnosis and 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 intended as practice parameters or guidelines and might 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 BRONJ at the paper's development, and it should be used with the clear understanding that continued research and practice could 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 in reliance on such information.

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#### Appendix I. BISPHOSPHONATE PREPARATIONS CURRENTLY AVAILABLE IN THE UNITED STATES

	Primary Indication	Nitrogen Containing	Dose	Route	Relative Potency*
Etidronate (Didronel)	Paget's disease	No	300-750 mg daily for 6 mo	Oral	1
Tiludronate (Skelid)	Paget's disease	No	400 mg daily for 3 mo	Oral	50
Alendronate (Fosamax)	Osteoporosis	Yes	10 mg/d	Oral	1,000
Risedronate (Actonel)	Osteoporosis	Yes	70 mg/wk 5 mg/d	Oral	1,000
Ibandronate (Boniva)	Osteoporosis	Yes	35 mg/wk 2.5 mg/d 150 mg/mo	Oral	1,000
Pamidronate (Aredia)	Bone metastases	Yes	3 mg every 3 mo 90 mg/3 wk	IV	1,000-5,000
Zoledronate (Zometa)	Bone metastases	Yes	4 mg/3 wk	IV	10,000+
Zoledronate (Reclast)	Osteoporosis	Yes	5 mg/yr	IV	10,000+

Abbreviation: IV, intravenous.

\*Relative to etidronate.