Pacific Guide for Prevention & Management of Medication-Related Osteonecrosis of the Jaw (MRONJ)
Pacific Guide for Prevention & Management of Medication Related Osteonecrosis of the Jaw

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Part I - Introduction

What is Medication-Related Osteonecrosis of the Jaw?

Medication-related osteonecrosis of the jaw (MRONJ) is defined as “a severe adverse drug reaction, consisting of progressive bone destruction [or necrosis] in the maxillofacial region of patients” as a result of obstructive blood supply. While it is a rare complication, with an incidence rate of 1-10% in those with IV bisphosphonate use, 0.001% in those with oral bisphosphonate use, and 0.2% in cancer patients with antiangiogenic use, the results of this complication are devastating. Osteonecrosis in these cases can be a result of two major classes of drugs: antiresorptive agents and antiangiogenic agents. On the next page, please find a table of commonly prescribed drugs in these categories that every dental practitioner should be familiar with.

MRONJ Definition & Classification

According to the AAOMS, MRONJ Diagnosis must have the following characteristics:

1. Current or previous treatment with antiresorptive or antiangiogenic agents;
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial regions that has persisted for more than eight weeks; AND
3. No history of radiation therapy to the jaw or obvious metastatic disease to the jaws.

Once diagnosed, MRONJ is further classified into a staging system: (AAOMS, 2014)
### Commonly Prescribed Medications Associated with MRONJ

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Route</th>
<th>Medical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax)</td>
<td>Bisphosphonate</td>
<td>Oral</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Monoclonal antibody</td>
<td>IV</td>
<td>Metastatic colorectal cancer, glioblastoma, metastatic renal cell carcinoma</td>
</tr>
<tr>
<td>Denosumab (Xgeva, Prolia)</td>
<td>RANKL Inhibitor</td>
<td>SQ</td>
<td>Bone metastases, osteoporosis</td>
</tr>
<tr>
<td>Ibandronate (Boniva)</td>
<td>Bisphosphonate</td>
<td>Oral or IV</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Neridronate (Nerixia)</td>
<td>Bisphosphonate</td>
<td>Oral</td>
<td>Osteogenesis imperfecta, Paget’s disease, bone metastases</td>
</tr>
<tr>
<td>Pamidronate (Aredia)</td>
<td>Bisphosphonate</td>
<td>IV</td>
<td>Bone metastases</td>
</tr>
<tr>
<td>Risedronate (Actonel)</td>
<td>Bisphosphonate</td>
<td>Oral</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Sirolimus (Rapamune)</td>
<td>Immunosuppressant</td>
<td>Oral</td>
<td>Organ rejection in renal transplants</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>Tyrosine kinase</td>
<td>Oral</td>
<td>Hepatocellular carcinoma, renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(chemotherapeutic</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>agent)</td>
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</tr>
<tr>
<td>Sunitrib (Sutent)</td>
<td>Tyrosine kinase</td>
<td>Oral</td>
<td>Gastrointestinal stromal tumor, renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>inhibitor</td>
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<td></td>
<td>agent)</td>
<td></td>
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</tr>
<tr>
<td>Tiludronate (skelid)</td>
<td>Bisphosphonate</td>
<td>Oral</td>
<td>Paget’s disease</td>
</tr>
<tr>
<td>Zoledronate (Zometa, Reclast)</td>
<td>Bisphosphonate</td>
<td>IV</td>
<td>Bone metastases, osteoporosis</td>
</tr>
</tbody>
</table>
Pathophysiology of MRONJ

The pathophysiology of MRONJ is often multi-factorial. There are many proposed hypotheses, however they all involve the use of an antiresorptive or antiangiogenic medication impairing bone turnover, coupled with a traumatic insult to the maxillofacial area (such as extraction, implant placement, or infection).

❖ **Antiresorptive Medications:**

➢ The most commonly used antiresorptive medications today consist of oral and IV bisphosphonates, as well as RANK ligand inhibitors (namely Denosumab). While they ultimately achieve the same antiresorptive effects, it is crucial to understand the difference in their mechanism of action and the clinical effects they have as it pertains to providing invasive dental treatment.

➢ There is a significant difference in the incidence of MRONJ in patients taking Bisphosphonates and patients taking Denosumab (a RANKL inhibitor) and it will undoubtedly affect their risk of developing MRONJ.

■ *How?* Well it has to do with their respective mechanisms of action; while bisphosphonates act directly on osteoclasts and impair their function, Denosumab (a RANKL inhibitor) acts on osteoclast precursors not only preventing the formation of new osteoclasts but also impairing the function of existing ones resulting in a more significant anti-resorptive effect.\(^5\)

*Anastakilakis, 2018*\(^5\)
➢ **What significance does this have clinically?** Well individuals taking bisphosphonates will show BRONJ on average 33 months after IV administration or 48 months after oral administration. On the other hand, the more potent Denosumab will result in DRONJ (Denosumab Related Osteonecrosis of the Jaw) early after treatment.

➢ The AAOMS predicts that since RANKL inhibitors such as Denosumab do not bind bone, their anti-resorptive effects will be sufficiently diminished after 6 months. On the other hand bisphosphonates can remain stable in the bone for years which is why patients remain at a high risk of BRONJ for years after their use.

❖ **Anti-angiogenic Medications**

➢ These medications are typically used to slow or stop the growth of cancerous cells by inhibiting blood supply. While this effect is beneficial in areas with cancer cells, the effects of the medication are systemic. This means that the blood supply to the bony structures of the maxillofacial regions are also compromised in these patients resulting in impaired healing and bone remodeling following extraction.
Part II - Your Role as a Dentist

Medication related osteonecrosis of the jaw is a rare yet aggressive complication which can be prevented through proper oral hygiene maintenance and properly managed if identified early, which is why the role of the dental provider is pivotal. Dental providers should be cognisant of the antiresorptive or anti-angiogenic medications that patients may be taking, and understand their effects on dental treatment. A prudent provider will recognize that the management of MRONJ requires a multidisciplinary approach and a solid long standing relationship with the patient’s oncologist or primary care physician (PCP).

The Medical Consult:

Treating patients who are on antiresorptive/antiangiogenic medications requires clear communication with their physician. When reaching out to the patient’s primary care physician or oncologist the following questions should be addressed:

1. What is the prognosis of the patient’s diagnosis?
2. What is the indication for antiresorptive/antiangiogenic therapy?
3. What time frame will the patient be initiating therapy and for how long?
   a. Is there a window of time available for you to provide dental care prior?
4. Any prior exposure to bisphosphonates or denosumab?
5. Is the patient immunocompromised? (Diabetes, Radiation, Corticosteroid use?)

Please remember that the medical consultation should be obtained in writing -- verbal communication with the physician is not adequate. Be sure your patient signs a release in order for you to obtain a medical consultation.
What are the risk factors for developing MRONJ?
Prior to providing dental treatment, a proper risk assessment should be completed. When identifying the risk of ONJ in patients taking any of the aforementioned drugs, it is important to consider a variety of systemic and local factors to understand the overall wellbeing and health of the patient. Oftentimes a detailed patient interview and medical consult from their physician are required to fully assess the risk.

The following is a list of MRONJ risk factors:

- **Drug type**
  - anti-resorptive
  - anti-angiogenic
- **Reason for use**
  - Individuals on antiresorptive medication due to osteoporosis have a significantly lower risk of ONJ as compared to those taking the medication as a part of cancer treatment. The risk is 100 times smaller. 4
- **Administrative route**
  - Risk of IV >>> Oral
- **Duration of treatment**
- **Date of last dose**
  - Bisphosphonates have a half life of over 10 years following a single dose IV administration. Thus the risk of ONJ remains constant regardless of the length of time since the last treatment dose. 6
  - Anti-resorptive agents such as RANKL inhibitors (Denosumab) do not incorporate into bone and thus have a decreased effect/risk after 6 months.
- **Systemic Disease:**
  - Diabetes
  - Obesity
  - Rheumatoid arthritis
  - Dialysis
  - Anemia
  - Hypocalcemia
  - Immunosuppression
- **Age**
- **Tobacco use**
- **Oral risk factors:**
  - Dental or periodontal infection
  - Peri-implantitis
  - Ill fitting removable dentures
  - Oral surgery
    - Tooth extractions, regenerative bone procedures, implant surgeries
    - Endodontic or periodontal surgeries (apicoectomies, crown lengthening surgeries, etc.)
The Low Risk Patient

Patients receiving antiresorptive therapy for osteoporosis (oral bisphosphonates) who do not present with any comorbidities are considered at low risk for MRONJ. The American Association of Oral & Maxillofacial Surgeons states that “elective dentoalveolar surgery does *not* appear to be contraindicated in this group”. If surgery is to be completed, the patient must be informed of the small risk of MRONJ and asked to sign a consent form stating they understand the risks, benefits, and alternatives of treatment.

It is important to note that if the duration of therapy exceeds four years, the risk increases, and appropriate precautions should be taken. If the patient has been taking oral bisphosphonates for over four years, a drug holiday may be prudent; please consult your OMFS faculty to initiate a medical consult to the physician requesting a drug holiday 2 months prior to oral surgery.

The High-Risk Patient

A patient receiving IV bisphosphonates or antiangiogenic drugs for a cancer diagnosis are considered to have significant risk of MRONJ. Any form of elective dentoalveolar surgery should be avoided (please refer to the section on “Comprehensive treatment planning for the high-risk patient”).

Drug Holidays

The use of drug holidays prior to invasive dental treatment is currently a controversial topic. While initially believed to be beneficial, due to the longstanding effects of bisphosphonates, their use is being reconsidered around the world. The American Association of Maxillofacial Surgeons (AAOMS) position paper in 2014 states that a 3 month drug holiday both *before* and *after* the delivery of invasive dental treatment is prudent. Additionally a systematic review done by an international ONJ task force also recommends the use of a drug holiday, however with the disclaimer that there is not sufficient evidence to properly support the claim. With the lack of high level evidence supporting drug holidays as an effective means of reducing ONJ risk, it is an area of controversy. Please consult with the oral surgeon on the clinic floor to discuss the option of a drug holiday for your patient.
MRONJ Risk Assessment Pathway

The following pathway along with the comprehensive risk assessment found on page 8 can be used in order to assess whether a patient is at high or low risk of MRONJ.

1) Treatment regimen
   - Low-dose
   - High-dose
     (See Table 1)

2) Treatment duration
   - No prior exposure or ≤ 3 years of treatment
   - > 3 years of treatment

3) MRONJ risk factors
   - Prior use of bisphosphonates or denosumab
   - Use of corticosteroids, chemotherapy, or angiogenesis inhibitors
   - Radiotherapy to head and neck
   - Poor oral hygiene, periodontitis, ill-fitting dentures
   - Smoking
   - Comorbidities (e.g. cancer, hematological disease, immunological disorders, diabetes mellitus, anemia)

   - No
     - Low MRONJ risk
   - Yes
     - Elevated MRONJ risk
After the risk assessment is completed, the following pathway may be used to guide with prevention strategies in comprehensive dental care.

**MRONJ risk assessment** (see Figure 5)

- **Low MRONJ risk**
  - No routine screening visit required
  - Usual recommendations on preventive dental visits for the general population apply
  - If patient has not complied with these recommendations, a check-up should be advised

- **Elevated MRONJ risk**
  - Screening visit required
  - Detect and treat pockets of occult infection
  - Extract teeth with poor prognosis
  - Check dentures
  - Encourage smoking cessation
  - Educate patient on recognizing signs and symptoms of MRONJ
  - Educate patients on maintaining good oral hygiene

**Prevention – during therapy**

- **Maintain optimal dental health**
  - Prophylactic dental cleaning
  - Tooth fillings
  - Non-traumatic treatments or prosthetics without bone anchoring
  - Patient education on maintaining good oral hygiene

- **No special precautions apply**
  - Very low MRONJ risk
  - All dental procedures may be performed as indicated
  - Recommendations for the general population on preventive dental assessments apply

- **Invasive dental procedures require expert advice**
  - Including dental extractions, periodontal surgery, root planing, and implants
  - Low threshold for referring patients to OMFS or a specialized dentist in case of unexplained symptoms (including dental pain, swelling, purulent discharge, etc.)
  - Use prophylactic antibiotics in case of unavoidable or emergency procedures

**If MRONJ is suspected**

- Refer to OMFS or oral oncology center with experience in treating patients with MRONJ
  - Consider starting chlorhexidine rinse (e.g. 0.12% three times daily) and/or empirical broad-spectrum antibiotic treatment (e.g. amoxicillin with clavulanic acid 500–125 mg three times daily)

*IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw; OMFS, oral and maxillofacial surgeon; SC, subcutaneous*

*Risk Assessment Pathway Courtesy of Ourania et al. 2019* 8
Comprehensive Treatment Planning for the High-Risk Patient:

Oftentimes, there is no window of time available for dental treatment prior to antiresorptive therapy, or the patient has already completed therapy and is now in need of dental treatment. Should the dental treatment be largely restorative in nature then it is safe to proceed (this includes caries control and nonsurgical endodontic treatment). Below is a guideline for the comprehensive treatment of patients with a high risk of MRONJ development:

1. **MRONJ Risk Assessment:**
   a. Following a medical consultation, identify the risk of invasive dental treatment.

2. **Providing the appropriate and necessary dental treatment:**
   a. **Periodontal Therapy**
      i. Scaling and root planing will reduce malignant oral microbial counts and aid with proper oral hygiene.
      ii. Periodontally involved teeth with mobility of 1 or 2 and favorable long-term prognosis should be splinted.
   b. **Restorative Therapy**
      i. ensuring there is no source of active infection in a preventive manner is crucial in high risk MRONJ patients. Treatment of carious teeth using direct or indirect restorations are not contraindicated.
   c. **Removable Dentures**
      i. It is critical to ensure proper fitting removable prostheses as mucosal irritation from appliances may induce MRONJ
      ii. Be sure to provide soft relines as necessary for proper fit.
   d. **Endodontic Therapy**
      i. Nonsurgical endodontic therapy is encouraged in high risk patients to eliminate infection
      ii. Some studies recommend avoiding apical extrusion of endodontic files thus caution should be used to avoid excessive apical patency.
   e. **Oral Surgery**
      i. *Any form of invasive surgical treatment should be avoided.* If unavoidable, please see the following section on non-restorable teeth.
My patient is about to start antiresorptive/antiangiogenic treatment -- What do I do?

If there is a small window of time prior to antiresorptive treatment, it is best to take advantage of this opportunity to stabilize oral health. The following should be addressed in order of priority:

1. Any existing sources of infections should be eliminated via root canal therapy or extraction depending on restorability
2. Any teeth with questionable long term prognosis should be extracted
   a. NOTE: It is best to allow for proper soft and hard tissue healing to occur following extraction prior to antiresorptive therapy.
3. Prosthodontic therapy of teeth with good prognosis
4. Stabilization of periodontal disease

Finally, it is crucial to provide anticipatory guidance regarding MRONJ with the patient. Patients should contact you immediately if they develop any symptoms of pain, swelling, or numbness of the gums or teeth. The primary goal of this phase is stabilization and patient education.

High-Risk MRONJ Patients & Non-restorable Teeth:

If a patient is determined to have a high MRONJ risk, and presents with an infection accompanying a non-restorable prognosis, it is important to proceed cautiously with treatment. The risks of MRONJ should be properly discussed with the patient and the following options presented after a consultation with OMFS faculty is obtained:

1. Extraction of the tooth
2. Coronectomy & Root Canal Treatment
   a. If the patient has a previous history of ONJ or presents with extremely high risk, this approach is recommended, given that it is possible.
   b. This approach requires endodontic sealing of the canals in order to resolve any infection at the apex prior to a coronectomy. A coronectomy involves amputation of the clinical crown of a tooth 2mm below the level of the bone and allows for soft tissue healing of the gums in an atraumatic manner.
   c. Oftentimes a CBCT is necessary to confirm the prognosis of RCT and to eliminate the possibility of a vertical root fracture.
   d. A CBCT can also give insight to the health of the bone and may be used to diagnose stage 0 MRONJ adding to your risk assessment.
Extraction Protocols for the High-Risk Patients:

The following protocol should be followed during the extraction of a non-restorable tooth in a high-risk patient:

1. **Prescribe Chlorhexidine gluconate 0.12% mouthrinse**
   a. 3x daily 1-week pre-op & continue post-op until complete healing has occurred.

2. **Systemic antibiotic regimen**
   a. 3 days pre-op & 4 days post-op
   b. Amoxicillin 500mg tid OR Clindamycin 300mg qid

3. **Extraction technique**
   a. Atraumatic extraction technique is crucial for successful healing
   b. Primary closure of the site is recommended
   c. Some studies suggest the use of PRGF to aid with socket healing. 11

4. **1-week & 1-month post-op appointments** to ensure proper healing
   a. Inform the patient to contact you immediately should they experience any symptoms of pain, swelling, or numbness in the gums around the healing site.

Other Risk Management Strategies:

There are many risk management techniques proposed however, the evidence is either controversial or not yet solidified. A well-established yet controversial strategy is one proposed by Marx which calls for the use of hyperbaric oxygen (HBO) chambers pre and post treatment in order to reduce the risk of MRONJ; it may also be used to treat existing MRONJ cases. The original proposal calls for a 20:10 protocol for prophylaxis meaning 20 hyperbaric dives prior to surgery and 10 dives post-surgery which boasts angiogenesis and increased healing potential; alternatively a 30:10 protocol is required in the treatment of diagnosed MRONJ cases. 12 While some surgeons may recommend this protocol for safety, the AAOMS position paper in 2014 states that the “use of HBO as the sole treatment modality cannot be supported”. While Marx was able to show success rates as high as 98.5% in his studies, recent studies have not found such clinically significant evidence. 13 Nevertheless, HBO chambers are still supported and indicated for use in certain situations either prophylactically or therapeutically; be sure to consult with your oral surgeon regarding this option.

Another newly proposed strategy for the prevention and treatment of MRONJ in high risk patients is the use of Pentoxifylline (an anti-inflammatory agent) and Tocopherol (a vitamin E derivative). While some studies show significant results in reducing risk of MRONJ, understand that it is an approach that has not been adequately researched. 14 This is not a protocol currently supported at the University of the Pacific however, it is good to be aware of approaches that are being researched currently.
Part IV - Managing Diagnosed MRONJ

While this document is focused on the prevention of MRONJ, if you suspect that your patient is suffering from complications post-extraction, please refer the case to the oral surgery department as soon as possible. Treatment of such complications if severe, are beyond the scope of a general practitioner and best managed aggressively by an oral & maxillofacial surgeon.

Osteonecrosis of the jaw may manifest in a variety of ways; sometimes patients will complain of pain with no visible areas of exposed bone however, it is important to carefully assess the situation and refer to oral surgery in a timely manner. In high risk patients it is always best to practice safe protocols and identify necrosing bone immediately.

Below is a table outlining treatment protocols for patients in different stages of MRONJ.

At the university, treatment is to be conducted in the oral surgery department exclusively.

<table>
<thead>
<tr>
<th>MRONJ† Staging</th>
<th>Treatment Strategies‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At risk category</strong> No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates</td>
<td>• No treatment indicated</td>
</tr>
<tr>
<td><strong>Stage 0</strong> No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms</td>
<td>• Patient education</td>
</tr>
<tr>
<td><strong>Stage 1</strong> Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection</td>
<td>• Systemic management, including the use of pain medication and antibiotics</td>
</tr>
<tr>
<td><strong>Stage 2</strong> Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage</td>
<td>• Antibacterial mouth rinse</td>
</tr>
<tr>
<td><strong>Stage 3</strong> Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone, (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor</td>
<td>• Symptomatic treatment with oral antibiotics</td>
</tr>
<tr>
<td></td>
<td>• Oral antibacterial mouth rinse</td>
</tr>
<tr>
<td></td>
<td>• Pain control</td>
</tr>
<tr>
<td></td>
<td>• Debridement to relieve soft tissue irritation and infection control</td>
</tr>
<tr>
<td></td>
<td>• Antibacterial mouth rinse</td>
</tr>
<tr>
<td></td>
<td>• Antibiotic therapy and pain control</td>
</tr>
<tr>
<td></td>
<td>• Surgical debridement/resection for longer term palliation of infection and pain</td>
</tr>
</tbody>
</table>
Part V

Concluding Remarks

The presence of medication related osteonecrosis of the jaw in patients has noticeably increased as more patients are undergoing treatments involving antiresorptive and anti-angiogenic therapies. As a dental provider it is crucial to consistently work to not only prevent, but to recognize the initial signs/symptoms of this complication. Treating a patient at risk for MRONJ requires a series of consultations from the physician in order to understand risk on a case by case basis, as well as an oral surgeon in order to safely deliver invasive surgery. When possible an endodontist should be involved in the consultation process, in order to consider more conservative approaches for providing dental care and infection control. Caring for these patients requires an **interdisciplinary** approach based on a solid foundation of the pathophysiology, risk factors, signs, and symptoms of MRONJ.
REFERENCES:


