Osteonecrosis and Other Inflammatory Conditions of the Jaw
Moffitt Clinical Grand Rounds
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Objectives

• Compare and contrast the various inflammatory conditions of the jaws, including
  o Medication-related osteonecrosis of the jaw (MRONJ)
  o Osteoradionecrosis
  o Chronic osteomyelitis
• Identify patients at risk for developing inflammatory conditions of the jaws
• Recognize patients who may be developing inflammatory conditions of the jaws and implement a treatment strategy
Background Information
Why Discuss This?

• Some cancers and their treatments create the greatest risks for developing osteonecrosis of the jaw (ONJ) and inflammatory conditions of the jaws

• Immunocompromised patients
• Radiation therapy in Head & Neck Cancer or Cutaneous patients
• Medications known to be associated with ONJ used in many cancer patients
  o Skeletal metastases, Multiple myeloma, Metastatic cancers

• Cancer patients have a lot of other things to worry about – priorities!
  o Time
  o Energy
  o Financial
Why Discuss This?

• These treatments are necessary and beneficial for patients
• Risk of ONJ is low
• *But* can be quite disruptive
  o Can alter treatment
  o Can be difficult to cure
  o Can cause severe pain
  o Can alter a patient’s quality of life
  o Can decrease patient’s nutritional status
• *And* preventative measures can be taken
• Osteoblasts, osteocytes, osteoclasts
• Osteoblasts form new bone and derive from a multipotent stem cell
• Osteocytes are “retired” osteoblasts and help remodel bone
• Osteoclasts resorb mineralized bone and derive from the monocyte/macrophage cell line
  o Many bone diseases are associated with increased function of osteoclasts
    • Pharmaceutical targets
  o Regulated by RANK/RANKL/OPG system
Anti-resorptive Medication Differences

- Osteoblast secretes RANKL
- RANKL binds to RANK receptor (on osteoclasts)
- Osteoclast is activated
- Resorbs bone

- Denosumab binds to RANKL such that RANKL can no longer bind to osteoclast’s RANK receptor
- Bisphosphonates simply get incorporated into the bone and inhibiting bone resorption by osteoclasts
### Key:
- OPG $\rightarrow$ Estrogen
- RANKL $\rightarrow$ Vitamin D3, TNF-$\alpha$, PTHrP, IL-1/11/17
- Denosumab
- RANK

### Diagram:
- HSC (Hematopoietic Stem Cell) and MSC (Mesenchymal Stem Cell) influence osteoclast and osteoblast differentiation.
- Osteoclasts and osteoblasts interact with osteocytes.

#### Osteoclast Apoptosis
- [OPG] > [RANKL]
  - Production and Resorption
  - Osteoclast apoptosis
  - +Denosumab

#### Osteoclast Survival/Activation
- [OPG] < [RANKL]
  - Low estrogen – menopause
  - Osteopenia/osteoporosis
  - Cancer-related skeletal defects
Compare and Contrast the Various Inflammatory Conditions
Similar But Different Diseases

- Clinical presentations for these three diseases can have some overlapping features
- Management and prevention is similar in some ways as well
- Still important to differentiate
Medication-Related Osteonecrosis of the Jaw (MRONJ)

• Formerly, Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)

Definition:
• Current or prior treatment with a bisphosphonate or other antiresorptive/bone-modifying agent or antiangiogenic therapies
• Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
• No history of radiation treatment to the jaws or metastatic disease of the jaws in the region of exposed bone
• ONJ-like Findings/Stage 0: history of at-risk medication use but not meeting other criteria or with evidence of other disease processes (e.g., < 8 weeks of exposed bone or purulent osteomyelitis)
Medication-Related Osteonecrosis of the Jaw (MRONJ)

- Bisphosphonates target the osteoclast but also
  - Stimulate osteoblasts to make more bone
  - Blood vessel cells, fibroblasts, keratinocytes
- Bisphosphonates have an antiangiogenic function also
  - Leads to decreased vascular exploitation → less blood vessels to support increased amounts of bone
  - Soft tissues may not heal as well also
  - May also help explain why antiangiogenic agents can cause ONJ, too
Osteoradionecrosis of the Jaw (ORN/ORNJ)

- Exposed and necrotic bone associated with ulcerated or necrotic soft tissue that persists for **greater than 3 months** in an area that has been previously irradiated, and is not caused by tumor recurrence/cancer.

- > 50 Gy ionizing radiation
  - Mostly head & neck cancer patients
    - Many with a prior history of smoking/drinking
    - Age 60+ years usually
    - Men > Women
  - Usually happens about around 5 years out from radiation treatment
  - Radiation causes hyalinization of vessels in the bone
    - Decreased nutrition/hypoxia of the bone → death of osteocytes
  - Affects more than just bone: skin, mucosa, muscles, salivary glands
  - Xerostomia → radiation caries/"cavities" → increased risk of infection
Osteoradionecrosis of the Jaw (ORN/ORNJ)

- Many different hypotheses on the pathophysiology
  - Radiation $\rightarrow$ local injury $\rightarrow$ infection
  - Three H’s: hypocellular, hypoxic, hypovascular state
    - Due to microvascular damage from radiation $\rightarrow$ endarteritis, thrombosis, obliteration of vessel
  - Suppression of osteoclast-mediated bone turnover
    - Loss of osteoclast function induced by irradiation
    - Supported by the existence of MRONJ
  - Fibroatrophy bone change
    - Radiation-induced fibrosis
    - Acute inflammation with endothelial changes, abnormal fibroblast activity with extracellular matrix disruption, fibroatrophy phase where tissues are friable and undergo late reactivation of the acute inflammatory response after injury
Osteomyelitis of the Jaw

- Inflammation of the bone
- Acute osteomyelitis
  - Usually caused by odontogenic infection
  - Symptomatic
  - Fever, swelling, pain, redness
  - Trismus
  - Tooth mobility
  - Purulence from the periodontium
  - Paresthesia of the lower lip
  - May show minimal changes on radiographs at outset
    - Eventual loss of trabecular pattern/radiolucency
    - Dental disease
Osteomyelitis of the Jaw

- Chronic osteomyelitis
  - > 4 weeks of acute osteomyelitis = “Secondary Chronic Osteomyelitis”
    - Less prominent swelling
    - Periosteal reaction radiographically
    - Sequestrum formation
    - Fistula formation
  - Average age is about 40 years old but with wide ranges
  - Usually caused by odontogenic infection, rarely hematogenous spread of systemic infection/other primary location
  - Greater chronicity, more likely marrow fibrosis and sclerosis of bone
  - Greater chronicity, harder to eradicate infection
  - Radiographs would show increased radiolucency, sequestrum formation, periosteal reaction, or pathologic fractures
Osteomyelitis of the Jaw

• Chronic osteomyelitis
  o Primary chronic osteomyelitis can be relatively asymptomatic
    • Radiographic findings, such as periosteal reaction or osteosclerosis
    • Non-suppurative inflammation
    • Uncertain etiology
Comparisons/Similarities

- Many different hypotheses regarding the pathophysiology of these but none are definitive....not surprisingly....
  - Probably because there is some component of overlap
  - Each patient case may have a different set of risk factors
  - Similarly, reduced bone healing capacity due to decreased blood supply, decreased ability to fight infection, infection causing symptoms and progression of disease
  - Therefore, the prevention strategies and treatments/management can be fairly similar
Comparisons/Similarities

• Symptoms:
  o Jaw vs. tooth pain – can be hard for patient to differentiate
  o Exposed bone
  o Mobile teeth
  o Numbness of lower lip
  o Symptoms of infection: swelling, tenderness, warmth, redness

• At varying stages of each, can be asymptomatic vs. symptomatic
  o Generally related to infection of the diseased bone
Comparisons/Similarities

• Oftentimes first diagnosed following dental surgery

• Chicken vs. the Egg = Tooth needing extraction vs. the ONJ/OM
  o Spontaneous ONJ/OM causing symptoms thought to be related to the tooth → Extraction → nonhealing socket/diagnosis of ONJ/OM
  o Extraction causes trauma/infection → causing nonhealing socket/ONJ/OM
  o Infected tooth/infection itself → causing ONJ/OM → Extraction with nonhealing socket
Comparisons/Similarities

- Many cases can be managed conservatively with oral rinses and antibiotics
- As the disease progresses to more symptomatic and dysfunctional, surgery is more likely to be rendered
- Increased risk of jaw fracture, fistula formation can occur
Contrasts/Differences

• Chronic osteomyelitis is less likely to have exposed bone
• Osteomyelitis is more likely to have a specific tooth ache/irreversible pulpitis
  o Cold or hot liquids causes a single tooth extreme pain that lingers
• Acutely altered sensation of the lower lip is more common if patient has experienced an acute osteomyelitis, unless there is a pathologic fracture which can occur in any disease and cause this same symptom
• MRONJ usually occurs in “sicker” patients with poorer overall prognoses
• Soft tissue status is often better in MRONJ and osteomyelitis than in ORN
• The mandible is much more often affected in ORN and osteomyelitis
  o The maxilla is more often affected by MRONJ
• Keep in mind that an acute infection of the bone can occur (and occurs more easily) in patients with osteonecrosis of the jaw, so they’re not necessarily mutually exclusive.
Identify Patients at Risk
Identifying Patients at Risk for ONJ

• MRONJ
  - History of exposure to bisphosphonates
    - IV for multiple myeloma and bone metastases: pamidronate (Aredia), zoledronic acid (Zometa)
    - IV for osteoporosis: zolendronate (Reclast), ibandronate (Boniva)
  - History of exposure to antiresorptives
    - RANK ligand (RANK-L) inhibitor: denosumab (Xgeva, Prolia)
    - Denosumab for bone metastases, adjuvant treatment, osteoporosis
Identifying Patients at Risk for ONJ

• Risk of MRONJ for osteoporosis patients (as compared to cancer patients receiving antiresorptive therapies) is ~100 times less
  o Risk increases each year for the first 3 years, then plateaus
  o Most osteoporotic patients that developed ONJ, median exposure time was 4.4 years

• Risk of MRONJ in osteoporotic patients on oral bisphosphonates
  o 0.1% overall (10 per 10,000 patients)
  o 0.21% if greater than 4 years of exposure (risk doubles but still quite low)
  o Other studies have shown much lower rates, approximating 0 at <1 per 100,000
  o Overall, the risk is exceedingly low for patients on oral bisphosphonates for osteoporosis
Identifying Patients at Risk for ONJ

- IV BP/SC RANKL inhibitors for osteoporosis
  - Yearly zoledronate: 0.017%
  - Denosumab: 0.04%
    - Osteoporosis patients with placebo: 0 - 0.02% risk for ONJ
Identifying Patients at Risk for ONJ

• Highest risk of developing MRONJ due to antiresorptive treatment for osteoporosis is present in oncologic patients with further compromising medications/conditions
  o Incidence for malignant disease patients: 1 to 20%
  o Secondary osteoporosis ~1%
  o Primary osteoporosis 0.1%
Identifying Patients at Risk for ONJ

**TABLE 1.** Bone-Modifying Agents and Risk of MRONJ

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Route</th>
<th>Dose, mg</th>
<th>Schedule</th>
<th>Frequency of MRONJ, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td>Bone metastases of solid tumors</td>
<td>IV</td>
<td>90</td>
<td>Every 3-4 weeks</td>
<td>3.2-5.0⁷,⁴</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Bone metastases of solid tumors</td>
<td>IV</td>
<td>4</td>
<td>Every 3-4 weeks or 12 weeks</td>
<td>1.0-8.0⁶,⁶</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjuvant treatment</td>
<td>IV</td>
<td>4</td>
<td>Every 3-6 months</td>
<td>0-1.8⁷-⁹</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Bone metastases of solid tumors</td>
<td>SC</td>
<td>120</td>
<td>Every 4 weeks</td>
<td>0.7-6.9¹⁰-¹²†</td>
</tr>
<tr>
<td></td>
<td>Adjuvant treatment</td>
<td>SC</td>
<td>60</td>
<td>Every 6 months</td>
<td>0¹³</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; MRONJ, medication-related osteonecrosis of the jaw; SC, subcutaneous.

*Risk of MRONJ varies by duration of treatment.

†The estimate of 6.9% is from the open-label extension phase of two phase III studies. It is not adjusted for patient-years of exposure or patient follow up and does not include cases that occurred during the blinded treatment phase. The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of denosumab treatment, 3.7% in the second year, and 4.6% per year thereafter.
Identifying Patients at Risk for ONJ

- **MRONJ**
  - History of exposure to antiangiogenics
    - TKIs: sunitinib (Sutent), sorafenib (Nexavar)
  - Some evidence suggests that TKI alone does not increase the risk but does when used in combination with a bisphosphonate
  - But have been case reports of patients with history of TKI-only use

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<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Primary indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib (Sutent®)</td>
<td>Tyrosine kinase inhibitor</td>
<td>GIST, RCC, pNET</td>
</tr>
<tr>
<td>Sorafenib (Nexavar®)</td>
<td>Tyrosine kinase inhibitor</td>
<td>HCC, RCC</td>
</tr>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>Humanized monoclonal antibody</td>
<td>mCRC, NSCLC, Glio, mRCC</td>
</tr>
<tr>
<td>Sirolimus (Rapamune®)</td>
<td>Mammalian target of rapamycin pathway</td>
<td>Organ rejection in renal transplant</td>
</tr>
</tbody>
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*Abbreviations: GIST gastrointestinal stromal tumor; RCC renal cell carcinoma; pNET pancreatic neuroendocrine tumor; HCC hepatocellular carcinoma; mCRC metastatic colorectal carcinoma; NSCLC non-squamous non-small cell lung carcinoma; Glio Glioblastoma; mRCC metastatic renal cell carcinoma

* While the FDA has issued an ONJ advisory only for bevacizumab and sunitinib, the committee remains concerned about a similar potential risk associated with several other medications within the same drug class which have a similar mechanism of action. Therefore further controlled, prospective studies will be required to more fully characterize the risk of jaw necrosis associated with these agents.
Identifying Patients at Risk for ONJ

- MRONJ
  - History of exposure to antiangiogenics
    - Bevacizumab is a VEGF-inhibitor
      - Breast cancer
      - Colorectal cancer
      - Lung cancer
    - Ziv-aflibercept: recombinant VEGF-receptor
Identifying Patients at Risk for ONJ

- MRONJ
  - History of exposure to
    - Everolimus: mTOR inhibitor
    - Sirolimus: mTOR inhibitor
    - Chronic Corticosteroids
      - Especially in combination with any of the other known medications

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Identifying Patients at Risk for ONJ

- ORN
  - History of radiation therapy 50 Gy or more to either jaw

- Chronic Osteomyelitis
  - History of untreated/undertreated dental infection
Other Medical Comorbidities

- Diabetes
- Smoking
- Immunosuppression
- Anemia
- Chronic steroid use
Operative Dental Treatment

• Typically precipitated by a dental surgery
  o Cause vs. Identification of Disease

• Procedures include:
  o Tooth extraction
  o Dental implant placement
  o Periodontal/gum surgery
  o Trauma/reconstruction
  o Ill fitting dentures/prostheses
Why Mostly in Jaw Bones?

- Under constant remodeling normally
- Contaminated environment
- Lack of dental care access
- Decreased focus on oral health due to other concerns
- Prone to trauma (eating, toothbrushing, etc.)
Identifying Patients at Risk for ONJ

- Mandible > Maxilla
  - Cortical bone
  - Blood supply differences
  - More often exposed to radiation therapy due to primary tumor site/neck
  - More difficult extractions
  - Greater risk of everyday trauma
  - Thin lingual mucosa

- MRONJ Occurrence: Mandible 73% vs. Maxilla 22.5% vs. Both 4.5%
Identifying Patients at Risk for ONJ

• The likelihood of infection and progression of disease and symptoms is dependent upon
  o Number of bacteria
  o Virulence of bacteria present
  o Local immune response
  o Local blood flow

• In normal patients, it is quite rare to have a dental infection cause osteonecrosis or chronic osteomyelitis
Recognize ONJ and Implement Treatment Strategy
## Table 1 Staging and Treatment Strategies

<table>
<thead>
<tr>
<th>MRONJ† Staging</th>
<th>Treatment Strategies‡</th>
</tr>
</thead>
</table>
| **At risk category** No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates | • No treatment indicated  
• Patient education |
| **Stage 0** No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms | • Systemic management, including the use of pain medication and antibiotics |
| **Stage 1** Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection | • 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, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage | • Symptomatic treatment with oral antibiotics  
• Oral antibacterial mouth rinse  
• Pain control  
• Debridement to relieve soft tissue irritation and infection control |
| **Stage 3** 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 or the sinus floor | • Antibacterial mouth rinse  
• Antibiotic therapy and pain control  
• Surgical debridement/resection for longer term palliation of infection and pain |

† Exposed or probable bone in the maxillofacial region without resolution for greater than 8 weeks in patients treated with an antiresorptive and/or an antiangiogenic agent who have not received radiation therapy to the jaws.

‡ Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.
MRONJ

• At Risk
  o No apparent necrotic bone
  o All patients who have ever been treated with of the listed medications
Stage 0
- No clinical evidence of necrotic bone
- Nonspecific clinical findings, radiographic changes, and symptoms
MRONJ

• Stage 1
  o Exposed and necrotic bone
  o Or fistula that probes to bone
  o Longer than 8 weeks’ duration
  o AND are asymptomatic *without* evidence of infection
MRONJ

• Stage 2
  o Exposed and necrotic bone
  o *Or* fistula(e) that probes to bone
  o Longer than 8 weeks’ duration
  o *AND* are symptomatic
  o *WITH* evidence of infection
    • Pain and erythema around area of exposed bone
    • +/- Purulent drainage
MRONJ

• Stage 3
  o Exposed and necrotic bone or fistula(e) that probes to bone
  o Longer than 8 weeks’ duration
  o AND symptomatic WITH evidence of infection
  o PLUS one or more of the following:
    • Exposed and necrotic bone extending beyond the region of alveolar bone → inferior border/ramus of mandible, maxillary sinus/zygoma in maxilla
    • Resulting in pathologic fracture
    • Extraoral fistula(e)
    • Oroantral or oronasal communication/fistula(e)
    • Osteolysis extending to the inferior border of the mandible or sinus floor of the maxilla
Prevention

• Before initiation (or as soon as possible after, in urgent cases), have patient comprehensively evaluated by a dentist
  o Any nonrestorative teeth or those with poor prognosis should be extracted beforehand
  o Complete necessary elective dentoalveolar surgery
    • Tori reduction
    • Dental implant placement
    • Gingival grafts
• Delay the therapy, if systemic conditions permit, until the extraction site has mucosalized completely (14-21 days) or until there is adequate osseous healing
• Good communication and coordination of care between providers
• Extent of treatment completed prior to initiation of therapy, depends upon urgency/patients disease process
  o (MASCC/ISOO/ASCO Clinical Practice Guideline)
TABLE 3. Descriptions of Complete, Partial, and Minimal Dental Evaluation Protocols Based on the Type of Dental and/or Periodontal Pathology

<table>
<thead>
<tr>
<th>Dental Pathology</th>
<th>Complete(^{154,155})</th>
<th>Partial(^{156,157})</th>
<th>Minimal, Incomplete, or No Clearance(^{154-158})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caries</td>
<td>Restore all teeth</td>
<td>Mild/moderate caries were restored if time permitted</td>
<td>Intervention only if symptomatic</td>
</tr>
<tr>
<td>Severe caries/pulp involvement/ dental abscess</td>
<td>Root canal treatment or extract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical periodontitis</td>
<td>Retreat</td>
<td>Symptomatic lesions and lesions ≥ 5 mm were treated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apicoectomy</td>
<td>Asymptomatic lesions and lesions &lt; 5 mm were observed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced periodontal disease</td>
<td>Extract teeth with:</td>
<td>Extract teeth with:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probing depth ≥ 6 mm</td>
<td>Probing depth ≥ 8 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Furcation I, II, III; Mobility III</td>
<td>Mobility III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe inflammation</td>
<td>Severe inflammation</td>
<td></td>
</tr>
<tr>
<td>Partially erupted third molars</td>
<td>Extract</td>
<td>Asymptomatic teeth were observed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Partially erupted third molars with purulence of pericoronitis were extracted</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. The proper protocol should be selected by the oncologist and dentist according to the patient's medical status.
Prevention

- If choice in initial medication use
- For those at higher risk, may consider denosumab vs. bisphosphonate
  - Denosumab is not incorporated into the bone
    - Has much shorter half-life (~6 months vs. 10+ years)
      - Drug holidays before dental surgeries are possible/more effective
      - Can reduce risk of progression when discontinued
    - Predominantly affects the communication between osteoblasts and clasts
      - Not on vasculature/fibroblasts → soft tissues may not be as greatly affected as with bisphosphonates
  - Should avoid transitioning from bisphosphonate to denosumab, however
    - Some evidence of potential for significantly increased risk of MRONJ in patients that have transitioned from BP to denosumab
Prevention

• Strict preventive dental care/surveillance.
  o Dental prophylaxis and exam
  o Caries control: Fluoride, Dental Cleaning, Limit consumption of sugar
  o Conservative restorative dentistry when needed
  o Examination of full/partial dentures for areas of mucosal trauma, especially lingual mandible (so visits are important even if patient is completely edentulous)
  o Every 3-6 months, depending on dental health and risks
• Particularly important for higher risk cancer patients
Prevention

• Educate Patient
  o Risk is small, so try not to discourage patient from taking the needed medication.
  o They can take control of their oral health and help prevent ONJ by seeing dentist regularly, diligent oral care/hygiene, avoidance of sugary foods/drinks

• Can provide patient with the MASCC/ISOO/ASCO Clinical Practice Guideline “Basic Oral Care Plan”
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Basic Oral Care Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flossing</td>
<td>Floss at least once daily. Waxed floss may be easier to use and minimize trauma to the gingiva. If flossing causes bleeding of the gums that does not stop after 2 minutes, consult your oncology team.</td>
</tr>
<tr>
<td>Brushing</td>
<td>Use a small, ultra-soft-headed, rounded-end, bristle toothbrush. Use prescription fluoride toothpaste; spit out the foam but do not rinse mouth. Use remineralizing pastes and chewing gum containing calcium and phosphate. Brush within 30 minutes after eating and before bed; ensure the gingival portion of the tooth and periodontal sulcus are included. Rinse toothbrush in hot water to soften the brush before using. Brush tongue gently from back to front. Rinse brush after use in hot water and allow to air dry. Change toothbrush when bristles are not standing up straight.</td>
</tr>
<tr>
<td>For patients with dentures</td>
<td>Remove dentures, plates, and prostheses before brushing. Brush and rinse dentures after meals and at bedtime. Remove from mouth for long periods (at least 8 hours per 24 hours) and soak in rinsing solution.</td>
</tr>
<tr>
<td>Rinsing</td>
<td>Rinsing the oral cavity vigorously helps maintain moisture in the mouth, removes the remaining debris, and reduces the accumulation of plaque and infection. Patients should rinse, swish, and spit with a bland rinse (1 teaspoon salt, 1 teaspoon baking soda in 4 cups of water) several times a day. Club soda should be avoided because of the presence of carbonic acids. Commercial mouthwashes with alcohol base or astringent properties are not recommended for patients with oral complications. Debridging should only be done if absolutely necessary, if tissue is loose causing gagging or choking.</td>
</tr>
<tr>
<td>Moisturizing the oral cavity</td>
<td>Moisturize the mouth with water or artificial saliva products or other water-soluble lubricants for use inside the mouth. Avoid glycerin or lemon-glycerin swabs as they dry the mouth and do not moisturize. Apply lubricant after each cleaning, at bedtime, and as needed. Water-based lubricant must be applied more frequently. Frequent rinsing as needed with basic mouth rinse.</td>
</tr>
<tr>
<td>Lip care</td>
<td>To keep lips lubricated and moisturized, use only animal or plant-based oils such as bees wax, cocoa butter, and lanolin. Avoid petroleum-based products as these will cause drying and cracking.</td>
</tr>
</tbody>
</table>

You should be having follow-ups a minimum of every 6 months with your dentist. If you notice any signs or symptoms, please advise either your dentist or oncologist.
Prevention

• Evaluate modifiable risk factors to optimize
  o Diabetes $\rightarrow$ good glycemic control
  o Tobacco use $\rightarrow$ smoking cessation
  o Sugar intake $\rightarrow$ substitute for alternative sweeteners
  o Xerostomia $\rightarrow$ stay hydrated with non-sugar drinks, salivary substitutes
Prevention

• Avoid elective dentoalveolar surgery
  o Alveoloplasties
  o Tori removal
  o Dental implants
  o Gingival grafts
  o Crown lengthening
  o Can sometimes consider, if patient has been fully informed, accepts the risks, and oncologist is also in support of it

• If dentoalveolar surgery is required or performed
  o Ideally, performed by an oral & maxillofacial surgeon
  o Close follow-up until complete mucosal healing
  o Continue routine general dental visits thereafter for continued surveillance
Prevention

• IV antiresorptive/antiangiogenic therapy for cancer patients
  o Tooth extraction should be avoided, if at all possible
  o If ONJ develops, consider discontinuing therapy until soft tissue closure has occurred, depending on disease status

• PO antiresorptive therapy for osteoporosis
  o Very low risk of ONJ
  o Assess based on duration of therapy and other risk factors
  o Systemic markers of bone turnover (e.g., serum C-peptide) is NOT recommended as a measure of risk
  o NO drug holiday is necessary as it has not been shown to alter risk
  o If > 4 years’ exposure, can consider drug holiday for 2 months prior to oral surgery until osseous healing occurs, if permitted
    • NOT evidence-based
Prevention

• Dentures cleaned daily and removed at night
• Leave dentures out immediately at the first sign of a denture sore until fully healed
• Still see the dentist, even if completely edentulous for denture checks and oral exams
Prevention – Recognize

• Specifically ask whether patient is having any mouth or tooth pain
• Ask when last visit was to general dentist
• Ask whether patient has had any dental treatment since last clinic visit

• Be aware that it can occur spontaneously, not precipitated by any known trauma or surgery
• May or may not be painful
• Jaw pain, may or may not be associated with a specific tooth
• Rough spot on the gums felt by tongue
• Soreness of the gums or adjacent tissues.
• Decreased sensation of the teeth, gums, or lower lip
• Pain when chewing
• Loose teeth
Prevention – Recognize

- May note new malodor/halitosis
- Poor oral hygiene
- White patches within the mouth which are rough to the touch
- New sores in the mouth
- Swelling or tenderness
- Fistulae intraorally or extraorally
- Change in occlusion / pathological fractures
Prevention – Recognize

- Exposed bone may be present without patient’s knowledge
- Exposed bone that is causing pain is likely suprainfected
- Can be causing pain within the jaw or the adjacent tissues being traumatized by the exposed bone (e.g., tongue pain due to the lingual mandible exposed bone)
  - Can cause odynophagia or dysphagia as a result of this
- Also need to rule out malignancy
Treatment for Active ONJ

- Mostly dependent upon symptoms
  - Aseptic vs. infected exposed bone
Identifying Patients at Risk for ONJ  Treatment for ONJ

• The likelihood of infection and progression of disease is dependent upon
  o Number of bacteria
  o Virulence of bacteria present
  o Local immune response
  o Local blood flow
Identifying Patients at Risk for ONJ  Treatment for ONJ

• The likelihood of infection and progression of disease is dependent upon
  o Number of bacteria → reduce the number of bacteria
    • Reduce oral bacterial load
      • Good oral hygiene practices
      • Regular dental visits/cleaning
      • Daily use of chlorhexidine (Peridex) oral rinses
    • Systemic antibiotics, ideally directed by cultures
Identifying Patients at Risk for ONJ  Treatment for ONJ

• The likelihood of infection and progression of disease is dependent upon
  o Virulence of bacteria present
    • Culture/antibiotic sensitivity directed antimicrobial therapies
      • Aerobic
      • Anaerobic
      • Actinomyces
      • Fungal
        • Don’t forget about the fungal component, especially in the mouth
Identifying Patients at Risk for ONJ  Treatment for ONJ

• The likelihood of infection and progression of disease is dependent upon
  o Local immune response
    • Higher risk for those with compromised immune system
      • Cancer
      • Diabetes
      • Autoimmune diseases on therapy
    • Greater focus on prevention
    • Lower threshold for antibiotic use
    • Greater likelihood of fungal component with neutropenia (?)
    • Optimize patient, hold offending agent, if possible
Identifying Patients at Risk for ONJ  Treatment for ONJ

- The likelihood of infection and progression of disease is dependent upon
  - Local blood flow
    - Radiation decreases local blood flow to both bone and soft tissues
      - MRONJ usually has better chance of healing after conservative surgical treatments, due to improved soft tissue health
    - Those with anemia may be at higher risk due to decreased oxygen carrying capacity
    - May consider hyperbaric oxygen therapy to improve oxygen delivery to the bone
      - But doesn’t necessarily improve antimicrobial delivery
    - May consider a buccal decortication, if remains symptomatic with conservative therapies
    - Peridex/Nystatin oral rinse is important to reach the areas that are not adequately vascularized for systemic therapy delivery
Identifying Patients at Risk for ONJ  Treatment for ONJ

- The likelihood of infection and progression of disease is dependent upon
  - Local blood flow
    - Bone is contaminated with bacteria $\rightarrow$ proliferate/colonize marrow
      - Haversian and Volkmann canals $\rightarrow$ affect periosteum
      - Edema under periosteum disturbs blood flow $\rightarrow$ ischemia of bone $\rightarrow$ sequestrum
    - Edema within the marrow can sometimes also restrict blood flow
      - Steroids in acute cases where there are paresthesias present
Identifying Patients at Risk for ONJ  Treatment for ONJ

• The likelihood of infection and progression of disease is dependent upon
  o Local blood flow
    • PENTOCLO Protocol for ORN (Some have used PENTO[CLO] for MRONJ)
      • Delanian, et al. out of France

Oral Disinfiltrating Treatment:
Four Weeks of Daily
20 mg prednisone
2 g of Augmentin
1 g ciprofloxacin
50 mg fluconazole

Then, Daily Maintenance:
BID 400 mg pentoxifylline
BID 500 IU vitamin E
QD 1600 mg clodronate M-F (5 days/week)
20 mg prednisone (Sa-Su) (2 days/week)
1000 mg ciprofloxacin (Sa-Su) (2 days/week)
• The likelihood of infection and progression of disease is dependent upon
  o Local blood flow
    • PENTO[CLO] Protocol
  • Pentoxifylline
    • Methylxanthine derivative
    • Multiple potential effects:
      • Vascular dilatation
      • Increased erythrocyte flexibility
      • Anti-TNF alpha activity → reduce cytokine cascade
      • Reduce proliferation of dermal fibroblasts
      • Limit extracellular matrix production by dermal fibroblasts
      • Promotion of collagenase activity (in vitro studies only)
    • Rebound tissue injury possible if treatment too short (< 3 months)
Identifying Patients at Risk for ONJ  Treatment for ONJ

• The likelihood of infection and progression of disease is dependent upon
  o Local blood flow
    • PENTO[CLO] Protocol
  • Tocopherol (Vitamin E)
    • Fat-soluble vitamin
    • Weak antioxidant agent
    • Scavenge reactive oxygen species
    • Partial inhibition of TGF-beta 1
    • Antifibrotic effect mediated by procollagen genes
Identifying Patients at Risk for ONJ  Treatment for ONJ

• The likelihood of infection and progression of disease is dependent upon
  o Local blood flow
    • PENTO[CLO] Protocol
  
  • Clodronate
    • First-generation, NON-nitrogenous bisphosphonate
      • Reduces bone resorption through reducing osteoclast numbers and activity
      • Reduce inflammatory cytokines IL-1B, IL-6, and TNF-alpha
      • Acts on osteoblasts to increase bone formation and reduce fibroblast proliferation
Treatment for ONJ

• Infection of the necrotic bone can lead to progression of the disease
  o Goal is to limit the infection
  o May require conservative debridement of necrotic bone
  o In all stages, loose, superficial sequestrum should be removed conservatively without disturbing the surrounding mucosa as much as possible

• Treatment is largely dependent upon symptoms, since symptoms typically are as a result of infection
  o If no symptoms, unlikely to have infection.
Treatment for or Concern of Active ONJ

- If concerns, obtain neck CT or maxillofacial CT
  - Moffitt CT Neck protocol is good even for maxillofacial evaluation
    - Outside evaluations may not mimic our protocols (anatomy included, thickness of imaging cuts/definition of sites)
    - Give radiologist comments to ensure evaluation of concerns/bone
  - Obtain with contrast, if able, especially if concern for soft tissue swelling/abscess
  - Okay to obtain without contrast, for evaluation of bone quality
- Imaging may show sclerotic changes, bony sequestrum, or lytic changes.
Treatment for or Concern of Active ONJ

• It is unclear whether the suspected medication associated with the osteonecrosis should be discontinued upon diagnosis of MRONJ
  o This can be discussed with the patient/providers and a risk/benefit analysis should be performed
Treatment for or Concern of Active ONJ

- **Initial Treatment**
  - Conservative measures (especially if asymptomatic)
    - Antimicrobial mouthrinses (Peridex)
    - Antibiotics, if clinically indicated (symptoms +/- signs)
    - Effective oral hygiene
    - Conservative surgical interventions (removal of superficial bone spicules)

- **Treatment of Refractory ONJ**
  - Persistent symptoms or significantly affects function/quality of life despite conservative treatments
  - Aggressive surgical interventions (e.g., mucosal flap elevation, resection of necrotic bone, or soft tissue closure)
    - Not recommended for asymptomatic bone exposure
Treatment for or Concern of Active ONJ

• Immediately discontinue use of any traumatic prosthesis/dentures
• Try to avoid traumatic foods
  o Soft diet for avoidance of mucosal trauma and fracture prevention
• 0.12% chlorhexidine gluconate rinse (Peridex)
  o I suggest at least twice daily but, ideally, after meals and before bed
  o Side effect of staining teeth and dorsal tongue brown
    • Is reversible with professional dental cleaning
    • Can be minimized by keeping teeth clean (no plaque/calculus)
  o Proper use suggested: swish for 30+ seconds (timer) and then spit out; avoid eating/drinking/rinsing/brushing for at least 30 minutes after
Treatment for or Concern of Active ONJ

- Consider adding Nystatin oral solution 100,000 U/mL
  - 5 mL PO QID x 14 days; retain in mouth as long as possible, may spit out or swallow
- Systemic oral antibiotic, if symptomatic
  - I generally empirically use Augmentin 875/125 mg
  - Consideration for adding a fluoroquinolone and/or antifungal, if not effective
  - Consideration of Medrol dose pack, if severe acute pain and/or acute paresthesias/numbness of lower lip.
Treatment for or Concern of Active ONJ

- Consideration for conservative debridement of any loose/mobile sequestra
- Loose teeth within/surrounded by necrotic bone can be removed, if symptomatic
- Pain control/management
- Management of contributory systemic diseases, as applicable
Treatment for or Concern of Active ONJ

- For patients with advanced disease and good survival prognosis, can consider more definitive/aggressive surgical procedures, if needed.
  - Segmental mandibulectomy or maxillectomy
  - Flap tissues for coverage/reconstruction
  - Risks/benefit ratio balanced with patient’s other disease processes
  - Therefore, flaps tend to be more common for ORN patients (vs. MRONJ)
### MRONJ Staging (AAOMS)

<table>
<thead>
<tr>
<th>MRONJ† Staging</th>
<th>Treatment Strategies‡</th>
</tr>
</thead>
</table>
| **At risk category** No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates | • No treatment indicated  
• Patient education |
| **Stage 0** No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms | • Systemic management, including the use of pain medication and antibiotics |
| **Stage 1** Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection | • 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, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage | • Symptomatic treatment with oral antibiotics  
• Oral antibacterial mouth rinse  
• Pain control  
• Debridement to relieve soft tissue irritation and infection control |
| **Stage 3** 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 | • Antibacterial mouth rinse  
• Surgical debridement/resection for longer term palliation of infection and pain  
• Antibiotic therapy and pain control |

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† Exposed or probable bone in the maxillofacial region without resolution for greater than 8 weeks in patients treated with an antiresorptive and/or an antiangiogenic agent who have not received radiation therapy to the jaws.

‡ Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.
<table>
<thead>
<tr>
<th>Staging of MRONJ</th>
<th>Treatment Strategy</th>
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<tbody>
<tr>
<td><strong>At risk:</strong> No apparent necrotic bone in patients who have been treated with oral or intravenous bone-modifying agents</td>
<td>No treatment indicated</td>
</tr>
<tr>
<td>Patient education and reduction of modifiable risk factors</td>
<td></td>
</tr>
<tr>
<td><strong>Increased risk:</strong> No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms</td>
<td>Symptomatic management, including the use of pain medication and close scrutiny and follow up</td>
</tr>
<tr>
<td>Refer to dental specialist and follow up every 8 weeks with communication of lesion status to the oncologist</td>
<td></td>
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<tr>
<td>Patient education and reduction of modifiable risk factors</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 1:</strong> Exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection</td>
<td>Antibacterial mouth rinse</td>
</tr>
<tr>
<td>Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist</td>
<td></td>
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<tr>
<td>Patient education and reduction of modifiable risk factors</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 2:</strong> Exposed and necrotic bone or fistulas that probe to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage</td>
<td>Symptomatic treatment with oral antibiotics and topical antibacterial rinse</td>
</tr>
<tr>
<td>Pain control</td>
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<tr>
<td>Debridement to relieve soft tissue irritation and topical antibacterial rinse</td>
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</tr>
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<td>Pain control</td>
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<td>Surgical debridement or resection for long-term palliation of infection and pain</td>
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**NOTE:** Adapted from Ruggiero et al. 7

Abbreviation: MRONJ, medication-related osteonecrosis of the jaw.

*Exposed or probable bone in the maxilofacial region without resolution for longer than 8 weeks in patients who were treated with an antiresorptive or an angiogenic inhibitor and who have not received radiation therapy to the jaws.*

*Regardless of disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. Extraction of symptomatic teeth within exposed necrotic bone should be considered because it is unlikely that extraction will exacerbate the established necrotic process.*
Other Treatments

- These treatments have no strong evidence to support their routine use
- They require further clinical trials but may be considered in some circumstances as there have been some reports of success
  - And there are some ongoing trials... not at Moffitt

- Hyperbaric oxygen (HBO) therapy
- PENTO[CLO] therapy: Pentoxifylline, Tocopherol, Clodronate
- Teriparatide (recombinant parathyroid hormone) for MRONJ
- Leukocyte-rich vs. Platelet-rich fibrin growth factors/membranes
- Low-level laser treatment
- Manuka Honey
Resources
Resources for Providers

References
References


• Oral health management of patients at risk of medication-related osteonecrosis of the jaw. NICE accreditation. 2017.

• Ikesue H, Doi K, Morimoto M, et al. Switching from zoledronic acid to denosumab increases the risk for developing medication-related osteonecrosis of the jaw in patients with bone metastases. Canc Chemo Pharm, 2021.


Questions?

Thank you!