Clinical Guideline 15 - Version 6

Valid to: December 2020

dental health services victoria
oral health for better health

Management of Dental Patients on Anti-resorptive Drugs (Bisphosphonates and Monoclonal Antibodies to RANK-Ligand)

Purpose

This guideline guides management of patients taking anti-resorptive drugs requiring oral treatment at the Royal Dental Hospital of Melbourne and all public dental agencies in Victoria.

Evidence-based clinical guidelines are intended to provide guidance, and are not a standard of care, requirement, or regulation. However, the application of clinical guidelines in publicly-provided oral health services allows for consistency to occur across large patients cohorts with a variety of oral health clinicians. Reasons for discrepancy should be noted down in patient's dental records.

The aim of the current guideline is to inform on:

- the potential risk of osteonecrosis of the jaws (ONJ) following dental procedures in patients who are currently prescribed anti-resorptive drugs for the management of both malignant and benign bone disease;
- current drugs, risk factors and incidence;
- Prevention, diagnosis and management of medication related ONJ.

Guideline

I. Introduction

Anti-resorptive drugs are a class of drugs that reduce bone resorption by inhibiting osteoclastic activity. They are widely used in the management of:

- Osteoporosis
- Paget's disease
- Skeletal malignancy – to prevent hypercalcemia and reduce bone loss
- Osteogenesis imperfecta

Ia. Common Anti-resorptive Drugs

Drug name	Trade name	Primary Indication	Class	Mode
Alendronic acid	Fosamax, Dronelan	Osteoporosis	BP*	Oral
Risedronate sodium	Actonel	Osteoporosis Paget's disease	BP	Oral
Zoledronic acid	Aclasta, Zometa	Paget's disease Skeletal events associated with bone metastases hypercalcaemia	BP	IV*
Etidronate disodium	Didrocal	Osteoporosis Paget's disease	BP	Oral
Denosumab	Prolia	Osteoporosis	MA*	SQ*
Tiludronic acid	Skelid	Paget's disease	BP	Oral
Pamidronate disodium	Aredia	Paget's disease Bone pain	BP	IV

		Skeletal events associated with bone metastases hypercalcaemia		
Sodium clodronate	Bonefos	Bone pain Skeletal events associated with bone metastases hypercalcaemia	BP	Oral

*BP – Bisphosphonate; MA – Monoclonal Antibodies to RANK- Ligand; SQ – Subcutaneous; IV – Intravenous

Ib. Mechanism of Action of Anti-resorptive Drugs

Anti-resorptive drugs can be administered orally, subcutaneously (SQ) or intravenously (IV). They are either deposited in bone at sites of active bone resorption in proximity to osteoclasts (bisphosphonates) or attach to the RANK receptor on osteoclasts (monoclonal antibodies to RANK-ligand). They both inhibit the action of osteoclasts to reduce bone remodelling, so that the resorption of bone is reduced with infilling of the remodelling space with more highly mineralised bone. In this way, bone mineral density is increased, but no new bone is formed. Due to strong binding to bone, bisphosphonates can be retained in the skeleton for up to 10 years. Hence their effects on bone are long-term. On the other hand, the half-life of denosumab in bone is six months, and its effects are completely reversible after this time.

In the jaws and at some other sites, bone is located close to the surface and the soft tissue envelope around bone is thin, so there is danger of bone becoming exposed to the external environment through micro-trauma induced by mastication, normal physiological function or through invasive dental treatment. This exposed area of bone is then at risk of being colonized by oral micro-flora. Until recently, complications such as osteonecrosis have only been reported in the oral cavity. This is called Medication Related Osteonecrosis of the Jaws (MRONJ). As well as being associated with anti-resorptive drugs, MRONJ may also occur with anti-angiogenic drugs used to treat cancer.

II. MRONJ

IIa. Definition

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

- exposure of the bone of the maxillofacial region including exposed bone that does not heal within 8 weeks;
- administration of or with history of administration of anti-resorptive drugs for bone disease or anti-angiogenic drugs for cancer;
- no history of radiation therapy to the jaw.

IIb. Signs and symptoms

- Asymptomatic
- Pain
- Swelling of soft tissues
- Infection
- Irritation
- Non-healing extraction socket
- Exposed alveolar bone, with progression to sequestrum formation associated with localized swelling and purulent discharge

- Numbness or paraesthesia

IIc. Risk Factors for MRONJ

Local Risk Factors

- Poor oral hygiene
- Oral infection – periapical and periodontal[1]
- Dental extractions
- Bone manipulation
- Trauma from ill-fitting dentures
- Anatomical site (mandible higher risk than maxilla)
- Extent of dental surgery (more extensive wounds with higher risk)
- History of MRONJ

Systemic Risk Factors

- Tobacco smoking
- Comorbidities - Diabetes, Cancer
- Immunocompromised
- Age over 65 years old
- Glucocorticoids e.g. Prednisolone, dexamethasone
- Anti-angiogenic drugs e.g. Sirolimus

Anti-resorptive Drug-related Risk Factors

- High dosage
- High potency
- Long period of therapy
- IV versus oral administration
- Half-life of drug

III. Incidence

According to current literature, incidence of MRONJ is as follows:

Osteoporosis patients on low dose anti-resorptive drugs is very low, ranging from 3.46%[2] to less than 0.001%[3].

Oncology patients on high dose and high potency anti-resorptive drugs is much higher, ranging between 1 - 15%[4].

However, MRONJ can occur at any stage with any amount of exposure. Some reports suggest that problems can arise with drug usage of less than a year especially in the IV group.

For patients on anti-resorptive drugs for osteoporosis, the average onset of MRONJ is around 4 years[5]

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[1] Tsao, et al 2013
[2] Borromeo, et al 2014
[3] Khan, et al 2017
[4] Khan, et al 2017
[5] Ruggiero, et al 2014
Due to ongoing research on the incidence of MRONJ, these statistics may change over time

IV. Prevention of MRONJ and Treatment Planning

1. Prevention

Prevention is critical as MRONJ is unresponsive to conservative curettage, antibiotic therapy or hyperbaric oxygen therapy. Hence, it is difficult to manage MRONJ.

Prior to anti-resorptive therapy, a full dental assessment with necessary treatment should be completed.

2a. Treatment Planning Before Anti-resorptive Drug Usage

- Maintain good oral hygiene. Studies have shown good oral hygiene has a marked effect in reducing MRONJ incidence.
- Perform all conservative, periodontal and endodontic treatment required.
- Extract teeth of poor prognosis.
- Inspect and adjust removable prostheses to prevent potential soft tissue injury.

The incidence of MRONJ is low within the first 6 months of anti-resorptive therapy. Patients who have just started the therapy should also have a full dental assessment with necessary treatment carried out prophylactically.

2b. Treatment Planning After Anti-resorptive Drug Usage

- Maintain good oral hygiene. Studies have shown that good oral hygiene has a marked effect in reducing MRONJ incidence.
- Routine restorative dentistry should avoid soft tissue injury.
  Perform routine scaling but avoid soft tissue injury.
- Inspect and adjust removable prostheses to prevent potential soft tissue injury.
- Endodontics is preferable to extraction. Coronectomy with root canal therapy may be an option.

V. Surgical Protocol During Anti-resorptive Drug Usage (Also see summary flow chart below)

When dental extraction or surgical intervention is unavoidable, assess the above risk factor in section IIc, together with:

- Degree of difficulty of extraction or surgery.

- Periodontally involved mobile teeth have little bone support which makes the extraction simple. However, a few studies have shown higher risk of MRONJ in periodontally involved teeth that could be due to pre-existing infection or increased remodelling of bone.[6] Hence, consideration needs to be given to antibiotic prophylaxis for extraction of mobile teeth.

- Presence of oral infection is another risk factor for MRONJ. Soft tissue abscess or sinus tract, radiographic evidence of periapical pathology indicates significant bacterial contamination of the surrounding alveolar bone. Hence, consideration needs to be given to antibiotic prophylaxis for extraction of teeth with chronic infection.

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[6] Tsao, et al 2013

- However, the value of antibiotic prophylaxis is controversial in practice and in the literature. A recent Cochrane review states one study provided low-quality evidence that 'antibiotics before dental extractions and the use of techniques for wound closure that avoid exposure and contamination of bone' are more effective for reducing the number of cases with MRONJ[7].

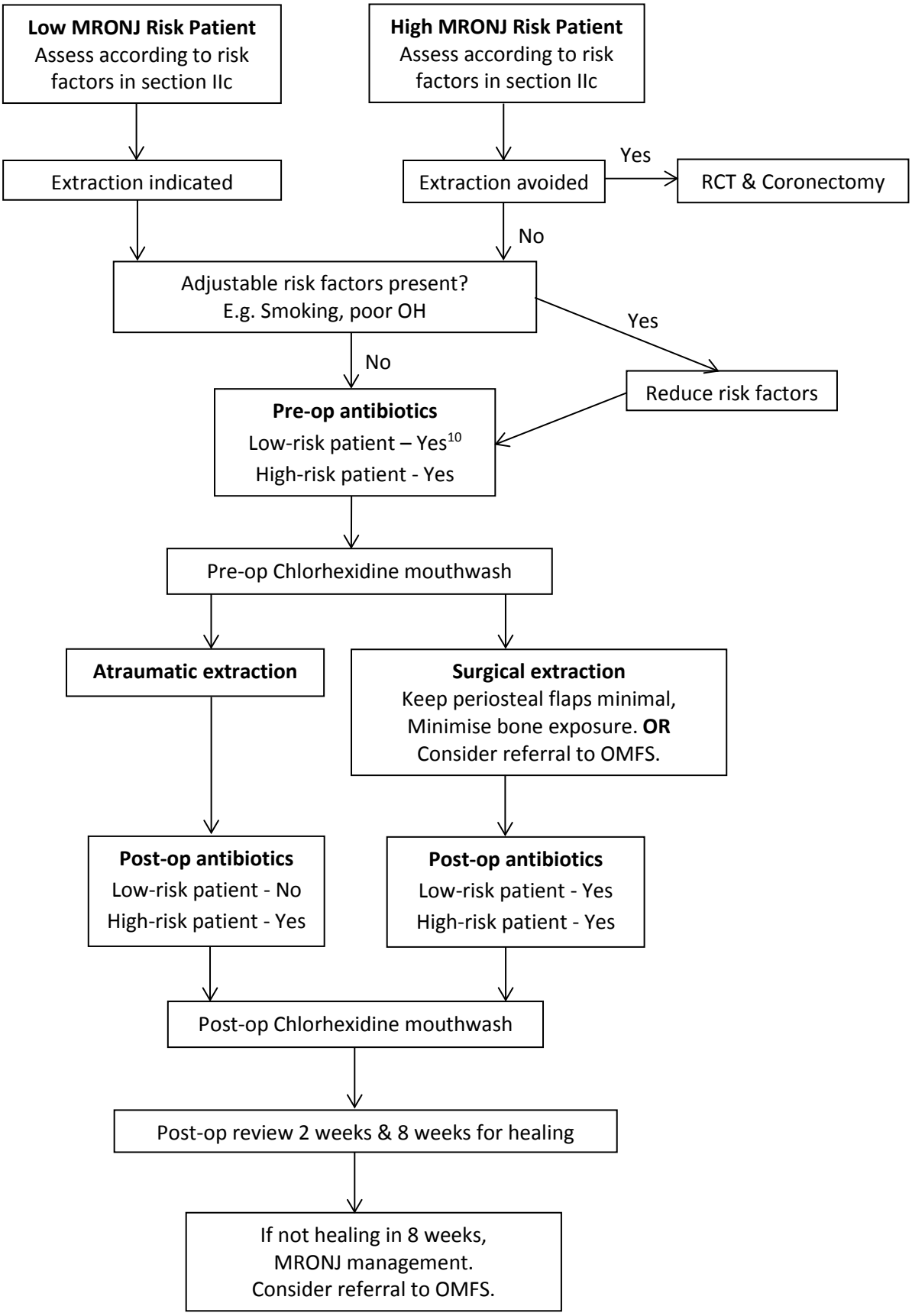
- According to a combined position paper[8], if the patient has high risk of MRONJ, consideration should be given to antibiotic prophylaxis (Amoxycillin 2g every 1 hour prior procedure; Or Clindamycin 600mg 1 hour prior procedure) for dental extraction or surgery.

- Consideration should also be given for post-operative course of antibiotics (Amoxycillin 500mg every 8 hourly for 5 days; Or Clindamycin 300mg every 8 hourly for 5 days) for high-risk patients[9].

- If multiple extractions are required, commence with symptomatic tooth first. Asymptomatic teeth with periapical radiolucencies should also be treated as pre-existing inflammatory dental disease is a risk factor for MRONJ[10].

- Extract single tooth at a time. Review at 2 weeks and 8 weeks for healing. After which proceed with next extraction. Do not create a new exposed bone area until the previous socket is healed.

[7] Beth-Tasdogan NH, et al 2017
[8] Sambrook, et al 2006
[9] Bermúdez-Bejarano, et al 2017
[10] Tsao, et al 2013



[10] Beth-Tasdogan NH, et al 2017

VI. CTX Testing

CTX testing is not indicated. Although CTX is used in clinical practice, it does not predict the clinical risk of MRONJ and hence is not recommended.

CTX levels also follow a circadian rhythm and are reduced by meals.

CTX testing should therefore never be used in isolation to make a decision about whether or not to extract a tooth. If a tooth needs to be extracted, CTX testing will not be helpful.

Consideration of the patient's overall risk factor based on comorbidities, health status and oral and periodontal health is essential, and needs to be documented, together with discussion about consent.

CTX testing does not replace adequate preparation of the patient prior to elective (non-emergency) procedure.

VII. Drug Holidays

There is no convincing evidence that taking patients off anti-resorptive drug therapy 3 months before and after any dental procedure will reduce the risk of osteonecrosis, particularly because of the long half-life of bisphosphonates in bone ranging from 3 months to more than 10 years. The offset of action of denosumab on bone is also more than 6 months. It is therefore extremely hard to evaluate any benefit of this approach.

Drug holiday is an option to consider however in high risk and elective (non-emergency) situations, but **only** after discussion with the patient's medical practitioner. It is the recommendation of this guideline that **dental clinicians must not advise patients to cease their anti-resorptive therapy.**

VIII. Consent

Patients on anti-resorptive drugs have varying degree of risk to MRONJ. The most common patients on these medications are those with osteoporosis. The risk of MRONJ in this group is relatively small. However, the morbidity can be serious and debilitating.

Therefore, informed consent must be obtained before any surgical procedure. Explanation of the risk and the morbidity involved with MRONJ must be given so the patient understands and provides an informed consent verbally and / or on a written form. Informed consent is not just signing a consent form.

IX. Management of patients with MRONJ

- Maintain optimal oral hygiene. Studies have shown that poor oral hygiene causes bacterial accumulation which impedes healing.
- Recommend regular mouth rinses e.g. warm salt water or alcohol free chlorhexidine 0.05% mouthwash.
- Areas of exposed bone can be gently brushed with a small soft toothbrush soaked in 0.05% chlorhexidine twice daily.
- Undertake minimal bony debridement, only to remove sharp bone but no attempt to remove exposed bone at the margins of the necrosis.
- Tweezers may be used to gently remove mobile sequestra. Rongeurs may be used to smooth gently at sharp immobile projections.
- Provide normal restorative treatment.
- Prescribe intermittent antibiotic treatment in cases of clinical exacerbation of infection. (Amoxycillin 500mg every 8 hourly for 5 days. Or Clindamycin 300mg every 8 hourly for 5 days.)

- Consult with or refer to Oral Surgery Specialists if unchanging. 40-50% of Stage I and Stage II MRONJ resolve over 3-6months without debridement. Refer to Appendix 1 for staging

Definitions

MRONJ – Medication Related Osteonecrosis of the Jaws
ONJ - Osteonecrosis of the Jaws
BP – Bisphosphonate
MA – Monoclonal Antibodies to RANK- Ligand
SQ – Subcutaneous
IV – Intravenous
CTX - C-terminal telopeptide

Revision Date	Policy Owner
December 2020	Clinical Leadership in Practice Committee

Approved by	Date Approved
Chief Oral Health Advisor	December 2017

Appendix 1

STAGING OF MRONJ

Stage 0
- No clinical evidence of necrotic bone,
- non-specific findings, signs and symptoms

Stage 1
- Exposed/necrotic bone
- Asymptomatic, no sign of infection

Stage 2
- Exposed/necrotic bone
- associated with infection (pain/erythema +/- suppuration)

Stage 3
- Exposed/necrotic bone, + one or more of the following …pathologic fracture, extra oral fistula, osteolysis extending to inferior border
- Infection/pain not manageable by antibiotics due to amount of necrotic bone

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