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American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw – 2009 Update

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Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws*

Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) adversely affects the quality of life, producing significant morbidity in afflicted patients. Strategies for management of patients with or at risk for 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 (1). 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 literature and revise the *Position Paper* and recommendations, where indicated. This update contains revisions to 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.

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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 in order to facilitate medical decision-making of both the treating physician and the patient;
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 management of patients with BRONJ based on the presenting stage of the disease.

Background

Indications and benefits of bisphosphonate therapy

Intravenous bisphosphonates are primarily used and are effective in the treatment and management of cancer-related conditions, including hypercalcaemia 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 (2–13). While 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®) was the only drug approved in the United States for treatment of metastatic bone disease. In 2002,

zoledronic acid (Zometa®) was approved for this indication by the US Food and Drug Administration (FDA) (13). More recently, a once yearly infusion of zoledronate (Reclast®) and a parenteral formulation of ibandronate (Boniva®) administered every three months have been approved by the FDA for management of osteoporosis (14).

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

Risks of bisphosphonate therapy

Oral and maxillofacial surgeons first recognised and reported cases of non-healing exposed bone in the maxillofacial region in patients treated with IV bisphosphonates (23,24). Since these initial reports, several case series and reviews have been published (25–32). In September 2004, Novartis, the manufacturer of the IV bisphosphonates pamidronate (Aredia®) and zoledronic acid (Zometa®), notified healthcare professionals of additions to the labelling of these products, which provided cautionary language related to the development of osteonecrosis of the jaws (33). This was followed in 2005 by a broader drug class warning of this complication for all bisphosphonates including the oral preparations (34,35) – See Appendix I for list of bisphosphonate medications that are 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 may be hypothesised based on the following observations: (i) a positive correlation between bisphosphonate potency and risk for developing BRONJ; (ii) a negative correlation between bisphosphonate potency and duration of bisphosphonate exposure prior to developing BRONJ; and (iii) a positive correlation between 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 jaw (36). Although causality may never be proven, emerging experimental and epidemiologic studies have established a firm foundation for a strong association between monthly IV bisphosphonate therapy and 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* (1):

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

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

It is important to understand that patients at risk for or with established BRONJ can also present with other common clinical conditions not to be confused with BRONJ. Commonly misdiagnosed conditions may include, but are not limited to alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology and TMJ 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 hypercalcaemia and bone metastases is well established (2–5). IV bisphosphonate exposure in the setting of managing malignancy remains the major risk factor for BRONJ. Based on case series, case-controlled and cohort studies, estimates of the cumulative incidence of BRONJ range from 0.8% to 12% (37–45).

Zoledronic acid (Reclast®) administered once per year for the treatment of osteoporosis was approved by the FDA in August 2007 (14). A single, large, prospective placebo-controlled study established its efficacy for this indication through 3 years of treatment (46). 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 over 190 million oral bisphosphonate prescriptions have been dispensed worldwide (47). The specialty's experiences have identified several

BRONJ cases related to oral bisphosphonates (24,26). Patients under treatment with oral bisphosphonate therapy are at a considerably lower risk for BRONJ than cancer patients treated with monthly IV bisphosphonates. Based on data from the manufacturer of alendronate (Merck), the incidence of BRONJ was calculated to be 0.7/100 000 person/years of exposure (48). 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 number of patient years. While this is the best available data to date, there may be serious under-reporting and, as noted above, none confirmed. Surveillance data from Australia estimated the incidence of BRONJ for patients treated weekly with alendronate as 0.01–0.04% (49). In a survey study of over 13 000 Kaiser-Permanente members, the prevalence of BRONJ in patients receiving long-term oral bisphosphonate therapy was reported at 0.06% (1:1700) (50). Felsenberg reported a prevalence of BRONJ among patients treated with bisphosphonates for osteoporosis of 0.00038%, based on reports of three cases to the German Central Registry of Necrosis of the Jaw (51).

Based on available data, the risk of BRONJ for patients receiving IV bisphosphonates is significantly greater than that 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 may encounter some patients with BRONJ. It is important to determine accurately the incidence of BRONJ in this population and to assess the risk associated with long-term use, that is greater 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 categorised as drug-related, local and demographic or systemic factors (1). Other medications, such as steroids, thalidomide and other chemotherapeutic agents, were thought to be risk factors, but no measurable associations were identified. Subsequently, two 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 a greater drug exposure than the oral route (37,38,45,52). 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 for BRONJ than cancer patients not exposed to IV bisphosphonates (37,53).

B. Duration of therapy: longer duration appears to be associated with increased risk (38,45).

II. Local risk factors include:

A. Dentoalveolar surgery, including, but not limited to (37,45,52)

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, for example tori, and concomitant dental disease were hypothesised to increase the risk for BRONJ in the setting of IV bisphosphonate exposure (1). Patients receiving IV bisphosphonates and undergoing dentoalveolar surgery are at least seven times more likely to develop BRONJ than patients who are not having dentoalveolar surgery (45,52). In the setting of IV bisphosphonate exposure, four studies reported that dentoalveolar procedures or concomitant dental disease increased the risk for BRONJ between 5.3 (odds ratio) and 21 (relative risk) (37,52,54,55). In other words, cancer patients treated with IV bisphosphonates who undergo dentoalveolar procedures have a 5- to 21-fold increased risk for BRONJ than 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 (24,26,56). 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, for example periodontal and dental abscesses, are at a sevenfold increased risk for developing BRONJ (45).

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 (1). Seven studies report increasing age as consistently associated with BRONJ (38,39,52,54,55,57,58). Sex was not statistically associated with BRONJ (38,39,52,54,55,57). Race was reported in one study to be a risk factor, with Caucasians having an increased risk for BRONJ compared with blacks (52).

Other systemic factors or conditions, that is renal dialysis, low haemoglobin, obesity and diabetes, were variably reported to increase the risk for BRONJ (53,54,59). Malignancy type was not statistically associated with an increased risk for BRONJ, although the presence of metastatic disease reached near statistical significance, that is, $P = 0.051$, in Wessel's report (38,53).

In contrast to the original *Position Paper*, a few current studies noted an increased risk for BRONJ among patients exposed to chemotherapeutic agents, that is cyclophosphamide, erythropoietin and steroids (54,57). Others, however, failed to confirm the association between chemotherapeutic agents and BRONJ risk (37,39,52,53,58). Wessel *et al.* reported an increased risk for BRONJ among tobacco users, but no increased risk associated with alcohol exposure (53).

IV. Genetic factors

Sarasquete *et al.* demonstrated that genetic perturbations, that is single nucleotide polymorphisms (SNPs), in the cytochrome P450-2C gene (CYP2C8) gene were associated with an increased risk for BRONJ among multiple myeloma patients treated with IV bisphosphonates (60).

V. Preventative factors

The AAOMS Task Force on BRONJ recommended that patients undergo dental evaluations and receive necessary treatment before initiating IV bisphosphonates therapy (1). In addition, given the long-term biologic activity of IV bisphosphonates, one may hypothesise that different dosing regimens may be equally effective and decrease the risk for BRONJ.

Using a retrospective cohort study design, Coso *et al.* evaluated the BRONJ and skeletal-related events, for example pathologic fracture, in multiple myeloma patients using different dosing schedules for zoledronate (58). These findings suggest that alternative dosing schedules that reduce IV bisphosphonate exposure have comparable outcomes in terms of preventing SREs 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 two largest risk factors for BRONJ are IV bisphosphonate exposure and dentoalveolar procedures. Recent studies suggest that manipulation of IV bisphosphonates dosing may be effective in reducing SREs and minimising BRONJ risk (58). In addition, preventative 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 have 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 reported that preventative dental treatment decreased BRONJ risk among patients with malignancy treated with IV bisphosphonates (61–63). These findings suggest that, while BRONJ is not eliminated, dental evaluations and treatment before initiating IV bisphosphonate therapy among cancer patients reduces BRONJ risk.

The risk of developing BRONJ associated with oral bisphosphonates, while exceedingly small, appears to increase when the duration of therapy exceeds 3 years. This time frame may be shortened in the presence of certain comorbidities, such as chronic corticosteroid use. *If systemic conditions permit*, the clinician may consider discontinuation of oral bisphosphonates for a period of 3 months before and 3 months following elective invasive dental surgery in order to lower the risk of BRONJ. The rationale for this approach is based on extrapolated data that demonstrate fluctuations of osteoclast function, which is related to bisphosphonate therapy, and recent outcomes studies that show improved outcome of BRONJ treatment with drug cessation (61–64). 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 may 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:

1. Prioritisation 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

2. 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 (26,31,65–67)

Patients about to initiate intravenous bisphosphonate treatment

The treatment objective for this group of patients is to minimise the risk of developing BRONJ. Although a small percentage of patients receiving bisphosphonates develop osteonecrosis of the jaw spontaneously, the majority of affected patients experience this complication following dentoalveolar surgery (37,45,52). Therefore *if systemic conditions permit*, initiation of bisphosphonate therapy should be delayed until dental health is optimised (61–63). This decision must be made in conjunction with the treating physician and dentist and other specialists involved in the care of the patient.

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

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

Medical oncologists should evaluate and manage patients scheduled to receive IV bisphosphonates similarly to those 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.

Asymptomatic patients receiving intravenous bisphosphonates

Maintaining good oral hygiene and dental care is of paramount importance in preventing dental disease that may require dentoalveolar surgery. Procedures that involve direct osseous injury should be avoided. Non-restorable teeth may be treated by removal of the crown and endodontic treatment of the remaining roots (67). 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 (4–12 times per year).

Zoledronic acid (Reclast®) administered once per year for the treatment of osteoporosis was approved by the FDA in August 2007 (14). A single, large, prospective placebo-controlled study established its efficacy for this indication through 3 years of treatment (46). 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 timing of dentoalveolar surgery (if required) is unknown and therefore requires further study.

Asymptomatic patients receiving oral bisphosphonate therapy

Patients receiving oral bisphosphonates are also at risk for developing BRONJ, but to a much lesser degree than those treated with IV bisphosphonates (24,26,27,56). 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 (68,69) (see 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 utilisation 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 (68). The efficacy of utilising a systemic marker of bone turnover to assess the risk of developing jaw necrosis in patients at risk will require further 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 may be associated with increased duration of treatment with oral bisphosphonates, that is $\geq$3 years. There has been no information to suggest that monthly dosing of oral bisphosphonates, that is ibandronate (Boniva®), risedronate (Actonel®), is associated

Table 1 Staging and treatment strategies

BRONJ† staging	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 non-specific clinical findings and symptoms	Systemic management, including the use of pain medication and antibiotics
Stage 1: Exposed and necrotic 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 associated with infection as evidenced by pain and erythema in the region of the 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 (i.e. inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement/resection for longer term palliation of infection and pain

†Exposed bone in the maxillofacial region without resolution in 8–12 weeks in persons treated with a bisphosphonate who have not received radiation therapy to the jaws. ‡Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered because it is unlikely that the extraction will exacerbate the established necrotic process. Discontinuation of the IV bisphosphonates shows no short-term benefit. However, if systemic conditions permit, long-term discontinuation may be beneficial in stabilising established sites of BRONJ, reducing the risk of new site development, and reducing clinical symptoms. The risks and benefits of continuing bisphosphonate therapy should be made only by the treating oncologist in consultation with the OMS and the 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 following 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. BRONJ, bisphosphonate-related osteonecrosis of the jaw; IV, intravenous; OMS, oral and maxillofacial surgeon.

with either an elevated or reduced risk of BRONJ when compared with weekly dosing regimens. The risk of long-term oral bisphosphonate therapy clearly requires continued analysis and research.

Sound recommendations based on strong clinical research designs are still lacking for patients taking oral bisphosphonates. The Task Force strategies 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 case series (63,65–68). The risk of developing BRONJ associated with oral bisphosphonates increased when 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 less 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, periodontists 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 less 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 are based on the opinion of experts with significant clinical experience and the hypothesis that concomitant treatment with corticosteroids may 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 are based on the opinion of experts and observational studies (68).

Patients with BRONJ

The treatment objectives for patients with an established diagnosis of BRONJ are to eliminate pain, to control infection of the soft and hard tissue and to minimise 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 (22–24,29). It may be difficult to obtain a surgical margin with viable bleeding bone as 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 (70). 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 may result in additional areas of exposed necrotic bone. Symptomatic patients with stage 3 disease may require resection and immediate reconstruction with a reconstruction plate or an obturator. Recent case series have described acceptable outcomes following surgical therapy for patients with stage 2 and stage 3 disease (69). The potential for failure of the reconstruction plate because of the generalised effects of the bisphosphonate exposure needs to be recognised by the clinician and patient. Immediate reconstruction with non-vascularised or vascularised bone is still considered potentially problematic as necrotic bone may be present at the resection margins or develop at the recipient site.

The effectiveness of hyperbaric oxygen therapy as an adjunct to non-surgical and surgical treatment is under investigation at two institutions where a randomised controlled trial is underway (71). 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 non-surgical treatment strategies, such as platelet rich plasma, parathyroid hormone and bone morphogenic protein (72). The efficacy of these treatment modalities needs to be established through additional research and controlled studies.

Staging and treatment strategies (see Table 1)

Staging

Since the publication of the original *Position Paper*, changes in the staging system are necessary so that patients could be more accurately stratified. Specifically, a Stage 0 category was added to include patients with non-specific symptoms, or clinical and radiographic abnormalities that may be 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 categorise advanced maxillary disease.

In order 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 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 present with non-specific symptoms or clinical and radiographic findings:

Symptoms

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

Clinical findings

- Loosening of teeth not explained by chronic periodontal disease

- Periapical/periodontal fistula that is not associated with pulpal necrosis due to caries

Radiographic findings

- Alveolar bone loss or resorption not attributable to chronic periodontal disease
- Changes to trabecular pattern – dense woven bone and persistence of unremodelled 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 non-specific findings, which characterise Stage 0, may occur in patients with a prior history of Stage 1, 2 or 3 disease who have healed and have no clinical evidence of exposed bone.

Stage 1

Exposed and necrotic bone 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, that is inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla
- Pathologic fracture
- Extra-oral fistula
- Oral antral/oral nasal communication
- Osteolysis extending to the inferior border of the mandible or sinus floor.

Treatment strategies

At risk – Patients who are at risk of developing BRONJ by virtue of the fact that 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 may include the use of medication for chronic pain and 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 in combination with antibiotic therapy. It is hypothesised that the pathogenesis of BRONJ may be related to factors adversely influencing bone remodelling. Additionally, BRONJ is not due to a primary infectious aetiology. Most of the isolated microbes have been sensitive to the penicillin group of antibiotics. Quinolones, metronidazole, clindamycin, doxycycline and erythromycin have been used with success in those patients who are allergic to penicillin. Microbial cultures should also be analysed 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 may require combination antibiotic therapy, long-term antibiotic maintenance, or a course of IV antibiotic therapy.

Stage 3 – These patients benefit from debridement, including resection, in combination with antibiotic therapy, which may offer long-term palliation with resolution of acute infection and pain.

Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered because 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 by controlling 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 may be beneficial in stabilising established sites of BRONJ, reducing the risk of new site development and reducing clinical symptoms (61–63). The risks and benefits of continuing bisphosphonate therapy should be made 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 (68). Discontinuation of oral bisphosphonates for 6–12 months may result in either spontaneous sequestration or resolution following

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 (73). 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: (i) the effect of bisphosphonates on intra-oral soft tissue wound healing; (ii) analysis of alveolar bone haemostasis and the response to bisphosphonate therapy; (iii) anti-angiogenic properties of bisphosphonates and their effects on jaw bone healing; (iv) pharmacogenetic research; and (v) development of valid BRONJ risk assessment tools.

Continued governmental and institutional support is required in order to elucidate the underlying pathophysiological 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 is providing this position paper on BRONJ 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 an expert Task Force composed of oral and maxillofacial surgeons and oncologists experienced in the diagnosis, surgical and adjunctive treatment of diseases, injuries and defects involving both the functional and esthetic aspects of the hard and soft tissues of the oral and maxillofacial regions, epidemiologists and basic researchers.

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Appendix I

Bisphosphonate preparations currently available in the US

	Primary indication	Nitrogen containing	Dose	Route	Relative potency†
Etidronate (Didronel)	Paget's disease	No	300–750 mg day^{-1} for 6 months	Oral	1
Tiludronate (Skelid)	Paget's disease	No	400 mg day^{-1} for 3 months	Oral	50
Alendronate (Fosamax)	Osteoporosis	Yes	10 mg day^{-1} 70 mg $week^{-1}$	Oral	1 000
Risedronate (Actonel)	Osteoporosis	Yes	5 mg day^{-1} 35 mg $week^{-1}$	Oral	1 000
Ibandronate (Boniva)	Osteoporosis	Yes	2.5 mg day^{-1} 150 mg $month^{-1}$ 3 mg every 3 months	Oral IV	1 000
Pamidronate (Aredia)	Bone metastases	Yes	90 mg every 3 weeks	IV	1 000–5 000
Zoledronate (Zometa)	Bone metastases	Yes	4 mg every 3 weeks	IV	10 000+
(Reclast)	Osteoporosis		5 mg $year^{-1}$	IV	

†Relative to etidronate. IV, intravenous.