American Association or Oral and Maxillofacial Surgeons' (AAOMS) Position Paper on MRONJ-2022 update (Dr. Jacobson's summary)

- Medications prescribed for dental and medical conditions have potential side effects
- Complications can be significant, alters wound healing capacity
- **Medications**
  - Bisphosphonates:
    - antiresorptive medications for cancer-related conditions, including hypercalcemia of malignancy, spinal cord compression, and pathologic fx associated with bone metastases of solid tumors (e.g. breast, prostate, lung cancer) and multiple myeloma.
    - Prevention of osteoporosis-related fx in pts with osteoporosis and osteopenia
      - Oral: alendronate (Fosamax), risedronate (Actonel)
      - Parenterally: zoledronic acid (Reclast), ibandronate (Boniva)
    - Paget's disease of bone and osteogenesis imperfecta
    - Denosumab: receptor activator of nuclear factor kappa-B ligand (RANK-L), effects on bone remodeling mostly diminished within 6 months
    - Denosumab (Prolia) subcutaneously every 6 moths
    - Denosumab (Xgeva) monthly
    - Romosozumab (monoclonal antibody for fx prevention osteoporotic women) subcutaneous
- **MRONJ definition**
  - Current or prev tx with antiresorptive tx or in combination with immune modulators or antiangiogenic medications
  - Exposed bone, or bone that can be probed though an intraoral or extraoral fistula in the maxillofacial region that has persisted for > 8 weeks
  - No hx of radiation therapy to jaws or metastatic dz to the jaws
- **Staging**
  - **Patients at-risk:** no necrotic bone in asymptomatic pts who have been tx with IV or oral antiresorptive therapy
  - **Stage 0 (nonexposed bone variant):** no exposed bone, have nonspecific symptoms of clinical and radiographic findings. Dull aching bone pain, sinus pain, altered neurosensory function, loosening of teeth, intra/extraoral swelling, radiographic bone loss, changes to trabecular pattern sclerotic bone, no new bone in extraction sockets, regions of osteosclerosis, thickening or obscuring of PDL
  - **Stage 1:** exposed and necrotic bone or fistula that probes to bone in pts that are asymptomatic with no evidence of infection/inflammation. May have radiographic findings from Stage 0.
  - **Stage 2:** exposed and necrotic bone or fistula that probes to bone, with evidence of infection, and one or more of the following: exposed necrotic bone beyond the region of alveolar bone (i.e. inferior border and ramus in the mandible, maxillary sinus, zygoma), pathologic fx, extraoral fistula, oral antral/oral-nasal communication, osteolysis extending to the inferior border of the mandible or sinus floor
- **Differential diagnosis**
  - Alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology, odontalgia, atypical neuralgias, fibro-osseous lesions, sarcoma, chronic sclerosing osteomyelitis, tmj disorders. Delayed healing, exposed bone, or sequestra (ie osteonecrosis)

  - Antiresorptive naïve have had necrosis linked to bacterial, viral, fungal infections, trauma, smoking, steroids, immunocompromised, autoimmune diseases, diabetes, chemotherapy
- **Poor oral hygiene** is associated with MRONJ
- **Pathophysiology:** MRONJ is multifactorial, multiple hypothesis including: bone remodeling inhibition, presence of inflammation (periodontal, periapical, poor oral hygiene), angiogenesis inhibition (decreased vascularity of periodontal tissue), innate or acquired immune dysfunction, genetic factors.
- **Risk Factors for MRONJ**
  - **Antiresorptive medications** (i.e. bisphosphonates and Denosumab)
  - **Therapeutic indication:**
    - Malignancy <5%
    - Osteoporosis <0.5%
  - **MRONJ among cancer patients**
    - Placebo group 0 - 0.7%
    - Zoledronate: <5% (range 0 – 18%)
    - Denosumab: <5% (range 0 – 6.9%)
  - **Other families of medications,** but few cases (e.g. isolated case reports): tyrosine kinase inhibitors (TKIs) such as sunitinib, monoclonal antibodies (bevacizumab), fusion proteins (aflibercept), mTOR inhibitors (everolimus), radiopharmaceuticals (radium 223), selective estrogen receptor modulators (raloxifene), and immunosuppressants (methotrexate and corticosteroids)
  - **MRONJ among osteoporosis patients**
    - Bisphosphonates
      - Placebo 0 – 0.2%
      - Risk 0.02 – 0.05%
      - IV zoledronate: ≤0.02% (<2 per 10,000)
      - Oral bisphosphonates ≤0.05% (≤5 per 10,000)
    - RANK-L inhibitors
      - Denosumab 0.04% - 0.3%
      - Romosozumab 0.03 – 0.05%
  - **MRONJ risk among patients with nonmalignant bone disease**
    - Denosumab 0.7 – 5% (to manage aggressive giant cell tumors of bone)
    - Limited data on pediatric population for osteogenesis imperfect and other cond.
  - **Duration of medication therapy**
    - Denosumab, cancer patients, 0.5-0.8% 1 year, 1-1.8% 2 years, 1.3-1.8% 3 years
    - Zolendronate, cancer patients, 1.6-4% after 2 years, 3.8-18% > 2 years
    - Denosumab, 1.9% <24 months, 6.9% >24 months
    - Bisphosphonates for osteoporosis, mixed results. Duration may be a factor, risk is low.
  - **Local Factors**
    - Tooth extraction as predisposing event 62-82%
    - MRONJ among osteoporotic patients exposed to Bisphosphonates following a tooth extraction 0 – 0.15%
    - Osteoporotic patient exposed to Denosumab, risk after extraction is 1%
  - **Anatomic Factors:**
    - 75% mandible, 25% maxilla, 4.5% both jaws

        - Denture use increased risk for MRONJ among cancer pts with zoledronate, ibandronate, or pamidronate, a 2-fold increase
            - Posterior lingual plate common site
    - **Concomitant oral disease**
        - Periodontal disease or periapical pathology
        - Spontaneous
    - **Demographic and systemic factors and other medications**
        - Females (e.g. osteoporosis, breast cancer)
        - <24 yo tx with antiresorptives for benign bone diseases have not shown any risk (small sample, more studies needed)
        - Corticosteroids
        - Corticosteroids may increase risk with antiresorptive
        - Comorbidities: anemia, diabetes, cancer
        - Tobacco (inc risk in some studies, not in others)
        - No comorbidity
        - Summary: risk of MRONJ in cancer patients taking antiresorptive > osteoporosis patients taking antiresorptive
- **Prevention of MRONJ**
    - Surgery before initiating therapy
    - Preoperative and postoperative antibiotics and antimicrobial mouth rinses
    - Primarily closing extraction sites
    - Maintaining good oral hygiene
    - Maximizing patient health: tobacco cessation, diabetes control
    - Multidisciplinary team approach
- **Optimization of oral health**
    - Screen patients
    - Identify acute infection and potential infection sites
    - Drug holiday = controversial, different conclusions to support or refute
    - Special concern for RANKL inhibitors in osteoporosis patients.
        - Several studies rebound increase in bone resorption after discontinuing Denosumab increasing risk of multilevel vertebral factures
        - If Denosumab is suspended, dentoalveolar surgery can be completed 3-4 months following the last dose, and reinstitute 6-8 weeks postsurgery.
- Bone turnover markers: none are validated for clinical decision making
- Other biomarkers: not yet validated
- **Prevention Strategies**
    - **Pts scheduled for antiresorptive treatment for cancer therapy**
        - Educate patient, majority of MRONJ occur after extraction but can occur spontaneously
        - Optimize dental health
        - Comprehensive dental exam
        - Extract non-restorable teeth and those with poor prognosis
        - Delay antiresorptive treatment until extraction sites have mucozalized or until adequate osseous healing
    - **Pts scheduled for antiresorptive treatment for osteoporosis**
        - *Lower risk/urgency than cancer therapy.*
        - Educate patient, majority of MRONJ occur after extraction but can occur spontaneously

        - Optimize dental health
    - **Asymptomatic pts receiving antiresorptive therapies for cancer**
        - Good oral hygiene
        - Avoid surgery if possible (eg coronectomy and RCT)
        - If unavoidable (eg fractured tooth, advanced periodontal dz) inform pt of the risks
        - Avoid dental implant placement in oncology patients receiving IV antiresorptive therapy or antiangiogenic medications
    - **Asymptomatic pts receiving antiresorptive therapies for osteoporosis**
        - 0.02-0.04% for BP and 0.3% for Denosumab
        - Dentoalveolar surgery is not contraindicated
        - Dental implants studies have conflicting results, informed consent and long-term follow up
- **Treatment Strategies**
    - For all stages
    - **Nonoperative therapy**
        - Patient education, reassurance, pain control, control of secondary infection to allow for sequestration of exposed, necrotic bone
        - 3D imaging to identify forming or fully formed sequestra (piece of dead bone that's become separated)
            - Radiographic assessment with panoramic AND CT (CBCT) or MRI or PET/CT scan
        - Stage 1: CHLX rinse
        - Stage 2: antibiotics for symptom control
        - Exfoliation of exposed necrotic bone will often result in disease resoluation
        - Stage 2 or 3: if a poor surgical candidate, nonoperative therapies may be indicated.
        - Little evidence that adjunctive therapy such as hyperbaric oxygen or ozone therapy lead to MRONJ resolution, not recommended
    - **Operative therapy**
        - All stages
        - In attempt to reduce progression
        - Segmental or marginal resection of the mandible and partial maxillectomy
            - Beyond necrotic bone to vital, bleeding bone
        - Active clinical and radiographic surveillance with all stages
        - Failure of nonoperative therapy, early operative is recommended.
        - If progressive dz or advanced dz, surgical resection without nonoperative measures first