

Dental extractions and bisphosphonates: the assessment, consent and management, a proposed algorithm

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VERIFIABLE CPD PAPER

IN BRIEF

- A method of placing patients into a risk category for bisphosphonate osteonecrosis of the jaws following a tooth extraction is proposed.
- This information can be used in the informed consent process prior to a planned tooth extraction.
- A management protocol is described in relation to each risk category in particular when to use adjuvants to treatment such as surgical antibiotic prophylaxis.

Bisphosphonate-associated osteonecrosis of the jaws (BONJ) is recognised as a significant complication related to the use of bisphosphonates and currently is gaining importance due to the increasingly widespread use of these medications. Patients are placed into low or high risk groups of developing BONJ depending on the systemic condition for which they have received bisphosphonates. Numerically, the largest group worldwide is patients receiving bisphosphonates for osteoporosis and these generally fall into the low risk group for BONJ. The high risk group, while numerically smaller, is composed of those patients receiving bisphosphonates in the management of malignancy affecting the skeleton, either primary or secondary (metastatic disease). A number of additional systemic and local risk factors are proposed, which have the effect of increasing the risk of BONJ following an extraction. These risk factors may have the effect of moving a low risk categorised patient into a medium, or perhaps more realistically an unknown risk category. An example of a systemic risk factor is the concurrent use of corticosteroids and a local risk factor is mandibular molar extraction. The purpose of this paper is to define and validate an algorithm to guide clinicians in the area of patient information, consent and management for patients currently taking or having previously taken bisphosphonates who require dental extractions.

INTRODUCTION

There is increasing concern in relation to the risks of invasive oral procedures in patients receiving bisphosphonates. The number and quality of publications on the same subject is also increasing and the authors considered that a simplified guideline directed towards dental extractions in this group would be welcomed.

This guideline proposes that patients who have received bisphosphonates can be placed initially into one of two risk groups for bisphosphonate-associated osteonecrosis of the jaws (BONJ). Patients

are placed into a low or high risk group depending on the systemic condition for which they have received bisphosphonates. The route of administration of the drug, ie oral or intravenous, should not influence the initial risk grouping of patients as this will not in itself inform on the potency or effective systemic dose of the regime.¹ The recognition of other risk factors, either systemic or local, can influence further the patient's risk status and generally have the effect of moving a subject from a lower risk to a higher risk category. The majority of patients receiving bisphosphonates worldwide are those receiving treatment for osteoporosis and initially they are placed in the low risk group. The high risk group, while numerically smaller, is made up of patients receiving bisphosphonates for the management of malignancy affecting the skeleton, both primary and secondary. The addition of secondary risk factors, for example the concurrent use of corticosteroids or the extraction of a mandibular molar, will theoretically at least move the patient to a higher risk category. As yet, attempts to accurately

assess the risk of BONJ developing in a particular individual are still proving very difficult. However some consensus appears to be emerging as regards prevention, diagnosis, prevalence and management of BONJ and the authors would consider that the algorithm presented here has the support of the expert opinion and the published evidence so cited.

The purpose of this algorithm is to provide guidance to clinicians in the area of patient information, consent and management of those patients who have received or who are receiving bisphosphonates when dental extractions are indicated.

BRIEF SUMMARY OF ACTIONS OF BISPHOSPHONATES

The mechanism by which bisphosphonates influence bone metabolism is not yet fully understood. However, these drugs are strong inhibitors of osteoclast mediated bone resorption, inhibiting both cell function and inducing early apoptosis (programmed cell death). Because bisphosphonates have a very high affinity for hydroxyapatite crystals,

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they have the ability to localise and accumulate on bone mineral surfaces, particularly at sites of high bone turnover. The alveolar processes of mammalian jaws are considered to have the ability to turnover at a high rate, especially in response to insult. Bisphosphonates containing nitrogen in their side chain (also called aminobisphosphonates) also exhibit several antitumour effects, including the inhibition of tumour cell ability to invade bone and induction of tumour cell apoptosis.² Some antiangiogenic properties have also been reported in animal studies.³


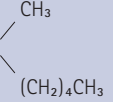

PATHOGENESIS

In physiologic bone homeostasis, osteoclastic resorption and osteoblastic deposition are interdependent functions for bone remodelling and wound healing. In the jaws, the bone undergoes high turnover remodelling to maintain biomechanical competence, a process that is accelerated after dental extractions.

A biological model has also recently been proposed, suggesting direct toxicity of bisphosphonates on oral epithelium as a significant aetiological factor.⁴ It is proposed that dental extractions or other intraoral trauma result in the release of bisphosphonates locally which will inhibit proliferation of adjacent epithelial cells and frustrate the healing of soft tissues, causing a prolonged exposure of underlying bone to the oral microflora.

Bisphosphonates also have demonstrated effects unrelated to osteoclastic activity. It has been suggested that they play a role in the regulation of blood circulation within bone through a complex interaction with growth factors and inhibition of endothelial cell function. These properties could also contribute to the apparent ischaemic changes noted in the compromised healing of affected areas. A fuller explanation of the pathogenesis will not be attempted here and the authors would direct those interested to consider the most current published knowledge in this rapidly growing area. The group of bisphosphonates that exclusively are associated with BONJ are shown in Table 1.

The algorithm presented in Figure 1 should be understood with reference to the following explanatory text.

Bisphosphonates (BPs)	R ₁ chain	R ₂ chain
alendronic acid (alendronate sodium)	-OH	-(CH ₂) ₃ -NH ₂
risedronate	-OH	
ibandronic acid (ibandronate sodium)	-OH	-CH ₂ -CH ₂ -N 
pamidronate	-OH	-CH ₂ -CH ₂ -NH ₂
zoledronic acid (zoledronate disodium)	-OH	

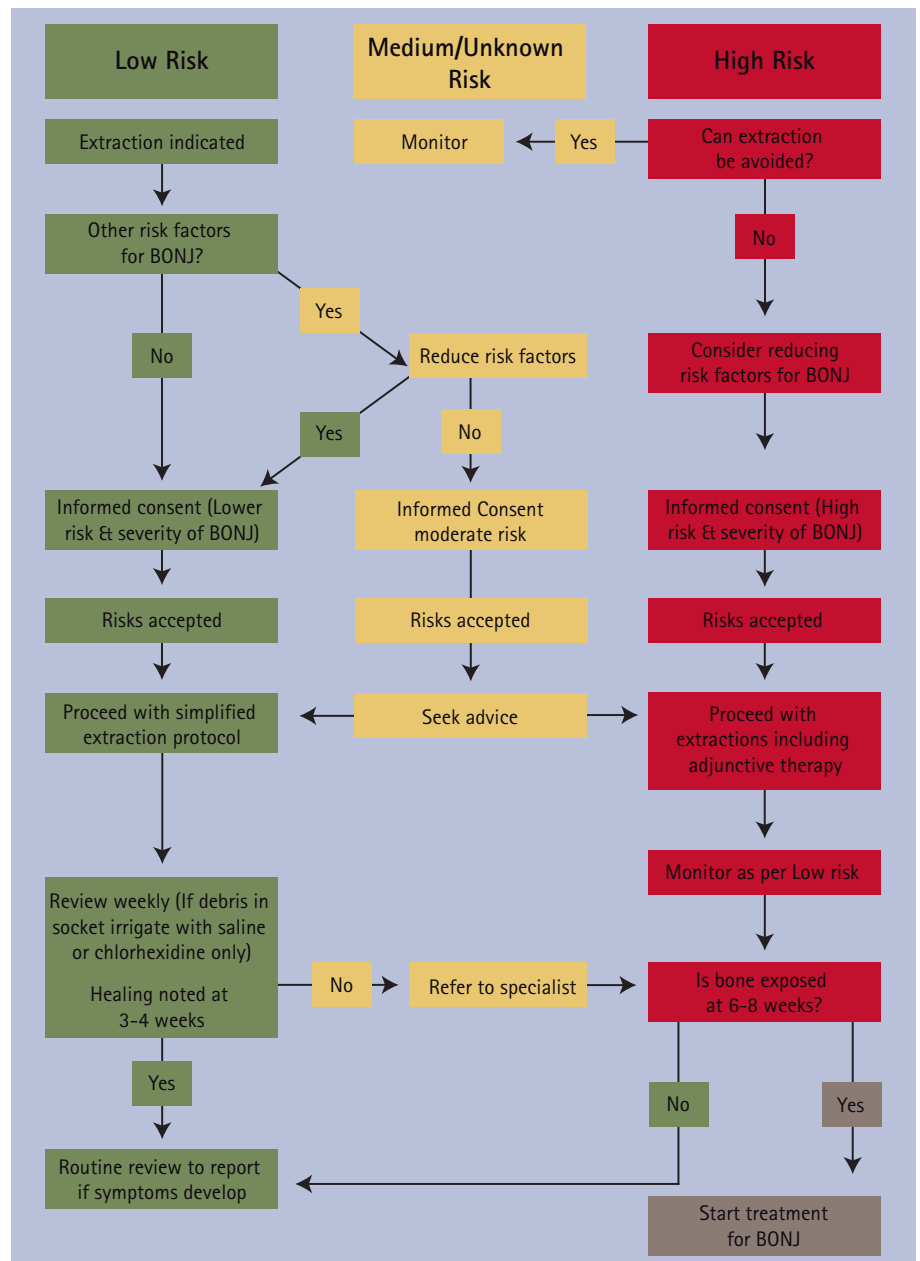


Fig. 1 Algorithm: Extractions in Bisphosphonate Patients, to be understood in conjunction with explanatory notes

RISK GROUPS

The initial risk grouping of patients is based on the indication for bisphosphonate therapy. Patients who are receiving bisphosphonate therapy for the treatment of osteoporosis and Paget's disease are categorised in the *low risk* group for BONJ (NB: Paget's disease is usually treated with only a short course of bisphosphonates). Oncology patients with hypercalcaemia of malignancy, multiple myeloma and skeletal metastases, most commonly from breast and prostate cancer, are included in the *high risk* group for BONJ. Drug-related factors, such as the dose, duration, route of administration, frequency and potency of the bisphosphonate will influence the risk of BONJ.⁵

It is well evidenced that the high dose, high potency bisphosphonates used in the treatment of malignancy are associated with a greater risk and severity of BONJ.⁵⁻⁷ It should be noted, however, that high potency bisphosphonates at lower doses are licensed for treatment of osteoporosis (zoledronic acid, Aclasta® / Reclast®, Novartis AG, and ibandronate, Bondronat® / Bonviva®, Roche). It is likely that the tailored doses (5 mg/year and 3 mg/3 months respectively) of intravenous regimens will have similar reduced risks and severity of BONJ as the lower potency oral preparations used to treat osteoporosis. However, high dose, high potency bisphosphonates can also be given orally in the management of oncology patients (Bondronat®, Roche, 50 mg/day), and these regimes should not be confused with the more common lower doses of the same drug prescribed orally in osteoporosis. Regardless of the route of bisphosphonate administration (intravenous or oral), oncology patients who have received these drugs should be considered in the high risk category for BONJ.^{8,9}

POSSIBLE FUTURE RISK GROUPS

The AZURE trial¹⁰ is a large multicentre study in which patients with high risk localised breast cancer (without metastasis) are being treated with an intravenous bisphosphonate for a five year period in the adjuvant setting of prevention of recurrence. The dose of drug is three times that given in the

treatment of osteoporosis but only 20% to 25% that given for the treatment of metastatic breast cancer over a similar five year period. It is likely that these patients and similar future patients will be at an intermediate risk of BONJ.

ADDED RISK FACTORS

Local risk factors

- Mandibular molar extractions: two thirds of BONJ cases have been reported in the mandible⁵
- All dentoalveolar surgery
- Periodontitis/poor oral hygiene: the bacterial biofilm present in periodontal disease is responsible for gingival inflammation and alveolar bone resorption. This pathology, together with the interactions between bacteria themselves and bisphosphonates can increase the possibility of BONJ⁵
- Trauma related to dentures
- Thin mucosal coverage, lingual to lower molars and bony tori.

General risk factors

- Concomitant therapies: corticosteroids, other immunosuppressants (eg methotrexate, thalidomide), chemotherapeutic agents (eg hormone antagonists)
- Systemic conditions affecting bone turnover: immunocompromised patients, rheumatoid arthritis, poorly controlled diabetes
- Smoking
- Sociodemographic characteristics: extreme of age (over 6th decade), gender.

Corticosteroids

Corticosteroid therapy has been associated with osteonecrosis affecting a number of skeletal sites, and has been recognised as the second most common cause of osteonecrosis of the hip next to trauma.¹¹ Knee, shoulder and ankle are also commonly affected and the severity of the condition is accepted as dose and duration related. Interestingly the jaws are not recognised as at risk of corticosteroid-associated osteonecrosis.^{2,11}

However, the general osteoporosis induced by corticosteroid therapy and the risk of low impact fractures associated with it is such that the concurrent prescribing of a bisphosphonate has been

recommended. Present guidelines advise that patients taking the equivalent dose of prednisolone 7.5 mg per day or more for >3 months should be considered for skeletal protection with a bisphosphonate or hormone replacement therapy.¹² The question therefore arises: are corticosteroids a risk factor for osteonecrosis of the jaws?

A number of molecular mechanisms of corticosteroid-induced osteonecrosis have been described.¹³ These include: i) suppression of sex hormones which normally have an inhibitory effect on osteoclasts; ii) direct suppression of osteoblast function; iii) induction of apoptosis of osteoclasts, osteoblasts and osteocytes; iv) increase of effect of parathyroid hormone; and v) increase of the bio-availability of bisphosphonates.¹⁴ Combine these with the suppression of inflammatory and immune mechanisms by corticosteroids and they could well explain why corticosteroids are emerging as a significant co-risk factor in the development of BONJ.

Although the cumulative dose has significance, it should be noted that a short term high dose of corticosteroids will act rapidly through the above mechanisms as a possible potent co-risk factor for BONJ.¹³ The potency of any inhaled corticosteroid should also be factored in when considering the total received dose. It may well be prudent at this stage to mention the rheumatoid arthritis group of patients who as yet may not be consistently prescribed bisphosphonates.¹⁵ This situation is likely to change, thereby increasing the relative number of patients receiving the combination of corticosteroids and bisphosphonates.

Smoking

Heavy tobacco smoking has an adverse effect upon the healing of extraction sockets and oral soft tissue wounds.¹⁶ The deleterious effects of carbon monoxide, tissue hypoxia, hydrogen cyanide and nicotine on healing tissues are well documented.^{17,18} Nicotine has been shown to increase the level of mammalian parathyroid hormone.¹⁹ It is proposed that the greater the tobacco consumption and duration of the habit, the greater the significance of tobacco as a co-risk factor for BONJ.

Gender

It has been proposed that females are more at risk than males of developing BONJ.²⁰ Women are prescribed bisphosphonates more commonly than men and therefore a higher prevalence of BONJ in women would be expected. Until further evidence is presented the authors would not consider females at greater risk than males for BONJ.

Extreme of age

Age has also been cited as a risk factor, however the vast majority of patients receiving bisphosphonates are over the age of 50. In consideration of certain accepted age changes within the jaws that include the reduction in blood circulation and ability to respond to trauma, it would seem reasonable to consider old age as a risk factor for this condition. Very few children are at present being prescribed bisphosphonates²¹ and there is currently a paucity of evidence from human or animal studies regarding the risk of BONJ in children or adolescents. Until this situation changes the authors would consider extractions in this group (including those for orthodontic purposes) to be categorised as moderate or unknown risk.

Previous history of BONJ

Patients who have previously been diagnosed with BONJ should be placed in a high risk category. Although variations within individual bones, including the jaws may well be the case, the effects of bisphosphonates must be assumed to be generalised throughout the skeleton and throughout the jaws.

Reduction of risk factors

Apart from old age, all other risk factors can potentially be reduced.

Cessation of smoking

Whenever possible, patients should be encouraged and counselled to stop smoking.

Improvement of oral hygiene and periodontal health

When possible, these areas of concern should be addressed prior to any extractions.⁹

Cessation of bisphosphonate drug therapy

Patients may not require to be on bisphosphonates long-term. Evidence is emerging that patients who have received bisphosphonates to reduce low impact fractures due to osteoporosis and then discontinue the drug do not suffer a sudden return of low impact fracture risk.²² This same group demonstrated some recovery of bone turnover, as measured through longitudinal bone marker monitoring. Although the period required before such recovery was generally beyond a year, it would be expected that extractions in cases where discontinuation of bisphosphonates has been instigated for 12 months or more would carry a reduced risk of BONJ. However, in the low risk group, delaying an extraction to allow for three months cessation of bisphosphonates is not considered to be an effective or appropriate preventative measure.²³

Reduction/cessation of corticosteroid therapy

If a reduction or discontinuation of corticosteroid therapy is planned as part of the patient's systemic management, then delaying dental extractions until such time that the corticosteroid dose is less than the equivalent of prednisolone 7.5 mg per day should be considered. This is based on the evidence that suggests the dose and potency of corticosteroids has a direct and immediate effect on the risk of BONJ.¹³

INFORMED CONSENT/WHAT ARE THE RISKS?

Current estimates on prevalence and incidence of BONJ are based on anecdotal reports, case series, voluntary surveillance systems and safety reports to pharmaceutical companies. There is a risk of spontaneous BONJ occurring in any patient on bisphosphonates. Based on Australian data,²⁴ a dental extraction can increase this risk of BONJ by a factor of up to seven. The frequency of BONJ in osteoporotic patients was suggested as 1 in 2,260 to 8,470 (0.04% to 0.01%). If extractions were carried out, the calculated frequency was 1 in 296 to 1,130 cases (0.34% to 0.09%), but fortunately severe destructive BONJ has only

rarely been reported in the osteoporosis group. The frequency of spontaneous BONJ in oncology patients was 1 in 87 to 114 (1.15% to 0.88%). If extractions were carried out, the calculated frequency of BONJ was 1 in 11 to 15 (9.1% to 6.67%) and these would be more likely to be examples of progressive, severe and destructive BONJ.²⁴ The incidence of BONJ in women with post-menopausal osteoporosis who received once-yearly infusion of 5 mg of zoledronic acid (Recast®, Novartis AG) was determined in a large, prospective three-year clinical trial. Recent prospective data from this study found one case of BONJ among more than 7,000 patients, and is the only published evidence from a randomised, placebo-controlled clinical trial.²⁵

In the South-East of Scotland, where over the last eight years *circa* 40,000 drug patient years (DPYs) of alendronic acid have been prescribed, nine cases of BONJ have so far presented. Three of these occurred spontaneously, another two were possibly denture trauma induced and four occurred post extraction (as yet unpublished data). This represents an incidence of one case per 4,400 DPYs.

SIMPLIFIED EXTRACTION PROTOCOL

Peri-operative antimicrobial rinsing with chlorhexidine mouthwash 0.12–0.2% is proposed.²⁶ The removal of a tooth should be performed with the least traumatic extraction technique and preferably one tooth at a time or a sextant-by-sextant approach. If obvious sharp socket wall margins or inter-radicular bone are observed following the procedure, these should be reduced selectively without lifting the periosteum from the bone. Post-operative chlorhexidine mouthwash should also be used until adequate healing is observed.⁹

Root fracture during extraction

In the low risk case, progression to a conventional surgical procedure should be considered. Minimising the unnecessary exposure of bone by keeping periosteal flaps small should be attempted where practical. If a decision is made to prescribe antibiotics, the most effective administration would be to deliver

preoperatively (see *Surgical antibiotic prophylaxis*). Primary closure is not considered imperative, especially if this is dependant on the further lifting of the periosteum.

Monitoring of socket healing

Weekly monitoring has been included in the algorithm but this should not be considered a hard and fast rule and may well be impracticable. The following, however, should be understood. Pain, *fetor oris* and bad taste are often late presenting symptoms in post-extraction BONJ cases. The removal of debris from an otherwise asymptomatic socket at one or two weeks post-extraction may have a beneficial influence on the healing process. The observation of exposed desensitised bone at 3-4 weeks would seem a reasonable point at which to seek advice or trigger a referral for suspected BONJ. Exposed bone at 6-8 weeks, by definition, is considered an established BONJ.⁷

ADJUNCTIVE THERAPIES

Surgical antibiotic prophylaxis (SAP)

There are no controlled studies to support surgical antibiotic prophylaxis for invasive dental procedures in bisphosphonate patients. In consideration of this and also the low incidence and severity of BONJ in the low risk group, and in light of the known risk and severity of reactions to penicillin-based and other antibiotics, the authors would consider the risk benefit equation to be heavily against the routine use of SAP in low risk cases. In contrast, in the high risk group where the incidence and severity of BONJ is greatly increased, the authors would consider that the risk benefit equation shifts towards the routine use of SAP.

One of the principles of SAP is that the agent of choice should have a spectrum most suited to act on those pathogens likely to infect the surgical site.²⁷ In BONJ the most common pathogens, based on culture and sensitivity tests, are considered to be *Actinomyces*, *Eikenella* and *Moraxella* species.²⁸ Therefore penicillin V (phenoxymethylpenicillin) 500 mg four times per

day is a suitable antibacterial drug. In penicillin allergic patients, doxycycline 100 mg once daily is suitable. Metronidazole 200 mg three times per day has proven effective in patients refractory to the above antibiotics. Considering the target pathogens, it should be noted that amoxycillin and clindamycin are not first line drugs for prophylaxis in this condition.⁸

A further principle of SAP is to deliver the antibiotic at a time which will ensure an effective blood level during the surgical procedure.²⁷ Oral antibiotics should therefore be given pre-operatively to be most effective; one hour prior to treatment is suggested.

Temporary and long-term discontinuation of the bisphosphonate (drug holiday)

In high risk cases, a three month drug holiday prior to extractions and cessation of the drug until wound healing is observed may have some merit. Certainly if non-healing of a socket is observed at 4-6 weeks post-extraction, these patients would then have had a four month period of bisphosphonate discontinuation, with hopefully some recovery of bone turnover ability. In the low risk case however, it should be stressed that a three month pre-operative drug holiday cannot be supported generally as a risk reduction measure with regards to BONJ.²³ As stated previously under *Reduction of risk factors*, if the continuation of bisphosphonate treatment is non-essential then as far as the long-term health of the jaws is concerned, the discontinuation of the drug would be beneficial. Inter-mittent drug therapy in the management of osteoporosis as a means of protecting the jaws from an unremitting bisphosphonate insult is a novel but as yet an untested proposal.¹

The patient's physician in consultation with the patient and dental surgeon should be in the best position to consider the benefits *versus* risks of discontinuation of bisphosphonate therapy. In the high risk group, discontinuing or interrupting bisphosphonate therapy as a means of risk reduction for BONJ is commonly considered, and this is balanced against the risk of more serious skeletal complications.

Avoiding/delaying extractions

Endodontics should be considered as an option before an extraction.

In symptomatic endodontically treated teeth, endodontic retreatment should be considered. Non-restorable teeth can be considered for coronectomy and kept in the dental arch as endodontically treated retained roots. Avoidance or delaying an extraction could in some cases be considered as a risk reduction strategy.⁹

However, the unnecessary delay or avoidance of appropriate treatment can not be supported²³ and each case should be considered on its own merits.

SEEKING ADVICE

It would be expected that oral and maxillofacial surgery units would have an opinion due to their interest in the management of these patients, but equally hospital dental services and the salaried dental services, as well as other specialists, may well be in a position to give advice.

CONCLUSION

In the majority of patients who have received bisphosphonates for the management of osteoporosis, the risk of post-extraction BONJ is low in comparison with those patients who have received bisphosphonates for the treatment of malignancy, where the risk of post-extraction BONJ is high. There is an increasing recognition of the influence of other risk factors in relation to post-extraction BONJ and concurrent corticosteroid use is emerging as a dose-related factor. Patients receiving bisphosphonates to counteract the osteoporotic effects of corticosteroids are numerically a rapidly enlarging group. This drug combination does appear to place the patient at a higher risk of spontaneous and post-extraction BONJ. The concurrent prescribing of methotrexate and other chemotherapeutic agents with bisphosphonates and corticosteroids is becoming more common and not confined to the malignancy group. Rheumatoid arthritis sufferers constitute a large group who will increasingly be offered these combinations of drugs. Although it may be an oversimplification to suggest that the more risk factors, the higher the risk of post-extraction BONJ, at the

present time the advice is that if practicable, a reduction in risk factors prior to an extraction may reduce the risk of BONJ.

At the other end of the scale, where high toxicity and dose bisphosphonates have been administered in patients suffering with malignancy, the jaws may have reached a 'state of no return'. In such cases the alveolar bone has such a reduced cellularity that it is effectively acellular. It is increasingly recognised that the healing ability of the oral soft tissues in these cases appears also to be compromised, the exact nature of which has not yet been established. When extractions are performed, the ensuing breach in the protective soft tissue envelope leads to long-term jaw exposure and secondary infective complications. The insidious, progressive osteomyelitis that often follows can be very destructive. Extraction avoidance strategies and adjunctive therapy may reduce or delay this disease process. A wide spectrum of jaw disease and risk of BONJ therefore exists, but unfortunately reliable tests or markers for assessing the healing ability of the oral soft tissues and the underlying bone are not yet available.

Until such pre-operative assessment becomes a practical proposition, an individual's risk status for BONJ resulting from an extraction should be based on the number and significance of the risk factors present. Although a crude method, it is the authors' view that an individual can be placed in a low, medium or high risk category for BONJ for the purposes

of informed consent prior to considering dental extractions.

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