

## Leading article

# Bisphosphonate osteonecrosis of the jaw: a literature review of UK policies versus international policies on the management of bisphosphonate osteonecrosis of the jaw

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## Abstract

Despite the increasing number of cases of osteonecrosis of the jaws related to bisphosphonate therapy described in the literature there is a paucity of evidence-based treatment for the condition.

In this second article on bisphosphonate-related jaw complications we discuss the different treatment strategies for the condition, review current literature, particularly in relation to the recommendations that have been published, and discuss the evidence behind them.

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## Introduction

Bisphosphonate osteonecrosis of the jaw (BONJ) remains a difficult condition to treat and most specialist units have relied on their experience of the management of osteomyelitis and osteoradionecrosis to act as a guide. However, as experience increases it is clear that there are differences in the behaviour of BONJ, and specific treatment strategies need to be developed.

A number of expert panels set up by national and international medical societies to review the evidence have published differing protocols, but there is little high quality evidence in medical publications to support different treatment strategies (Table 1).<sup>1–12</sup>

To establish clear guidelines for treatment it is important to ensure that outcomes are compared appropriately. As this relies on accurate and reliable staging of a disease it poses the first challenge in the management of BONJ.

We aimed to review all guidelines published by national or international medical associations and expert panels, and to compare their advice together with the evidence used to formulate the guidelines.

## Diagnosis and staging

There is currently no consensus on the exact diagnostic criteria for BONJ, which raises the initial difficulty in discussing its management.<sup>1</sup> Most authors do not clearly state the definition they have used, but where it is defined, that given by the American Association of Oral and Maxillofacial Surgeons (AAOMS) is used most widely, but is not universally accepted.<sup>4–6,13–16</sup>

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Table 1  
Published guidelines on the prevention of bisphosphonate osteonecrosis of the jaw.

Reference number	Referred to within text	Expert panel representation or endorsement	Year published
1	American	American Experts in oral and maxillofacial surgery, oral medicine, endocrinology, and medical oncology	2006
2,3	ADA	American Dental Association	2006, 2008 (updated)
4,5	AAOMS	American Association of Oral and Maxillofacial Surgeons	2007, 2009 (updated)
6	CAOMS	Canadian Association of Oral and Maxillofacial Surgeons Canadian Society of Endocrinology and Metabolism Ontario Society of Oral and Maxillofacial Surgeons Canadian Academy of Oral and Maxillofacial Pathology, and Oral Medicine American Association of Clinical Endocrinologists International Bone and Mineral Society International Society of Clinical Densitometry	2008, 2009
7	Spanish	Spanish expert panel Oncology, Hematology, Urology and Stomatology	2007
8	AAOM	American Academy of Oral Medicine	2005
9	French	French Expert Panel	2009
10	ASBMR	American Society for Bone and Mineral Research	2007
11	BDA	British Dental Association	2008
12	Novartis	Expert panel convened by Novartis	2007

The staging system proposed by Ruggiero et al. to help categorise the severity of BONJ has been most widely adopted, and is used in most publications and guidelines on the disease.<sup>17</sup> It was revised in the AAOMS position paper in 2007 (Table 1).<sup>4</sup>

The Novartis staging system based on the National Cancer Institute Common Toxicity Criteria has not been supported by other authors.<sup>12</sup>

McMahon et al. proposed a different classification system which took into account early and intermediate findings from clinical imaging and biopsy material.<sup>18</sup> They argued that their staging system more clearly identifies patients with early disease and allows decisions to be made about continuing bisphosphonate therapy and undertaking treatment. Kwon et al. used the serum C-terminal cross-linking telopeptide of type 1 collagen in an osteonecrosis scoring system to try to stage patients more accurately on the basis of outcome.<sup>19</sup>

The AAOMS, the Canadian Association of Oral and Maxillofacial Surgeons (CAOMS), and Wutzl et al. have proposed treatment protocols based on the classification of patients according to the AAOMS staging guidelines while most other guidelines do not fully describe how decisions about treatment were reached.<sup>5,6,20</sup>

Not all guidelines include treatment strategies that are based on clearly defined staging, which makes it more difficult to ensure that treatment results for the severity of disease are appropriately controlled.

### Delineation of necrosis in BONJ

Once a diagnosis is established clinically it is necessary to assess the extent of necrotic bone, particularly when extensive resection is being considered. Most radiographic features of BONJ are relatively non-specific and do not provide accurate diagnostic information, although it has been suggested

that they should be included in the criteria for staging.<sup>18</sup> It is beyond the scope of this article to review the imaging of BONJ, but because the effect of bisphosphonate drugs are systemic, no margin of bone is strictly unaffected, and decisions about the extent of any resection need to be made on clinical grounds intraoperatively.

### Management of BONJ

The management objectives for patients with a diagnosis of BONJ are to eliminate clinical symptoms such as pain, treat any infection of the soft tissues or bone, and minimise the progression of bony necrosis.<sup>5</sup> Clinical markers of success include an intact mucosa with no signs of infection or sinus formation, and radiographic markers include the cessation of progression of the bony abnormality or remodelling of the affected area.<sup>14</sup>

Management can be categorised into several broad treatment strategies (Table 2).

Table 2  
Management strategies for bisphosphonate osteonecrosis of the jaw.

Strategy	Treatment
Conservative treatment	Mouthwash and analgesia
Non-surgical treatment	Antibiotics and antifungals
Surgical management	
Local intervention	No surgical flap Surgical flap
Radical intervention	Marginal resection Segmental resection
Adjunctive measures	Hyperbaric oxygen Parathyroid hormone Platelet-rich plasma LASER Ozone

We discuss the basis for these strategies and the evidence to support them. As previously mentioned treatment cannot be categorised according to clinical presentation or staging because most expert reviews and publications do not consistently describe the criteria used for diagnosis, staging, or selection for the different treatments proposed.

### Conservative management

This includes giving information to patients who are identified as being at risk of BONJ about the signs and symptoms they should watch out for.<sup>5</sup>

The approach consists of the use of antiseptic mouthwashes (chlorhexidine gluconate or hydrogen peroxide) twice daily with analgesia, or analgesia alone, and is indicated when patients have clinical evidence of BONJ such as exposed bone, but no evidence of infection (AAOMS stage 1).<sup>7,11,12</sup> It is essentially a strategy to reduce the likelihood of the condition progressing further and to avoid infection of exposed bone.<sup>21</sup> Although little evidence is available to support the approach it is widely advocated.<sup>5,10,12</sup>

Splints may be used to protect exposed bone, or to protect the oral mucosa from masticatory trauma, and prostheses should be carefully designed to avoid trauma to the oral mucosa.<sup>1,22–25</sup>

As a feature of BONJ is impaired healing of oral wounds, and there is no evidence to support aggressive attempts to provide coverage of exposed bone in the absence of clinical symptoms, this non-interventional approach is prudent.<sup>1</sup>

### Non-surgical management

This approach includes the use of antibiotics (systemic or topical) and antifungals in addition to mouthwashes and appropriate analgesia.<sup>12,16,25,26</sup>

Bagán et al. recommend that exposed bone should be irrigated with 0.12% chlorhexidine every 72 h for 4 weeks rather than use of chlorhexidine mouthwash only. The patient should be reviewed clinically, and then treated in the same way for another month.<sup>7</sup>

Before systemic antimicrobials are prescribed, wound or pus samples, or both, should be taken for microscopy and sensitivity testing, including testing for the presence of *Actinomyces* spp.<sup>1,5</sup>

Empirical commencement of antimicrobial therapy with a penicillin-based antimicrobial (phenoxymethylpenicillin, amoxicillin, co-amoxiclav, or clindamycin with or without metronidazole are suggested).<sup>7,9,21,26</sup>

The duration of this treatment is not clear, and suggestions range from between 7 and 15 days to long term treatment.<sup>5,7,21</sup>

This approach is indicated for patients with evidence of local inflammation or infection, and is advocated in AAOMS and CAOMS guidelines for patients with stage 2 BONJ.<sup>5,6,10</sup> It may also be the preferred approach in patients with BONJ

and cancer with very poor prognosis, for whom more extensive treatment is not indicated.<sup>9</sup>

Many other authors who advocate non-surgical management to treat local infection and stop the progression of lesions acknowledge that it is not expected to result in the resolution of all mucosal lesions, and that exposed bone in itself is not a problem.<sup>21,27–31</sup>

The use of a purely non-surgical approach in patients with orocutaneous fistula is less well known. Bocanegra-Pérez et al. suggest irrigation of the fistula with an intravenous perfusion of ciprofloxacin and application of hydrogel with alginate (Nu-Gel®, Ethicon). They reported that in two patients it resulted in the resolution of the fistula within 2–3 weeks with no recurrence at 6 months.<sup>31</sup>

Certainly in the short term a conservative approach has benefits for those who do not have stage 3 disease, but doubts exist about its viability as many patients who respond well initially relapse later because the disease has progressed.<sup>20,32</sup>

### Surgical management

A surgical approach is based on the premise that exposed bone, particularly with sharp or irregular edges, and sequestrum formation, increase the risk of further inflammation and infection, and therefore should be eliminated. However, it is the extent of surgery necessary that provokes the most debate, and several strategies have emerged (Table 2).<sup>14,17,21</sup>

The difficulty with any approach to remove necrotic bone is deciding how much is sufficient.<sup>25,33</sup> French guidelines highlight the difficulties in deciding how to determine the limits of bone removal because the systemic administration of bisphosphonate means that effectively all bony margins are affected, and bleeding from bone adjacent to that which is exposed may be limited by the osteosclerosis that the drug induces.<sup>9</sup> Where more than minimal intervention is advocated, resection to a margin of bleeding and normally coloured bone is the standard used as it indicates that there is enough metabolic potential for healing to take place.<sup>34,35</sup>

The use of a Wood's lamp after prescription of tetracycline (250 mg four times a day for at least 3 days) or doxycycline (100 mg twice daily for 10 days) has been suggested as a technique to detect the extent of the necrotic bone and to delineate radical resection margins with good success.<sup>36,37</sup>

Tissue biopsy examination is recommended only as a part of surgical treatment when there is a reasonable degree of suspicion of underlying malignancy as it requires further manipulation of soft tissue, which may exacerbate the condition.<sup>5,6</sup>

### Local intervention

Local intervention involves operating on the bone of the alveolar process, but not on the basal bone of the mandible or maxilla. It implies an attempt to remove loose or develop-

ing bony sequestra and not the formal removal of all necrotic bone.

Guidelines from the British Dental Association (BDA) and the American Society of Bone and Mineral Research (ASBMR) advocate a delayed or conservative surgical approach in the absence of large segments of necrotic bone or pathological fracture, with removal of sharp edges to prevent soft tissue trauma, but exactly what is meant by a delayed approach is not clear.<sup>10,11</sup>

The most common approach recommended is the removal of symptomatic bony sequestra alone with minimal disturbance of overlying soft tissues. It avoids the exposure of further bone, and positive outcomes in at least 80% of cases have been reported.<sup>1,5,13,14,16,25,26,38–44</sup> Antibiotics and mouthwashes are routinely included in this approach with variations in protocol that are comparable to those used in the non-surgical approach.

Several authors, however, present good results with the use of local flaps to expose the necrotic bone fully, and aid its removal with saucerisation of the cavity and primary closure of the wound.<sup>8,14,20,24,44–46</sup> This can be done under local or general anaesthetic depending on the amount of bone that needs to be removed. Preoperative and postoperative antibiotics with chlorhexidine mouthwash have been recommended routinely by most groups, although Markose et al. advocate preoperative antibiotics only.<sup>45</sup>

Saussez et al. reported a better outcome in patients with oral mucosal defects of less than 1 cm, but it was not replicated by Thumbigere-Math et al. who reported similar outcomes for all stages of disease with lesions less than and more than 1 cm.<sup>16,43</sup>

Williamson advocated minimal intervention for 3 months after which the patient should be reassessed. When disease is considered to be progressive or patients are symptomatic they are offered more extensive surgical debridement and primary closure.<sup>14</sup>

Proponents of the more aggressive surgical approach report very impressive success rates, however, Badros et al. reported that more than half the patients with multiple myeloma and BONJ who were treated using this approach had serious complications, and several groups have reported that most patients treated in this way eventually develop large necrotic bony defects.<sup>21,23,32,47</sup>

Montebugnoli et al. did a non-randomised prospective trial of conservative and local surgical approaches and found no difference in outcome.<sup>27</sup> However, as the patients treated conservatively had no evidence of bony sequestra whereas those treated surgically did, one might actually conclude that either approach is successful in appropriately selected patients.

In keeping with this, most authors recommend conservative treatment in most patients, with surgery limited to refractory cases.<sup>21,34,48</sup>

The extraction of symptomatic teeth or those with a very poor prognosis may be considered in areas of BONJ as it is not likely to exacerbate the existing condition and would

eliminate potential sources of additional inflammation and infection which could cause problems later.<sup>5,6</sup>

A secondary issue to affect the more aggressive removal of bone is the increased risk of pathological fracture of the thin rim of basal bone in the mandible.<sup>13</sup>

Where pathological fractures develop, management using a more radical approach is advocated.

## Radical intervention

Radical management refers to treatment where large sections of the jawbones are resected with the aim of removing all necrotic bone, and generally implies resection of bone beyond the alveolus. It is principally recommended where there are large segments of necrotic bone or where there is pathological fracture (AAOMS stage 3).<sup>10,11</sup>

Mandibular resections are referred to specifically as “marginal resections” (resection of the alveolus without loss of mandibular continuity), and “segmental resections” (mandibular continuity is broken and reconstructed with bone plates).

Marginal resections of the mandible are done when clinical and radiographic examinations identify necrotic bone that is isolated to the alveolus of the mandible. Segmental resections are done when extensive necrotic bone in the mandible approaches or involves the basal bone, or when an oro-cutaneous fistula is present. In the maxilla partial maxillectomies are done. Prophylactic antibiotics are given intravenously. Treatment is generally deemed successful if mucosal closure has been maintained without infection and there is acceptable radiographic healing for 12 months.<sup>49</sup>

Carlson and Basile, whose approach with formal segmental resection of the bone is probably the most radical, have reported excellent results<sup>49</sup>; a total of 87/95 patients (92%) showed good healing.

Radical resection of bone poses the problem of reconstructing the defect. Surgical options include resection with immediate or delayed rigid plate fixation with replacement of soft tissue, or immediate or delayed reconstruction by bone graft.<sup>25,34</sup>

When considering radical resection and reconstruction Marx considered three elements: the degree of secondary infection present; the amount of soft tissue lost; and the anaesthetic or medical indications for surgery.<sup>34</sup>

In most cases reported to date reconstruction has been done using rigid fixation plates, which can be inserted immediately, or as a secondary procedure after resection of necrotic bone and management of existing infection.<sup>13,34</sup>

Delayed reconstruction of the mandible is advocated in the presence of serious secondary infection when there is not enough tissue for local soft tissue reconstruction, the patient is not suitable for reconstruction with a microvascular free flap, or when prognosis from other medical conditions makes reconstruction inappropriate.<sup>50</sup> When there is a substantial

soft tissue defect the pectoralis major myocutaneous flap is the most reliable option for reconstruction, although trapezius myocutaneous or sternomastoid muscle flaps may also be used.<sup>34</sup>

Where bony reconstruction of the mandible is desired options include cortical or cancellous bone grafts, or microvascular osseous flaps. Theoretically, although this may produce a secondary problem at the donor site when autogenous grafts are used, it has not been reported as a problem by those who advocate it.<sup>23,34,51,52</sup> Ferrari et al. even placed osseointegrated implants at the time of reconstruction with a fibular free flap and had no problems with healing of the implants which they attributed to having been placed in bone with a lower concentration of bisphosphonate than might be found in the jawbones.<sup>52</sup>

Engroff and Kim also used a soft tissue only free flap to provide coverage of a palatal BONJ defect with good success.<sup>53</sup>

Resection of necrotic bone and placement of an obturator is recommended for maxillary defects, although reconstruction of the defect with a buccal fat pad advancement flap or temporalis muscle flap are alternatives.<sup>34</sup>

### Alternative management of BONJ

Several different adjunctive treatments have been advocated to improve healing in BONJ. With the exception of hyperbaric oxygen therapy (HBO) they are limited to case reports or small series, and further trials are required to elucidate their benefit.

The use of HBO in the management of BONJ has generated great interest because of its asserted benefits in osteoradionecrosis. It is an adjunct to more conventional non-surgical and surgical treatments, but its benefits remain to be clarified.<sup>31,54</sup> Proponents suggest that it is effective because it encourages the production of reactive oxygen and nitrogen species that positively modulate the redox-sensitive intracellular signalling molecules involved in bone turnover.<sup>54</sup> Results of an early case series and the preliminary results of a randomised controlled trial from Duke University indicate a potential benefit of HBO as an adjunctive measure in the management of BONJ.<sup>54,55</sup> Several case reports and series have similarly reported beneficial effects with adjunctive HBO, but no beneficial effect has been reported by others.<sup>41,56–59</sup>

Further studies are clearly necessary before HBO can be considered as part of routine treatment of BONJ.<sup>1,13,23,54</sup>

Harper and Fung used minimal intervention to treat a patient with the addition of a daily low dose parathyroid hormone, and reported resolution of symptoms and the mucosal lesion within 3 months.<sup>60</sup> Parathyroid hormone increases the metabolic activity and number of osteoclasts through its action on osteoblasts, and it was postulated that this increase in bone metabolism permitted an increase in bone remodelling, which enabled resolution of the osteonecrosis.

Curi et al. reported on three patients treated with platelet-rich plasma at the time of marginal resection of the mandible, and suggested that the high concentration of autologous protein growth factors it contained should aid wound healing.<sup>61</sup> All patients showed resolution of the lesions without discontinuation of bisphosphonate therapy. Lee et al. reported on a further two patients treated with platelet-rich plasma in addition to HBO and conventional therapies with good results.<sup>59</sup>

Vescovi et al. reported the use of Nd:YAG laser biostimulation with and without surgical treatment for BONJ and concluded that of the nine patients treated with lasers, eight were clinically successful and one showed symptomatic improvement. In comparison, of 10 patients treated without lasers five were clinically successful and one showed symptomatic improvement.<sup>62</sup>

Stübinger et al. also published a preliminary report of nine patients treated with Er:YAG lasers and reported success in all cases. The operations and postoperative wound healing were without complications, and complete soft tissue covering was achieved within 4 weeks. During follow-up examinations over 12 months soft tissue conditions were stable.<sup>63</sup>

While both these reports certainly indicate the merits of further investigation into the use of LASERS in the management of BONJ there is not enough evidence to support their use over more conventional techniques.

Ozone therapy as an adjunct to a surgical approach has been trialled by Agrillo et al. who reported significant improvement in symptoms and clinical variables for 84% of 33 patients.<sup>64</sup> However, there was no control group so their results require further validation before the technique could be recommended.

### Continuation of bisphosphonate therapy

Whether to continue or suspend bisphosphonate therapy in the presence of a diagnosis of BONJ remains controversial, and there are no prospective or controlled studies to provide guidance. The arguments for and against are similar to those concerning the discontinuation of treatment before dental work.<sup>65</sup> The Novartis guidelines succinctly state that, in patients at high risk of hypercalcaemia of malignancy or skeletal-related events, consideration should be given to maintaining bisphosphonate therapy, while in those not at risk its discontinuation should be considered after consultation with the prescribing physician or oncologist, and the treating surgeon.<sup>10,12,26</sup> Bagán et al. recommend cessation of bisphosphonate therapy and discussion with the physician about when it could be reintroduced in cases of active bone disease after having evaluated the risk:benefit ratio, whereas Williamson generally recommends continuing with the drug during treatment of BONJ.<sup>7,14</sup> The ultimate problem is that the skeletal effects of bisphosphonates are known to be long lasting, and any changes associated with stopping treatment are likely to take a long time to become apparent.<sup>19</sup>

Any patients with a diagnosis of BONJ should be seen by an oral and maxillofacial surgeon with an interest in the condition who should liaise with the prescribing physician to ensure that individualised decisions are made.<sup>1,13,20,23</sup>

One recently proposed strategy was to replace nitrogen with non-nitrogen-containing bisphosphonate.<sup>66</sup> While this was a report of only two cases, there is no question that most cases of BONJ are related to the use of nitrogen-containing bisphosphonate, and substitution of the drug where it is not otherwise contraindicated may be an alternative to stopping the treatment completely.

## Conclusion

This review suggests that there are many protocols, guidelines, and suggestions on the management of BONJ, with little in the way of clear evidence to support one strategy over another. Better quality trials are undoubtedly required to answer many of the current uncertainties.

For most patients a conservative approach with minimal local intervention when necessary seems to be most sensible, with extensive debridement of necrotic bone when it fails, and radical resection of bone and reconstruction in the small number of cases where other interventions fail or pathological fracture develops.<sup>34</sup>

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