

Prevention of Osteonecrosis of the Jaw (ONJ) in Patients on Bisphosphonate Therapies

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Summary This document provides a consensus based guideline, drawing on current documented best practices, for the undertaking of invasive dental/oral surgical procedures on patients taking bisphosphonate agents so as to minimise the risk, or prevent the development of osteonecrosis of the jaws.

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PREVENTION OF OSTEONECROSIS OF THE JAW (ONJ) IN PATIENTS ON BISPHOSPHONATE THERAPIES

PURPOSE

The NSW Centre for Oral Health Strategy recognises that there has been growing concern regarding the number of patients who take bisphosphonate agents, thereby placing them at potential risk for developing osteonecrosis of the jaws, especially following invasive dental/oral surgical procedures such as extractions. This document provides a consensus based guideline, drawing on current documented best practices, for the undertaking of invasive dental/oral surgical procedures on patients taking bisphosphonate agents so as to minimise the risk, or prevent the development of osteonecrosis of the jaws.

KEY PRINCIPLES

1. An increasing number of patients are taking bisphosphonate agents that act to down-regulate bone turnover. The majority of patients take orally administrated bisphosphonates for the treatment and prevention of osteoporosis. Multi-dose intravenous bisphosphonates are generally used in patients with cancer. (Section 3.1)
2. A small number of patients, predominantly those taking intravenous bisphosphonates have developed localised death and destruction of sites in the bone of mandible and maxilla ("osteonecrosis") following invasive dental treatment such as extractions that can be associated with considerable pain and morbidity. (Section 3.2)
3. The causal link of Bisphosphonate usage and ONJ is not yet fully understood, and there is no known treatment that is proven to prevent this from occurring. Ideally, patients should be fully dentally fit and invasive dental procedures should be completed before patients commence bisphosphonate therapy (Section 4.1.2). This is not always practical, and so called "spontaneous" cases of ONJ have been reported in some patients on bisphosphonate therapies that have not been associated with invasive dental procedures or surgery.
4. Prevention of the need to undertake invasive dental procedures to address oral health problems, through good oral hygiene and early dental treatment, is extremely important in patients taking bisphosphonates. (Section 4.1)
5. For the greater majority of patients, who are taking **oral** bisphosphonates requiring routine dental treatment, including extractions under local anaesthetic in the dental chair, **do not** require any special precautions. (Section 4.1.3)
6. Select patients who have been on a long term course of **intravenous** bisphosphonate therapy for the treatment of cancer may benefit from a pre- and post-operative course of a suitable antibiotic, such as clindamycin, in combination with regular (4x/daily) anti-microbial mouthwash, such as chlorhexidine. (Section 4.1.4)
7. All patients taking bisphosphonates and needing invasive dental treatment should be provided with proper, informed consent advising them of the potential risk of developing ONJ. (Sections 4.1, 4.1.3 and 4.1.4)

These guidelines have been developed through the consensus agreement of the following NSW Public Oral Health Clinicians, convened by Dr Mark Schifter, (Staff Specialist Oral Medicine/Oral Pathology, Sydney West Area Health Service (SWAHS)):

- Dr Malcolm Coombs, Sydney South West Area Health Service (SSWAHS)
- Dr Anastasia Georgiou (SWAHS)
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- Dr Sue-Ching Yeoh (SSWAHS).

Consultation has also involved the Australian Dental Association Inc., through meetings with members of the *Therapeutic Guidelines: Oral and Dental* Expert Group, and the NSW Medicines Information Centre.

USE OF THE GUIDELINE

The intended audience for these guidelines is NSW Health Public Oral Health Practitioners. As has been previously acknowledged, this workforce is made up of a mix of dental professionals with a great range of training and experience. It needs to be acknowledged that that public dental sector provides services to populations who may not be fully informed of the need and benefits of regular and/or timely dental check-ups and treatment, particularly in reference to the commencement of bisphosphonate therapy. These guidelines take into account these issues specific to the public sector.

Dental practitioners, particularly those who are not working within the NSW Public Oral Health sector, should be aware of other existing guidelines and treat individual patients using their best clinical judgement. These guidelines include, but are not limited to;

- Therapeutic Guidelines: Oral and Dental guidelines (developed in consultation with the Australian Dental Association Inc.)
- Journal of Oncology Practice: Practical Guidelines for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaw in Patients With Cancer
- Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: An advisory statement from the American Dental Association Council on Scientific Affairs
- American Association of Oral and Maxillofacial Surgeons, Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw - 2009
- Canadian Consensus Practice Guidelines for Bisphosphonate Associated Osteonecrosis of the Jaw

Medical practitioners who prescribe bisphosphonate therapies should be aware and ensure their patients are aware of the potential risk of Bisphosphonate Related Osteonecrosis of the Jaw, and should ensure that patients have a dental check and necessary treatment before commencing treatment (when practical). For patients commencing bisphosphonate therapies, it is also vital that medical and dental practitioners provide advice on maintaining good oral hygiene and making lifestyle changes which reduce oral health risk factors (eg. smoking cessation). (Section 4.1)

REVISION HISTORY

Version	Approved by	Amendment notes
June 2008 (GL2008_010)	DDG Population Health Chief Dental Officer	New guideline advising Bisphosphonate Related Osteonecrosis of the Jaws – Prevention
June 2010 (GL2010_010)	A/ DD-G Population Health Chief Dental Officer	<p>Rescinds GL2008_010.</p> <p>Amended to fit new guideline format.</p> <p>Alterations:</p> <ul style="list-style-type: none"> - Reinforces role of prevention - Window Periods and clarification of window period definition (p. 16) - Use of antibiotics (p. 20) and antibiotic dosages (pp. 21-23) - Updated prevalence rates (p. 9-10) - Updated references <p>Additions:</p> <ul style="list-style-type: none"> - Staging system (p.13) - High Risk patient – High dose systemic corticosteroid therapy. (Table 5, p. 18) <p>Consideration for alteration of bisphosphonate therapy in consultation with medical practitioner (p.24).</p>

ATTACHMENTS

1. Prevention of Osteonecrosis of the Jaw in Patients on Bisphosphonate Therapies

**PREVENTION OF OSTEONECROSIS OF THE JAW (ONJ) IN
PATIENTS ON BISPHOSPHONATE THERAPIES**

NSW HEALTH
PROCEDURES

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Synonyms and Acronyms

Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ);
Bisphosphonate Associated Osteonecrosis of the Jaws (BAONJ);
Bisphosphonate-associated Osteonecrosis (BON);
Osteochemonecrosis of the Jaws (OCNJ);
Osteonecrosis of the Jaws (Bisphosphonates)/(Bisphosphonate Associated)
“Bis-phossy Jaw”.

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1 Purpose Statement

The Centre for Oral Health Strategy, NSW Health, recognises that there has been growing concern regarding the number of patients who take bisphosphonate agents, thereby placing them at potential risk for developing osteonecrosis of the jaws, especially following invasive dental/oral surgical procedures such as extractions. This guideline has been developed in recognition of this concern, and to provide guidance in the provision of dental and oral care and treatment to minimise, and if practical, prevent ONJ from developing in patients who are on bisphosphonate therapies.

The intended audience is NSW Health Public Oral Health Practitioners. As has been previously acknowledged, this workforce is made up of a mix of dental professionals with a great range of training and experience. It needs to be acknowledged that the public dental sector provides services to populations who may not be fully informed of the need and benefits of regular and/or timely dental check-ups and treatment, particularly in reference to the commencement of bisphosphonate (BP) therapy. This guideline recognises that in select cases dental extraction of teeth with a poor or hopeless prognosis in patients receiving BP's is an inevitable necessity with recommendations in such cases to try and lessen the risk of BRONJ from occurring.

Clinicians, particularly those who are not working within the NSW Public Oral Health sector, should be aware of other existing guidelines and treat individual patients using their best clinical judgement. These guidelines include, but are not limited to;

- Therapeutic Guidelines: Oral and Dental guidelines (developed in consultation with the Australian Dental Association Inc.)
- Journal of Oncology Practice: Practical Guidelines for the Prevention, Diagnosis, and Treatment of Osteonecrosis of the Jaw in Patients With Cancer
- Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: An advisory statement from the American Dental Association Council on Scientific Affairs
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- Canadian Consensus Practice Guidelines for Bisphosphonate Associated Osteonecrosis of the Jaw

2 Scope

2.1 Expected Outcomes

These guidelines are intended to:

- Assist in the identification of those patients needing dental/oral surgical treatment who are at potential risk of ONJ in patients taking, or about to commence Bisphosphonate therapies;
- Provide guidance to clinicians to minimise and, if practical, prevent ONJ occurring;
- Provide support and thereby reassurance for public dental health professionals in managing patients at-risk of developing ONJ;
- Provide support and reassurance, through the best available evidence of treatment alternatives and adjuncts, to patients attending public dental health clinics who are at-risk of ONJ;
- Provide amended/updated guidelines as new information or evidence becomes available.

2.2 Definitions

Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ)

Patients may be considered to have BRONJ if:

1. The patient is currently receiving, or has previously received, treatment with a bisphosphonate; and
2. There is exposed, necrotic bone in the maxillofacial region (jaws) that has persisted for more than 8 weeks; and
3. There is no evidence of cancer at the site; and
4. The patient has no history of radiation therapy to the jaws.

Additional characteristics of note

- associated with potent nitrogen-containing bisphosphonates (“amino-bisphosphonates”)
- usually associated with trauma to the jaws (extractions), however “spontaneous” or idiopathic cases have been reported
- There is a differential diagnosis for metastasis or localised myelomatous deposit in patients taking BP’s for skeletal related complications with a solid malignancy or multiple myeloma who develop BRONJ.

3 Background

Bisphosphonates (previously termed diphosphonates) are a class of drugs that principally act to prevent the resorption of bone and inhibit bone turnover. In recent years, highly potent second and third generation, nitrogen-containing, amino-bisphosphonates have been developed which appear to be implicated in the aetiology and pathogenesis of a painful destructive lesion affecting the jawbones (maxilla and mandible) termed bisphosphonate-related osteonecrosis of the jaws (BRONJ), or more colloquially expressed as “bis-phossy jaw”. In terms of its presentation, and associated pain and destruction it is akin to the condition termed osteo-radionecrosis which can follow head and neck radiotherapy. However BRONJ clearly has a different aetio-pathogenesis and is far more refractory to treatment than osteo-radionecrosis.

The term “bis-phossy jaw” is derivative, and reflects a historical association with another painful and destructive condition confined to jaws, and related to the occupational exposure to white phosphorus of matchstick makers (‘Lucifer “strike-anywhere” matches’) of the 1830’s, then termed “phossy jaw”.

3.1 Bisphosphonates: Therapeutic Indications

Bisphosphonates are used to significant clinical benefit in both the *treatment* and *prevention* of conditions associated with pathology secondary to bone resorption and turnover (Table 1). Accordingly, the use of bisphosphonate therapies has increased markedly, particularly in the treatment of age related and post-menopausal osteoporosis, and breast cancer and other solid malignancies where long-term survival is greatly increased.

Table 1 Bisphosphonates – Therapeutic Indications

Indication	Comments
Osteoporosis	Post-Menopausal Cortico-steroid Induced/Related “Male” age-related osteoporosis Male Hypogonadism
Skeletal (bony) Metastases (from solid malignancies)	Breast Cancer Lung Cancer Prostate Cancer
Heterotopic ossification	Prevention and treatment when associated with spinal cord injury
Total Hip Replacement	1 month pre-operatively 3 months post-operatively
Hypercalcemia	
Multiple myeloma	
Osteitis Deformans (Paget’s Disease)	
Other/Rare Conditions	Osteogenesis Imperfecta Reflex Sympathetic Dystrophy (Complex Regional Pain Syndrome (CRPS))

3.2 Epidemiology of BRONJ

The prevalence of BRONJ is difficult to estimate. The first cases were reported in November 2003. By March 2006, there were sixteen papers detailing some 191 cases, in contrast to the millions of patients world-wide taking second and third generation bisphosphonate agents.

The most recent available data indicates that for patients taking intravenous bisphosphonates in the setting of, or for the prevention of malignancy related skeletal events, the incidence of BRONJ varies between 0.8% to as high as 15%. The data regarding the incidence of BRONJ in patients taking bisphosphonates for age-related and/or post-menopausal osteoporosis is still limited, and may be under reported. This would suggest that the incidence is still so low that it is difficult to accurately determine what the true incidence of BRONJ is in this patient population. Indeed, some authors note that a direct causal link has not been established in the patient population taking low-dose bisphosphonates.

So far the epidemiological data has identified two main risk factors associated with the development of BRONJ:

- 1) Type (potency), duration and route of bisphosphonate administration, and;
- 2) Trauma, overwhelmingly any form of surgical trauma to the jaws, including the extraction of teeth.

3.2.1 Intravenous (IV) Bisphosphonates

Clinical efficacy of IV bisphosphonates for the treatment of hypercalcemia and bone metastases is well established, as is its potential role in prevention of bone fractures in osteoporosis using a regimen of lower cumulative doses. However these studies are limited retrospective studies using small sample sizes. Estimates of the cumulative incidence of BRONJ with intravenous bisphosphonates ranges from 0.8%-12% occurring in patients having taken these agents.

3.2.2 Oral Bisphosphonates

The clinical efficacy of oral bisphosphonates for the treatment of osteopaenia/osteoporosis is well established. Note, for example, that over 190 million oral bisphosphonate prescriptions have been dispensed worldwide. Based on data from Merck, the manufacturer of Fosamax (alendronate), patients on oral bisphosphonate therapy are at a considerably lower risk for BRONJ. The incidence of BRONJ was calculated at: 0.7/100,000 person/years of exposure, meaning that the risk of BRONJ after 1 year of therapy is calculated at 0.0007% of patients (p.a), rising to 0.0021% by the third year of ongoing treatment. One study in Australia puts the risk in patients taking Fosamax of developing BRONJ following an extraction (alendronate) at 0.09-0.34%. The annual risk, nor whether this risk is cumulative with each year of Fosamax use was not clearly stated. This data suggests that as little as 4 in 1000 patients taking long-term oral Fosamax may, with extractions develop BRONJ.

A recent study from a patient group in Northern California found an incidence rate of between 1 in 952 and 1 in 1,537 people who were on chronic oral bisphosphonate therapies.

3.2.3 Risk Factors

Overwhelmingly, the evidence, to date, indicates that the main risk factors for BRONJ are the type (potency), duration, and route of bisphosphonate therapy. The use of highly potent, third generation, nitrogen-containing, bisphosphonate agents for more than a year, given intravenously, namely Zometa® (zoledronic acid) is by far and away the leading agent associated with the development of BRONJ. Nonetheless, all patients taking any of the second or third generation bisphosphonates, who are required to have any form of dental/oral surgery, are at risk of developing BRONJ. This risk can be stratified; from being a very small or almost negligible risk of BRONJ occurring in those patients using oral bisphosphonates in the prevention and treatment of osteoporosis to a prevalence of 10% of patients on long-term, frequent (more than once annually), potent, and intravenous agents such as Zometa, used for the treatment of malignancy, for example multiple myeloma.

The duration of bisphosphonate therapy and, to lesser extent, the route of administration (intravenous injection [ivi] versus oral) are also important risk factors. One major study identified that the mean time to the onset of BRONJ among patients with metastatic malignancy receiving the most potent bisphosphonate Zometa (zoledronic acid) intravenously was as little as 18 months, compared with 36 months (3 years) for the moderately potent bisphosphonate Aredia (pamidronate).

The most frequent initiating event for BRONJ is any form of trauma to jaw bones, e.g. a recent history of dental extraction and/or surgery to the jaws. Importantly, the presence of dental infection and/or abscesses, and the use of limited forms of surgical intervention to treat such infections, such as periodontal (scaling and cleaning) treatment and endodontic (root canal) therapy have also been clearly implicated as a cause of BRONJ. Ill-fitting prosthetic devices (dentures) have also been associated with initiating BRONJ. So-called “spontaneous” cases of BRONJ have also been reported, with apparently no recent history of trauma of any form, to the jaws or teeth.

In regards to therapeutic indications, use of bisphosphonate agents for treatment and prophylaxis of bony complications associated with solid malignancies (predominantly breast cancer) and multiple myeloma is a highly significant risk factor relative to the use of these agents for osteoporosis (17:1). This may reflect the fact that the more potent, third-generation nitrogen-containing bisphosphonates are more frequently used for the management of malignancy-related skeletal complications, than are used for osteoporosis. However, use of ancillary agents such as corticosteroids, and thalidomide (specifically in myeloma) may also increase the risk of BRONJ, but this has not yet been proven.

In terms of epidemiology, women were more affected than men, by a ratio of 6:4 and the mandible was a more common site than the maxilla (7:3). These findings were not unexpected. More women than men use bisphosphonates. The finding

of greater prevalence of involvement of the mandible may yet prove to be of some biological significance in regards to our understanding of the aetiology of BRONJ, given the relative avascularity of the mandible relative to the maxillae.

Critically, analysis of the evidence of aetiopathogenesis of BRONJ, suggests that strategies can be developed to significantly lower the risk of patients developing BRONJ. These strategies are based on our knowledge that type and duration of bisphosphonate therapy influences the risk for BRONJ, and that aggressive anti-microbial prophylaxis and treatment for patients who require dental/oral surgery, may also be useful in lowering the risk of BRONJ.

Prevention is still the best option. Ideally, excellent levels of oral hygiene should be maintained so that dental extractions and surgery can be avoided. All members of the health team, including doctors, pharmacists and oral health practitioners should encourage their patients, who have recently commenced, or, are about to commence bisphosphonate therapy to have, as a minimum, an assessment of their dental fitness, preferably with definitive treatment of all teeth with a poor prognosis and a preventive care plan put in place.

3.3 BRONJ: Aetiology and Pathogenesis

Bisphosphonates are effective because they are analogues of pyrophosphate, a naturally occurring inhibitor of bone metabolism. The double phosphonate groups on the carbon atom (see Figure 1) enable the bisphosphonates to bind specifically to calcified bone matrix just like the double phosphate groups on the oxygen atom of pyrophosphate, but unlike the natural analogue, the P-C-P bond is completely resistant to enzymatic hydrolysis. The type of side-chain, off the central carbon atom, in the R2 position determines the potency of the bisphosphonate agent. Nitrogen containing side-chains induces significant therapeutic potency.

Figure 1 Bisphosphonates – Chemical Structure

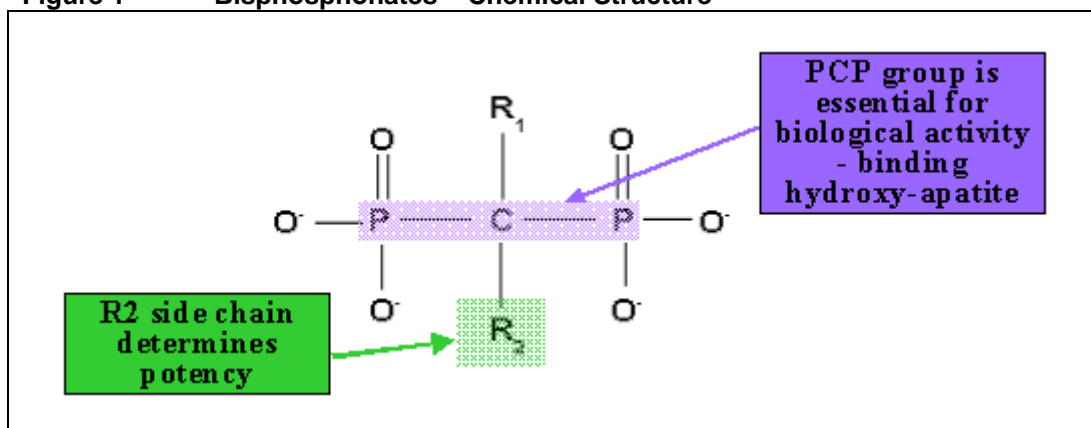

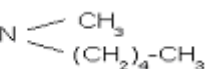
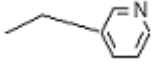
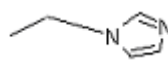


Table 2 Bisphosphonates – Potency and Side Chains

Name	Generic Name	Potency	R2-Side Chain
Non-nitrogen Containing			
Didronel	Etidronate	1	-CH ₃
Bonefos	Clodronate	10	-Cl
Skelid	Tiludronate	10	-S- 
Nitrogenous (N-containing) Bisphosphonates			
APD, Aredia	Pamidronate	100	-CH ₂ -CH ₂ -NH ₂
Fosamax	Alendronate	500	$\overline{-(CH_2)_5-NH_2}$
Boniva	Ibandronate	1,000	-CH ₂ -CH ₂ N 
Actonel	Risendronate	2,000	
Zometa	Zolendronate	10,000	

Bone is actively turned over and remodelled by the “bone multicellular units” (BMU) - comprising osteoclasts and osteoblasts - which require a rich blood supply (vessels lined by endothelial cells) due to the intense metabolic and energy requirements of these cells. Micro-damage and micro-fractures of both the maxilla and mandible, from the forces generated during mastication, are thought to occur daily and are then repaired by the BMU. Such bone repair and remodelling is increased greatly if infection is present, or following the trauma associated with an extraction.

Bisphosphonates are potent inhibitors of osteoclastic activity, and can induce osteoclast cell death by apoptosis, thereby significantly inhibiting bone resorption with the net result of impairment, even possibly, complete cessation, of normal, physiological bone remodelling and turnover. Further, the more potent bisphosphonates, such as Zometa, are also thought to have anti-angiogenic activity (hence its value in preventing metastases). Therefore, BRONJ is thought to occur due a complex interplay of overlapping, synergistic adverse affects of the bisphosphonates, causing a generalised impairment of bone metabolism, to which the jawbones are particularly sensitive; the presence of local infection and/or trauma; and hypo-vascularity. The net result is that the jawbone is unable to meet the “peak demand” for bone repair and remodelling, subsequent to trauma from extraction of a tooth, or teeth, or more extensive oral surgery. This lack of healing presents as (osteo)necrosis, ie. death of localised living cells and tissue, in an otherwise viable organism.

Jaws are also uniquely different from other bones. Their relative vascularity and high degree of bone turn-over (activity) may result in a greater uptake of bisphosphonate agents than other bones. The presence of oral bacterial flora “contamination” (infection) occurs frequently via periodontal disease, periapical abscesses, trauma to the fragile thin mucosa, and with extractions. The fragility of the mucosal barrier is demonstrated in cases of lingual mandibular sequestration with ulceration resembling mild cases of BRONJ.

The American Association of Oral and Maxillofacial Surgeons position paper provides the following staging system for the stratification of patients with, or at risk of BRONJ.

- **At risk category:** No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates
- **Stage 0:** No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms.
- **Stage 1:** Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection.
- **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.
- **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 or sinus floor.

3.4 BRONJ: Risk Factors

Risk factors for BRONJ can be grouped into:

1. drug-related
2. local risk factors
3. demographic/systemic factors

3.4.1 Drug-Related Risk Factors

- a) Potency of the Bisphosphonate (Table 2)
- b) IV Route of Administration results in a greater drug exposure than the oral route
- c) Duration of Therapy (cumulative dose)

3.4.2 Local Risk Factors

- a) Dentoalveolar Surgery (extent/degree of trauma)
 - i) Extractions
 - ii) dental implant placement
 - iii) periapical surgery
 - iv) periodontal surgery involving osseous injury

Patients receiving intravenous bisphosphonates and having dento-alveolar surgery are seven times more likely to develop BRONJ than those patients who do not have such surgery. However, caution must be applied in assessing this relationship, given that the presence of a dental infection or abscess is a frequent indication for surgery/extraction.

- b) Local Anatomy
 - i) Mandible
 - lingual tori
 - mylohyoid ridge
 - ii) Maxilla
 - palatal tori

BRONJ is more common in the mandible than in the maxilla (2:1 ratio) and more common in areas with thin mucosa overlying bony prominences such as tori, bony exostoses and the mylohyoid ridge

- c) Concomitant Oral Disease

Patients with a history of inflammatory (possibly infective) dental disease, e.g., periodontal and dental abscesses are at a seven times greater risk for developing BRONJ.

3.4.3 Demographic and Systemic Factors

- a) Age
 - i) With each passing decade - there is a 9% increased risk for BRONJ in multiple myeloma patients treated with IV bisphosphonates.
- b) Cancer Type
 - i) Multiple Myeloma>> breast cancer > other cancers
 - ii) Osteopaenia/osteoporosis concurrent with cancer
- c) Concomitant Risk Factors
 - i) Corticosteroid therapy
 - ii) Diabetes
 - iii) Smoking
 - iv) Alcohol use
 - v) Poor oral hygiene
 - vi) Chemotherapeutic drugs

4 Guidelines for Oral Health Care

4.1 Prevention of BRONJ

Given the potential risk of BRONJ, the same preventive measures that are important in the maintenance of good oral health in the general population are vitally important for patients on bisphosphonate therapies. Maintaining good oral hygiene through regular brushing, and limiting or ceasing oral health risk behaviours such as smoking and drug and alcohol use, and having regular dental examinations will help reduce the need for invasive dental procedures.

Ideally, where clinically appropriate, a patient will have a full dental examination and complete any required dental treatment so that they are fully dentally fit prior to commencing bisphosphonate therapy (See also Section 4.1.2).

Prevention of BRONJ is still not completely understood, given there are as yet no extensive, or evidence-based published guidelines. Prevention is based on the following key principles:

- Identification (from the patients medical history) of at-risk patients
- Knowledge and recognition of the limited number, that is later generation, potent, nitrogen-containing, bisphosphonate agents associated with BRONJ
- Treatment planning for patients identified as being at-risk for BRONJ requires common sense approach, and flexibility to exploit preventive measures to reduce the opportunity for infections, and minimise the invasiveness of treatments proposed.
- Intervention for BRONJ is based on as yet unproven, but clinically derived understanding of the critical risk factors for aetiology and pathogenesis of BRONJ, namely the type, duration, and route of bisphosphonate administration; minimising wound exposure to bacteria at the time of tooth extraction/surgery; and gentle, atraumatic (as far as practical) surgical technique.

4.1.1 Identification of Patients at-risk for BRONJ

In order to identify patients who are at-risk of BRONJ, the clinician should undertake:

- a) A detailed medical history to identify past/present history of:
 - i) BRONJ
 - ii) Bisphosphonate therapy
 - iii) Osteoporosis, established by Bone Mineral Density scan, or history of fractures – spinal compression, hip or neck of femur.
 - iv) Previous sustained high-dose systemic corticosteroid therapy
 - v) Treatment for solid malignancy
 - vi) Multiple myeloma

- b) A comprehensive oral/dental examination, including, but not limited to, an assessment of:
 - i) Oral Hygiene
 - ii) Charting dental caries and periodontal disease
 - iii) Bitewings, periapical and orthopantomogram radiographs of any “suspect” teeth,
 - iv) Assessment of patients’ ability to maintain their dentition (interest/understanding, capacity - manual dexterity/financial considerations)

4.1.2 Treatment Planning for Patients at-risk for BRONJ

Ideal treatment planning for patients at-risk for BRONJ should involve:

- 1) Completion of all necessary dental treatment **before** the commencement of second and/or third generation bisphosphonates (Table 3)
- OR
- 2) Treatment occurring as soon as possible following commencement of bisphosphonates, ensuring that treatment is completed within the “window” period (Table 3) for the specific bisphosphonate agents. The window period applies from the commencement of the bisphosphonate therapy and is the time in which dental procedures, including extractions, may be undertaken with a **relatively lower risk** of BRONJ occurring. It must be noted that the risk is not completely removed, and that cases of BRONJ may still occur within the window periods.

In accordance with the relevant NSW Health Policy Directive, the consent process for all treatment requires that the patient must be informed, and understand, the risks associated with their treatment as part of the formal process of gaining informed consent (Refer to NSW Health PD2005_406: *Consent to Medical Treatment - Patient Information*)ⁱ.

ⁱ http://www.health.nsw.gov.au/policies/PD/2005/pdf/PD2005_406.pdf

Table 3 “Window Periods” for Specific Amino-Bisphosphonate Agents (agents that contain a nitrogen-containing R2 side-chain) in which invasive dental procedures can be undertaken with a lower risk of BRONJ occurring

Brand Name	Generic Name	Route of Administration	Indication	Window Period: Months from commencement of Bisphosphonate Therapy
Zometa	zoledronic acid	Intravenous	Malignancy-related skeletal events	6
Bondronat	ibandronate	Intravenous		9
Aredia Pamisol	disodium pamidronate	Intravenous		24
Bondronate	ibandronate	Oral		24
Didronel	disodium etidronate	Oral	Paget's Disease; heterotopic ossification with spinal cord injury; total hip replacement	36
Zometa	zoledronic acid	Intravenous	Osteoporosis (treatment/ prophylaxis)	Undefined ⁱⁱ
Aredia Pamisol	disodium pamidronate			
Actonel	risedronate	Oral		
Fosomax	alendronate			

To ensure these window periods are maintained, high risk patients should be given a Category A coding under the Priority Oral Health Program, and should be placed on a preventive program with regular review appointments every 4-6 months.

4.1.3 Risk Stratification and Protocol Recommendations

There are three risk categories, Minimal, Medium OR Significant, which will assist the clinician in determining if the use of the recommended protocol, using protracted antibiotic prophylaxis pre- and post treatment is indicated.

ⁱⁱ Currently there is insufficient evidence to suggest that, for these patient groups, the risks of developing BRONJ as a result of invasive dental procedures are lowered by undertaking these procedures within a defined time period from the commencement of bisphosphonate therapies. Normal clinical benchmark times are recommended in these cases.

Table 4 Main Criteria for Risk Assessment

Factor	Indicators
1. Patient Related Factors	<p><u>Amino-Bisphosphonate:</u></p> <ul style="list-style-type: none"> • potency of agent • route of administration • duration • indication <p><u>Co-Morbidities Known to increase risk of potentially adverse surgery and/or healing outcomes:</u></p> <ul style="list-style-type: none"> • age • immuno-suppression
2. Procedural (Surgical) Factors	<ul style="list-style-type: none"> • one or more surgical sites • contiguous teeth or multiple separate sites • extent of surgery • mandibular posterior (molar) teeth • proximity of tori

If in doubt, or if referral to an appropriate specialist is required please contact one of the following: specialist oral medicine practitioner, oral surgeon, oro-maxillo-facial surgeon, or special needs dentist.

Table 5 Risk Stratification Definitions

Lower Risk Patient	Lower Risk Procedure
<ul style="list-style-type: none"> • Amino-Bisphosphonate Treatment for Osteoporosis <ul style="list-style-type: none"> - Fosamax (alendronate) - any intravenous agent administered only once yearly (or less). Eg. Zometa (zoledronic acid) - any Bisphosphonate agent within designated window period (see Table 3) 	<ul style="list-style-type: none"> • Routine Office Surgery <ul style="list-style-type: none"> – routine dental extraction, done under local anaesthetic (LA) in the dental chair (up to 3 contiguous teeth or 4 separate sites)

Higher Risk Patient	Higher Risk Procedure
<ul style="list-style-type: none"> • Patient on long-term bisphosphonate therapy beyond designated window periods (see Table 3) • Bisphosphonate therapy related to malignancy <ul style="list-style-type: none"> - solid cancer metastases (Breast Cancer) - Multiple Myeloma • Aged Patients <ul style="list-style-type: none"> - 70 years of age or older • Immuno-Suppression <ul style="list-style-type: none"> - recent (within 2 weeks) administration of cytotoxic chemotherapy (with resultant leucopenia) • Current or previous use of high-dose systemic corticosteroid administrationⁱⁱⁱ 	<ul style="list-style-type: none"> • Extensive oral surgery or number of dental extractions <ul style="list-style-type: none"> - 5 teeth or more - a dental quadrant • Surgical extraction of mandibular molar teeth, with risk of impinging lingual cortical plate/mylohyoid ridge • Surgery with risk of impinging of maxillary or mandibular tori

Table 6 Risk Stratification Assessment

Risk of BRONJ	Patient-Related Risk Factors	+	Surgical Procedure Risk Factors
MINIMAL	Lower Risk Patient	+	Lower Risk Procedure
MEDIUM	Lower Risk Patient	+	Higher Risk Procedure
	Higher Risk Patient	+	Lower Risk Procedure
SIGNIFICANT	Higher Risk Patient	+	Higher Risk Procedure

Table 7 Risk Stratification Categories and Protocol Recommendation

Risk Stratification Group	Referral Recommendation
MINIMAL	<ul style="list-style-type: none"> • No special precautions indicated. • Use of recommended protocol, using protracted antibiotic prophylaxis pre- and post treatment NOT indicated. • Proceed with all routine non-invasive dental care, and any routine dental extractions or oral surgery (if so indicated).
MEDIUM	<ul style="list-style-type: none"> • Consider use of protocol involving protracted antibiotic prophylaxis pre-and post procedure. • Consult with immediate (local) senior clinician or contact appropriate specialist.
SIGNIFICANT	<ul style="list-style-type: none"> • Use of protocol, involving protracted antibiotic prophylaxis pre-and post procedure RECOMMENDED

ⁱⁱⁱ High dose systemic corticosteroid therapy can be defined as: long term (at least 3 months), high dose (at least 7.5mg per day prednisolone or equivalent) corticosteroid therapy.

4.1.4 Suggested Preventive Regimes for Dental Procedures

Use of Antibiotics: General Principles

The use of an antibiotic regimen to lessen the risk of BRONJ from occurring in patients at high-risk for BRONJ is controversial, and expert opinion is divided on the appropriateness of this approach. While not well defined, bacterial infection is noted in the existing literature as having some role in the aetio-pathogenesis of BRONJ, so the use of antibiotic prophylaxis does seem logical.

It must be noted that:

- All antibiotic therapy is the responsibility of the prescriber. It is important that a prescribing clinician consider **all** the relevant clinical information and prescribe in the best interests of their patient including providing information about the risks and benefits of the proposed therapy.
- The treating clinician, in consultation with the patient, has the responsibility to determine the most appropriate treatment regime to be followed based on their clinical assessment of the risk to the patient. This includes monitoring for any adverse events related to antibiotic use and responding appropriately.
- It is recommended that antibiotic therapies should be streamlined once cultures and sensitivities are obtained.

Use of Clindamycin

The use of systemic antibiotics, to lessen local bacterial contamination and infection, associated with any form of surgery, which must include dental extraction, is a long-standing surgical practice, although there is conflicting evidence supporting this practice. The choice of clindamycin is based on its well-known properties. Both aerobic and anaerobic bacteria are susceptible to clindamycin, an ideal property given the mixed bacterial flora that inhabits the mouth. Clindamycin has had long-standing role as a first line agent in penicillin-allergic patients to treat oro-dental infections and abscesses, and as one of the prophylactic agents of choice for patients requiring invasive dental procedures who are at-risk of infective endocarditis. In addition, clindamycin has the added advantage of good uptake and penetration of bone, an important quality, given its use to lessen the risk of BRONJ.

There are concerns about the risk associated with the use of clindamycin. Of course, it is a general principle that all drugs, particularly antibiotics, have the potential to cause mild to serious adverse effects and induce allergy. The well documented concern with clindamycin is that its use has been associated with development of clostridium difficile colitis. Most antibiotics, including the penicillins have this potential. The reports linking clindamycin with Clostridium Difficile colitis were principally in patients who had been taking protracted intravenous clindamycin therapy for six weeks or more. Allergy to clindamycin is exceptionally rare.

Suggested Regimes for Minimising the Risk of BRONJ

Table 8 Regimen for Minimising the Risk of BRONJ

Pre-Operative Regimen – starting 5 days pre-operatively (Day 1-5)			
Clindamycin	<ul style="list-style-type: none"> • 300 mg stat, then • 300 mg, by mouth, 4x daily 	Chlorhexidine Mouthwash (ideally 0.12% aqueous)	<ul style="list-style-type: none"> • 10-15 ml swish up to 3 minutes and then spit out well (after meals) 4x daily
Peri-Operative Protocol (Day 5) <ul style="list-style-type: none"> • minimise local anaesthetic <ul style="list-style-type: none"> ▪ (regional blocks (if possible) rather than local infiltration, use lower concentrations of vaso-constrictor) • atraumatic technique • encourage bleeding (from socket - if possible) • primary closure <ul style="list-style-type: none"> ▪ (reduce/trim (gently) alveolar bone to ensure closure) 			
Post-Operative Regimen – starting Day 5 (Days 5-11)			
Clindamycin	<ul style="list-style-type: none"> • 300 mg stat, then • 300 mg, by mouth, 4x daily 	Chlorhexidine Mouthwash (ideally 0.12% aqueous)	<ul style="list-style-type: none"> • 10-15 ml swish up to 3 minutes and then spit out well (after meals) 4x daily

Alternate Antibiotic Regimes to Clindamycin-Containing Regimens

**Table 9 Antibiotic Regimens as an Alternate to Clindamycin-Containing Regimens
(amoxicillin/metronidazole combination)**

(amoxicillin/metronidazole combination)

Pre-Operative Regimen – starting 7 days pre-operatively (Day 1-7)			
Indications: 1. Known allergy/hypersensitivity to clindamycin 2. Patient known to have previous clindamycin-related (<i>Clostridium Difficile</i>) diarrhoea			
amoxicillin	<ul style="list-style-type: none">• 500 mg stat, then• 500 mg, by mouth, 3x daily	Chlorhexidine Mouthwash (ideally 0.12% aqueous)	<ul style="list-style-type: none">• 10-15 ml swish up to 3 minutes and then spit out well (after meals) 4x daily
metronidazole	<ul style="list-style-type: none">• 400 mg stat then• 400 mg 3x daily		
Peri-Operative Protocol (Day 7) <ul style="list-style-type: none">• Minimise local anaesthetic<ul style="list-style-type: none">▪ Regional blocks (if possible) rather than local infiltration, use lower concentrations of vaso-constrictor• Atraumatic technique• Encourage bleeding (from socket if possible)• Primary closure<ul style="list-style-type: none">▪ Reduce/trim (gently) alveolar bone to ensure closure			
Post-Operative Regimen – starting Day 7 (Days 7-14)			
amoxicillin	<ul style="list-style-type: none">• 500 mg stat, Then• 500 mg, by mouth, 3x daily	Chlorhexidine Mouthwash (ideally 0.12% aqueous)	<ul style="list-style-type: none">• 10-15 ml swish up to 3 minutes and then spit out well (after meals) 4x daily
metronidazole	<ul style="list-style-type: none">• 400 mg stat Then• 400 mg 3x daily		

Table 10 Antibiotic Regimens as an Alternate to Clindamycin and Penicillin-Containing Regimens (roxithromycin/metronidazole combination)

Pre-Operative Regimen – starting 5 days pre-operatively (Day 1-5)			
Indications: 1. Known allergy/hypersensitivity to clindamycin AND penicillins (amoxicillin) 2. Patient known to have previous clindamycin-related (<i>Clostridium Difficile</i>) diarrhoea			
Rulide (roxithromycin)^{iv}	300 mg stat, then 300 mg, by mouth, 2x daily	Chlorhexidine Mouthwash (ideally 0.12% aqueous)	10-15 ml swish up to 3 minutes and then spit out well (after meals) 4x daily
metronidazole	400 mg stat then 400 mg 3x daily		
Peri-Operative Protocol (Day 5) <ul style="list-style-type: none">Minimise local anaesthetic<ul style="list-style-type: none">Regional blocks (if possible) rather than local infiltration, use lower concentrations of vaso-constrictorAtraumatic techniqueEncourage bleeding (from socket if possible)Primary closure<ul style="list-style-type: none">Reduce/trim (gently) alveolar bone to ensure closure			
Post-Operative Regimen – starting Day 5 (Days 5-10)			
Rulide (roxithromycin)	<ul style="list-style-type: none">300 mg statThen 300 mg, by mouth, 2x daily	Chlorhexidine Mouthwash (ideally 0.12% aqueous)	<ul style="list-style-type: none">10-15 ml swish up to 3 minutes and then spit out well (after meals) 4x daily
metronidazole	<ul style="list-style-type: none">400 mg statThen 400 mg 3X daily		

^{iv} Rulide (roxithromycin) is a semisynthetic macrolide antibiotic, of the same class and characteristics as erythromycin, but a later generation, superior in activity to erythromycin and is much less likely to cause gastro-intestinal upset

4.1.5 Post Operative Review

It is recommended that patients at risk of developing BRONJ should be reviewed post operatively at the following intervals:

- 1 week
- 1 month
- 3 months
- 6 months
- 12 months

Thereafter, high risk patients should be placed on a 4-6 month preventive recall program.

4.2 Treatment of Established BRONJ

BRONJ has proven highly refractory to the traditional approaches, namely extensive surgery with or without hyperbaric oxygen therapy, which are proven to be successful in the treatment of osteomyelitis and radiation-related osteonecrosis (radio-osteonecrosis).

The published experience is that conservative measures are best, including;

- avoidance of any further or extensive surgery;
- if necessary, gentle debridement, of any sequestra;
- use of anti-microbial mouthwashes (such as chlorhexidine), and;
- antibiotic therapy when/where active infection is clinically evident.

Table 11 Patients with Established BRONJ Needing Subsequent Extractions/Oral Surgery

Extraction/ Oral Surgery AND Previous BRONJ	Avoid Invasive Procedures	<p>Alternative Treatment/s For teeth with irreversible pulpitis: Endodontic (root canal) dressing, and if indicated de-coronation of the crown</p> <p>For teeth with advanced periodontal disease: Scaling and cleaning of the affected teeth, with post-operative chlorhexidine mouthwashes for 1 week</p> <p>Referral to Oral Surgeon/Specialist Centres (Westmead/SDH)</p>
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In consultation with the treating medical practitioner, consideration might also be given to altering the patient's bisphosphonate regime, such as switching from a nitrogen containing to a non-nitrogen containing bisphosphonate or discontinuation of bisphosphonates.

4.3 Dental Implant Placement

As yet there is no evidence that implant placement is contraindicated in patients taking or having taken amino-bisphosphonate agents.

The risk of BRONJ with implant placement has to be balanced against the potential benefit to the patient. The patient and other health professionals involved in the patient care should be so advised (preferably in writing) and consulted.

Immediate placement of implants into the sockets of extracted teeth is not recommended. This is particularly relevant when teeth are extracted because of recent or current infection or in the presence of an abscess.

The patient related risk factors would still apply as stated in Table 5, and the risk stratification, of Minimal, Medium and Significant then so calculated.

The implant placement procedures may be classified as minimal but clinicians must be aware of the increased risk of BRONJ in cases where implant placement in the posterior mandible may impinge on the lingual cortical plate or tori.

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