

For Dentists and Other Dental Professionals:

Dental Guidelines for Patients Who Have or are at Risk for Medication-Related Osteonecrosis of the Jaw (MRONJ)

What Is MRONJ?

Medication-related osteonecrosis of the jaw (MRONJ) is a condition in the mouth characterized by areas of necrotic maxillary and/or mandibular bone that is often associated with soft tissue infection and pain. MRONJ can be seen in patients receiving antiresorptive or antiangiogenic agents for cancer, osteoporosis, and metabolic and developmental bone diseases (see Table 1). Predisposing factors include extractions, other local trauma, and dental infection. However, many cases arise spontaneously, frequently involving the mylohyoid ridge.

Radiographic findings are variable and may include:

- Altered bony trabeculae with mottled osteosclerotic changes
- Bone sequestra and osteolytic changes
- Thickened lamina dura and narrowed periodontal ligament space
- Persistent rarefaction at the site of dental extractions (≥6 months after extraction)

Table 1. Medications associated with MRONJ		
Mechanism of action	Medication	Indications
Anti-resorptive agents		
Impaired osteoclast activation and function resulting in inhibition of bone resorption and remodeling	<p>Bisphosphonates</p> <ul style="list-style-type: none"> • Zoledronic acid (Zometa®, Reclast®) • Pamidronate (Aredia®) • Alendronate (Fosamax®) • Ibandronate (Boniva®) • Risedronate (Actonel®, Atelvia®) • Etidronate (Didronel®) • Tiludronate (Skelid®) <p>RANK-ligand inhibitor</p> <ul style="list-style-type: none"> • Denosumab (Xgeva® and Prolia®) 	<p>Oncologic</p> <ul style="list-style-type: none"> • Multiple myeloma • Solid tumor bone metastases (e.g. breast, prostate and lung cancer) • Pathological fracture • Bone pain • Nerve root and spinal cord compression <p>Non-oncologic</p> <ul style="list-style-type: none"> • Heterotopic ossification, especially after spinal cord injury • Osteoporosis • Osteopenia • Paget disease • Osteogenesis imperfecta

Anti-angiogenic agents		
Disruption of vascular endothelial growth factor (VEGF) signaling resulting in inhibition of angiogenesis	<ul style="list-style-type: none"> • Sunitinib (Sutent®) • Sorafenib (Nexavar®) • Bevacizumab (Avastin®) • Ziv-aflibercept (Zaltrap®) 	<ul style="list-style-type: none"> • Renal cell carcinoma • Gastrointestinal stromal tumor • Neuroendocrine tumor • Hepatocellular carcinoma • Thyroid cancer • Metastatic colorectal cancer • Non-squamous, non-small cell lung cancer • Glioblastoma • Cervical cancer

Epidemiology of MRONJ

The incidence of MRONJ is primarily influenced by the type of medication and the total dose/duration of therapy. The best available evidence suggests that less than 5% of cancer patients treated with antiresorptive therapies will develop MRONJ. Incidence rates are between 0.1-0.2% for those treated for osteoporosis and other non-oncology-related indications. The precise incidence of MRONJ associated with anti-angiogenic agents is unknown but appears to be very low (i.e. $\leq 1\%$).

Diagnosis of MRONJ

The American Association of Oral and Maxillofacial Surgeons proposes the following criteria for the diagnosis of MRONJ:

- Current OR previous treatment with antiresorptive OR antiangiogenic agents
- Exposed bone OR bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

Differential Diagnosis

Obtaining a thorough medical history in addition to appropriate clinical and radiographic examination is essential for accurate diagnosis. The differential diagnoses may include the following:

- Alveolar osteitis ("dry socket")
- Periodontitis
- Periapical infection
- Chronic osteomyelitis
- Sinusitis
- Primary bone disease (e.g., osteosarcoma, chondrosarcoma)
- Metastatic disease

Staging and Management of MRONJ

Staging and management of MRONJ is based on clinical and radiographic features and symptoms (see Table 2). Treatment includes oral antibacterial rinse for all stages of disease, and antibiotics and local surgical intervention when indicated. Close follow up of these patients is important due to the variable and somewhat unpredictable nature of the condition.

Table 2. Staging and management		
Stage	Clinical presentation	Treatment
At risk	No clinical or radiographic changes consistent with MRONJ in patients who have been treated with either oral or IV bisphosphonates	<ul style="list-style-type: none"> • No treatment indicated • Patient education
Stage 0	No clinical evidence of necrotic bone, but radiographic changes, <u>symptoms</u> and <u>nonspecific clinical findings consistent with MRONJ assuming other possible odontogenic causes have been excluded</u>	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Systemic management, including the use of pain medication and antibiotics
Stage 1	Asymptomatic, exposed bone, or fistulae that probes to bone, with no evidence of infection	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone, with pain, erythema and infection with or without purulent drainage	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Antibiotic therapy • Pain control • Debridement to remove necrotic bone and to relieve soft tissue irritation and infection control
Stage 3	Exposed and necrotic bone or a fistula that probes to bone with pain, erythema and 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	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Antibiotic therapy • Pain control • Surgical debridement/resection for longer term palliation of infection and pain

Modified from Ruggiero et al. Journal of Oral and Maxillofacial Surgery 2014

Dental Management of Patients Prior to Initiation of Therapy

Patients should be evaluated by a dentist prior to initiation of antiresorptive or antiangiogenic therapy according to the guidelines below. All invasive dental procedures that involve manipulation of bone should be completed at least 4-8 weeks (or longer if clinically feasible) prior to initiation of therapy.

- Update (within one year) radiographs sufficient to rule out dental disease (e.g., caries and periodontal disease) and evaluate previously endodontically treated teeth and third molars
- Dental treatment plan the patient
- Extract teeth that are non-restorable or with poor long-term prognosis (including root tips)
- Complete all restorative dentistry, endodontic therapy, and periodontal therapy as appropriate depending on the clinical circumstances
- Place the patient on regular follow-up schedule

Guidelines for Extractions in Patients at Risk for MRONJ, or with MRONJ

When indicated, extractions should be completed with the least manipulation and removal of bone as possible.

- Perform surgical procedures as atraumatically as possible
- File any sharp edges and remove any unsupported bone fragments
- Following the extraction, gently curette the socket and irrigate with saline
- Try to achieve primary closure if possible
- Prescribe antibiotic therapy (e.g., amoxicillin 500 mg TID or clindamycin 300 mg TID) for at least two weeks following the surgical procedure
- Prescribe 0.12% chlorhexidine mouth rinse BID
- Re-evaluate the extraction site in approximately two weeks to ensure adequate healing, with additional follow-up scheduled as needed

Long-Term Dental Follow-Up

Regular dental follow-up appointments allow for monitoring of the patient and to address any new issues with the objective of minimizing the need for invasive dental procedures in the future. Below are some guidelines:

- Reinforce the importance of good home oral care
- Prescribe fluoride for patients at risk for caries
- Provide routine professional dental hygiene visits at least twice a year
- Manage dental caries and any other new dental issues that may have arisen
- Obtain periapical and panoramic radiographs upon diagnosis of MRONJ
- Obtain CBCT or medical CT as appropriate for advanced cases of MRONJ

Frequently Asked Questions (FAQs)

- **Which dental procedures are safe to perform in patients at risk for or with MRONJ?**

Any procedure that does not involve manipulation of the bone may be safely performed. These generally include delivering local anesthesia, scaling and prophylaxis, placing restorations including crowns and fixed prostheses, fabricating dentures and conventional root canal therapy.

- **Which dental procedures should be avoided in patients at risk for or with MRONJ?**

Any invasive elective procedure that involves manipulating the bone should be avoided if possible but if performed, should be followed by two weeks of antibiotic coverage as noted above. This includes periodontal surgery (e.g., crown-lengthening and bone grafting), endodontic surgery (e.g., apicoectomy), and placement of dental implants (see section below). In addition, orthodontic treatment outcomes may be negatively affected in patients with a history of bisphosphonate use.

- **What should I do if the patient needs a dental extraction?**

An evaluation must be made on a case-by-case basis. If the patient has an infected tooth that is not salvageable and mobile, the tooth should be extracted because infection itself may lead to MRONJ. Bear in mind that teeth may become infected and mobile because MRONJ has already developed around the tooth. If the tooth is not mobile but has apical pathology, there are two options. One is to perform root canal therapy and restore the tooth. This tooth can then be permanently restored or decoronated and sealed. A second option if the apical lesion is large (and prognosis guarded), is to extract the tooth. In all cases, the patient must be informed of the risk for development of MRONJ.

- **Should patients at risk for, or with MRONJ be prescribed antibiotics prior to dental treatment?**

There is no need to prescribe antibiotics for dental prophylaxis, routine caries control or other non-invasive procedures. However, antibiotic therapy is indicated for any dental procedure involving manipulation of the bone (e.g., extraction) and should be administered for two weeks following the dental procedure or until the overlying mucosa has healed.

- **Is a drug holiday indicated for patients at risk for, or with MRONJ prior to invasive dental procedures?**

There is insufficient evidence to support a drug holiday prior to invasive dental procedures. Some experts suggest possible benefit of a two-month drug holiday in patients who have taken oral bisphosphonates for more than four years. Ultimately the patient's need for antiresorptive therapy should supersede drug holiday considerations and the decision should be made by the oncology team or other physician. At this time, there is no consensus regarding a drug holiday for patients on denosumab.

Similarly, no recommendation pertaining to a drug holiday can be made for antiangiogenic agents due to lack of data. In these cases, best clinical judgment should be used taking into consideration the patient's disease status and consultation with the oncology team.

- **Should bone metabolism marker levels [N-telopeptide cross-linked (NTX) and C-terminal crosslinked telopeptide (CTX)] be obtained for risk assessment and/or follow up of MRONJ?**

NTX and CTX levels have not been validated as markers for developing MRONJ or for predicting MRONJ outcomes, and recommendations for their use in clinical practice were removed from the American Association of Oral and Maxillofacial Surgeons (AAOMS) guidelines in 2014.

- **Can patients at risk for, or with MRONJ, receive dental implants?**

Although the incidence of dental implant failure is unknown in cancer patients with exposure to antiresorptive and antiangiogenic agents, implant placement is generally not recommended, especially in patients with established MRONJ. Dental implants may be placed with caution in patients with osteoporosis at risk for MRONJ because MRONJ occurs infrequently in these patients. Patients should be carefully counseled and radiographs of the patients should be examined for evidence of bone changes as noted above.

- **Should patients at risk for, or with MRONJ receive any adjunctive therapies prior to invasive dental procedures?**

There is insufficient high-quality evidence to support or refute the use of adjunctive therapies such as hyperbaric oxygen, pentoxifylline and tocopherol, low-level laser, ozone, teriparatide, bone morphogenic proteins and platelet-rich plasma prior to dental procedures.

References

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