MRONJ, ORN

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OUTLINE

- MRONJ
  - Causes
  - Pathophysiology
  - Risk factors
  - Treatment goals/options
- ORN
  - Prevention
  - Treatment

American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update

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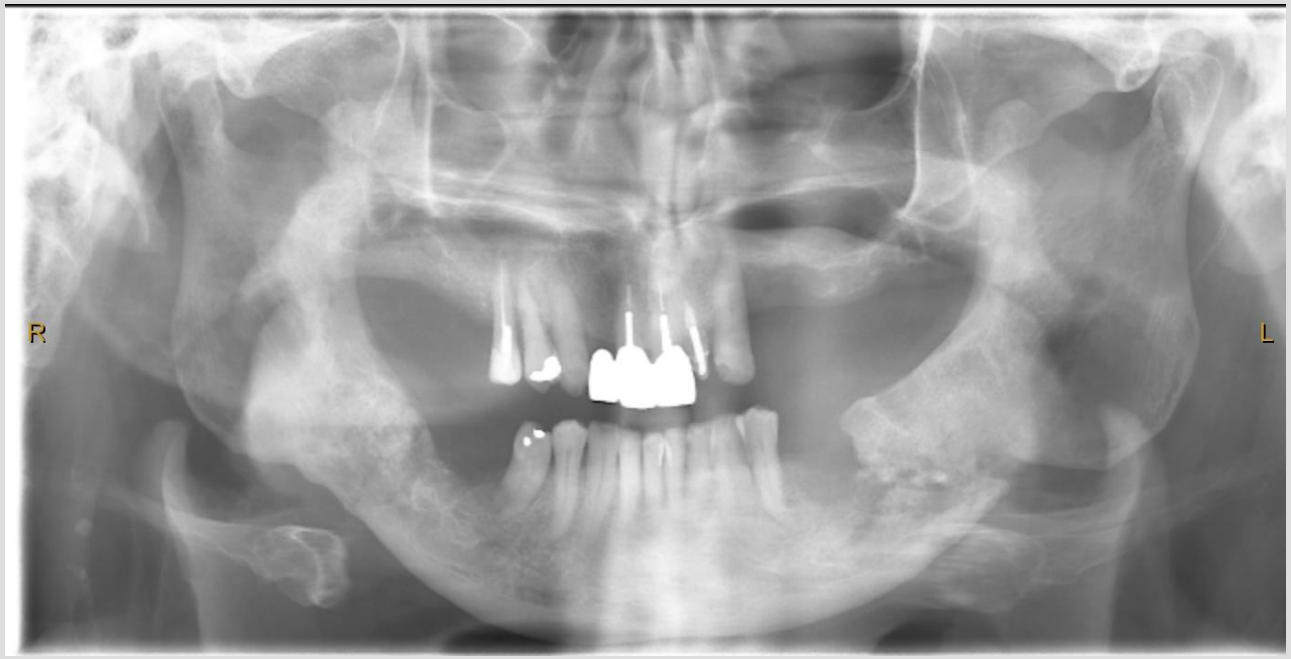

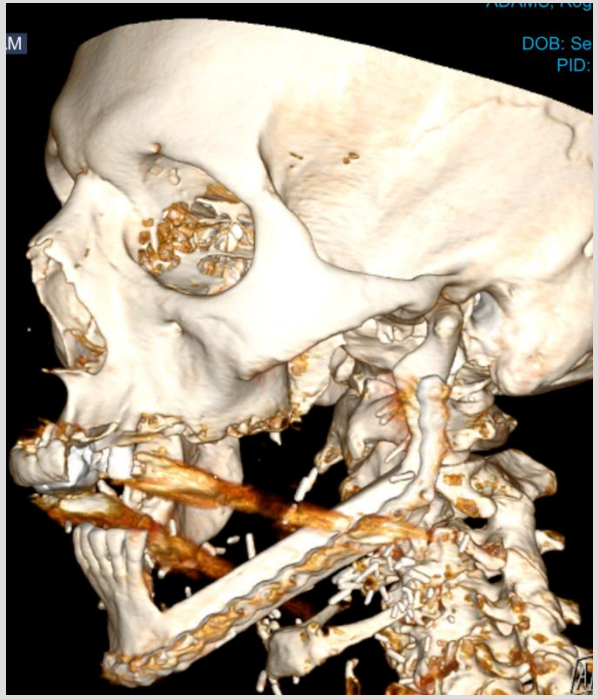

WHAT IS MRONJ

- (1) A breach in oral mucosa leading to exposed bone (or bone that can be probed through intra/extraoral fistula) that fails to heal in 8 weeks in someone with a (2) history of receiving antiresorptive therapy and (3) no previous head and neck radiation

Stages of MRONJ (AAOMS)	Exposed or necrotic bone	History and clinical findings
Stage 0	No clinical evidence	Non-specific clinical and radiographic findings
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone	Asymptomatic with no evidence of infection
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone	Associated with infection, Pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Exposed and necrotic bone, or fistulae that probes to bone	Pain, infection, and one or more of the following: • Exposed necrotic bone extending beyond the alveolar bone region resulting in pathological fracture • Extraoral fistula, oro-antral or oro-nasal communication • Lytic changes extending to the lower border of the mandible or sinus floor

Notani et. al classification for ORNJ	Clinical features
Type I	ORNJ confined to dentoalveolar bone
Type II	ORNJ limited to dentoalveolar bone or mandible above the inferior canal or both
Type III	ORNJ involving the mandible below the inferior dental canal or pathological fracture or skin fistula

Epstein et. al classification for ORNJ	Clinical features
Type I	Resolved, healed; a. No pathologic fracture, b. Pathologic fracture
Type II	Chronic persistent (nonprogressive); a. No pathologic fracture, b. Pathologic fracture
Type III	Active progressive; a. No pathologic fracture, b. Pathologic fracture

CAUSALITY

- Well-known that MRONJ is rare, multifactorial, and patients exist with same clinical presentation and no exposure to antiresorptive medication
  - Can be linked to infections, trauma, smoking, steroids, autoimmune disease, diabetes, chemotherapy
  - Many patients receiving antiresorptives have other comorbidities, which are likely exacerbating or contributing factors
- Definitive causality remains difficult task to prove + many confounding variables make incidence and prevalence difficult to estimate

BISPHOSPHONATES

- Pyrophosphate analogues
- Indications:
  - Prevention and treatment of postmenopausal and steroid-induced osteoporosis
  - Paget's diseases of bone
  - Hypercalcaemia of malignancy, multiple myeloma
  - Bony metastases (e.g. breast, prostate, lung)
  - Potential to improve cancer-specific survival controversial, but significant positive effect on QOL

BISPHOSPHONATES MECHANISM

- Pyrophosphate analogues that bind to hydroxyapatite binding sites on surface of bone tissue, subsequent uptake by osteoclasts impairs bone resorption ability
- Non-nitrogen-containing bisphosphonates
  - Etidronate, tiludronate
  - Metabolised intracellularly and inhibit ATP-dependent enzymes, resulting in osteoclast apoptosis
- Nitrogen-containing (more potent)
  - Alendronate, risedronate (oral), pamidronate, ibandronate, zoledronic acid (parentally)
  - Binds and blocks enzyme (farnesyl pyrophosphate synthase) needed for attaching osteoclast to bone surface = osteoclast detaches, impairs bone resorption

ADVERSE EFFECTS

- Hypocalcaemia and hypophosphatemia (usually transient and mild)
- ONJ
- Atypical fractures (particularly of the femur)
- MSK pain
- AF
- Renal impairment
- Ocular inflammation and visual disturbances
- Oral bisphosphonates
  - Oesophageal inflammation: Swallow with water and maintain upright for 30 mins
- IV bisphosphonates
  - Acute-phase reaction with flulike symptoms 24-72 hours after administration

DENOSUMAB

- RANK ligand inhibitor
- Monoclonal antibody against RANK ligand (RANK-L - a receptor activator of nuclear factor kappa B ligand; a ligand of osteoclast receptors)
  - Reversibly inhibits bone resorption by reducing osteoclast formation and differentiation and increasing apoptosis
  - Targets the RANKL by mimicking osteoprotegerin
  - In contrast to BPs, RANKL inhibitors do not bind to bone - effects on bone remodeling are mostly diminished within 6 months of cessation
- Indications:
  - Significant reduction in risk of vertebral, nonvertebral and hip fractures in osteoporotic patients when SC 6 monthly
  - Effective in reducing skeletal-related events related to metastatic bone disease from solid tumours when administered monthly
  - Also proven efficacy in treatment of giant cell tumours and fibrous dysplasia

BONE CELLS - OSTEOBLASTS

- Derived from mesenchymal osteoprogenitor (stem) cells located under the periosteum in the developing bone, and in medullary space later in life
- Secrete osteoid to form an extracellular organic matrix on which hydroxyapatite crystals deposit + regulate its mineralisation
- As bone-forming activity nears completion, some osteoblasts become enclosed in lacunae as osteocytes
- RANKL
  - Expressed on osteoblasts and marrow stromal cells
  - Binds to receptor RANK (receptor for activation of nuclear factor kappa B) on macrophages (osteoclast precursor)
    - RANKL + RANK activates transcription factor NF-kB essential for
      - Differentiation osteoclasts
      - Suppression of osteoclast apoptosis (so they survive)
- Osteoprotegerin
  - Secreted by osteoblasts
  - Soluble, high-affinity decoy ligand for RANKL, which restricts osteoclast differentiation
- Express receptors for PTH, calcitriol and other promoters of bone resorption
  - Osteoblasts promote osteoclast differentiation via PTH-activated expression of cell surface RANKL - binds to RANK on immature osteoclasts and triggers differentiation - and downregulate osteoprotegerin

OSTEOCYTES

- Major cell type of mature bone, distributed throughout matrix and interconnected by dendritic processes to form a complex network
- Derived from osteoblasts that have become enclosed within the rigid matrix
- Help to control calcium and phosphate levels, detect mechanical forces, and translate them into biologic activity (mechanotransduction)
- Secretes RANKL to activate osteoclasts
- Produces Sclerostin which inhibits osteoblasts

OSTEOCLASTS

- Large, specialised multinucleated macrophages located on the surface of bone
- Responsible for structural changes - decalcify and remove bones - resorb bone
- Differentiate from myeloid stem cells via macrophage-colony-forming units
  - Regulated by macrophage-colony stimulating factor (secreted by osteoblasts), and RANKL (expressed by osteoblasts)
- Responsible for the local removal of bone during growth and remodelling
  - Dissolve bone minerals by secreting acid and neutral proteases (predominantly matrix metalloproteases)
  - Stimulated to resorb bone by signals from local cells (osteoblasts, macrophages, lymphocytes) and PTH, calcitriol
    - Calcitonin, produced by C cells of thyroid, reduce osteoclast activity

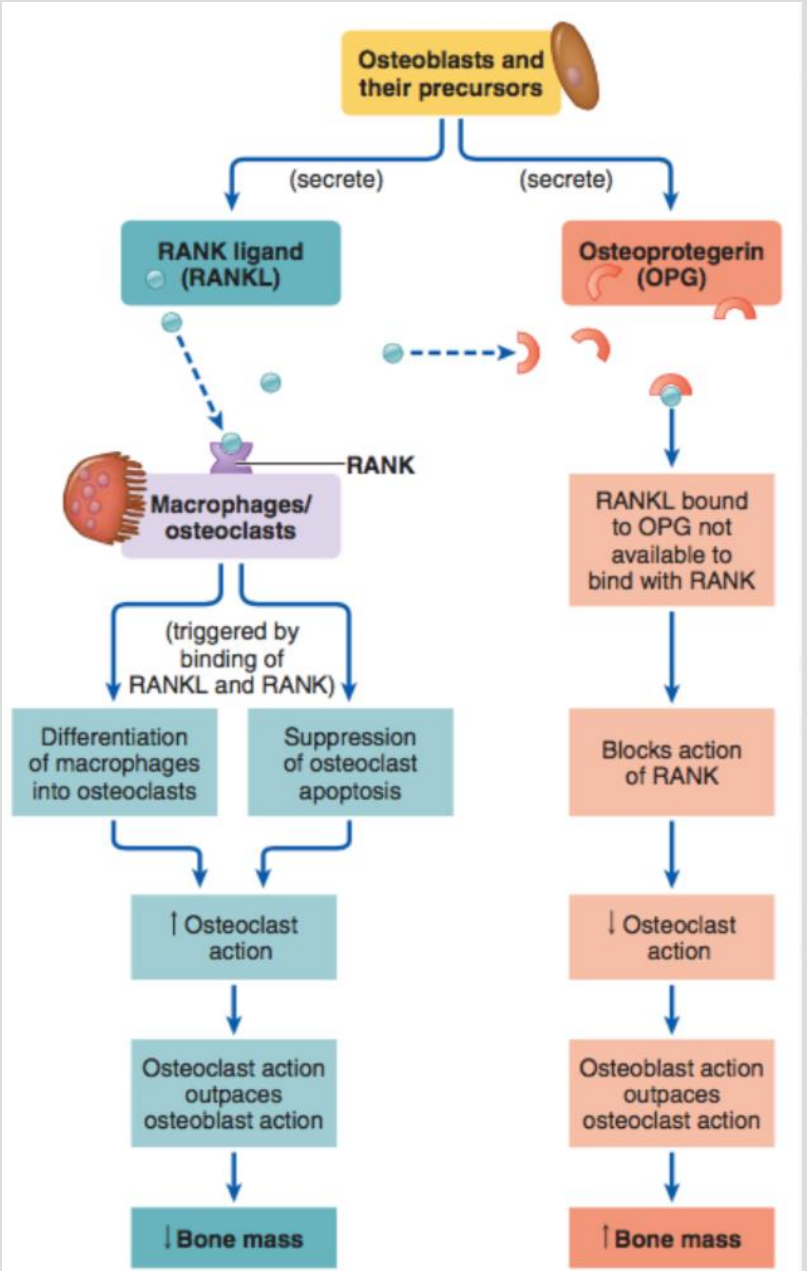

FIGURE 19-22 Role of osteoblasts in governing osteoclast development and activity.

DENOSUMAB (AGAIN)

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MRONJ PATHOPHYSIOLOGY

Multifactorial process, and likely that multiple hypotheses can explain overall pathophysiology

- *Bone Remodelling Inhibition*
- *Inflammation or Infection*
- *Angiogenesis Inhibition*
- *Innate or Acquired Immune Dysfunction*
- *Genetic Factors*

BONE REMODELING INHIBITION

- Leading hypothesis
- Antiresorptive medications have direct effects on osteoclast formation, differentiation or function
  - Animal jaws demonstrate absent osteoclasts around alveolar bone of DMB-treated mice
  - Human bone specimens show increased number of non-functional osteoclasts surrounding necrotic bone in BP-treated patients
- Animal studies evaluating withdrawal of BPs or DMB further highlight importance of remodelling in MRONJ prevention and resolution
  - Rodents with established ONJ failed to resolve when antiresorptives were withdrawn
  - BUT discontinuing DMB (not BPs) prior to extraction successfully prevented MRONJ development in rats

INFLAMMATION OR INFECTION

- Most studies report tooth extraction as major inciting event for MRONJ, but is clear that most had pre-existing periodontal or periapical disease
- Presence of inflammatory cytokines at site of MRONJ support strong role of inflammation
- Evidence of increased systemic inflammation and its contribution to MRONJ - mice with experimentally-induced RA had more severe MRONJ with increased bone resorption, more pronounced radiographic features, intense local inflammatory infiltrate, and larger areas of histologic necrosis
- Presence of bacteria on exposed necrotic bone also contributes to disease severity
  - Poor OH and biofilm presence associated with MRONJ development, and OH maintenance and dental prophylaxis before initiating antiresorptive therapy can decrease MRONJ prevalence
  - Clinical treatment protocols to reduce biofilm and eradicate infection have emerged as important alternatives to debridement and resection

ANGIOGENESIS INHIBITION

- BPs such as zoledronic acid directly inhibit angiogenesis in vitro and in vivo, and animal models demonstrate decreased vascularity in sites of MRONJ and decreased microvessel numbers during early stages of healing
  - BPs also inhibit angiogenesis normally seen during healing of sockets
  - Both BPs and DMB shown to decrease arterial area, venous area, and overall vascularity of periodontal tissues during early and late MRONJ development
- Antioangiogenic medications (VEGF inhibitors, tyrosine kinase inhibitors, immunomodulatory drugs) associated with MRONJ (much lower incidence than ARs)
  - MM patients on both antiresorptive and antiangiogenic medications have a higher MRONJ prevalence

INNATE OR ACQUIRED IMMUNE DYSFUNCTION

- Well-known that patients with medical comorbidities (diabetes, RA, immunocompromised state) at significantly higher risk of MRONJ with or without exposure to antiresorptive agents
- Replenishing area of nonhealing MRONJ lesions with mesenchymal stem cells to overcome immune dysfunction is potential area of therapeutic interest
  - Preclinical studies demonstration healing or prevention of MRONJ lesions after systemic infusion with adipose or bone marrow-derived MSC

GENETIC FACTORS

- Increasing evidence supporting role of sing-nucleotide polymorphisms associated with MRONJ
  - Located within gene associated with either bone turnover, collagen formation or metabolic bone diseases
- Other genes reported to increase MRONJ risk through their role in angiogenesis, bone remodelling and immune responses e.g. PPAR gamma, CYP2C8 and others
- Overall, current studies document either a weak or no association between genetic factors measured and risk for MRONJ

RISK FACTORS

- Medication-related
  - Cancer patients
  - Osteoporosis patients
  - Non-malignant bone disease
- Local factors
- Demographic and systemic factors

MEDICATION-RELATED – CANCER PATIENTS

- Risk of MRONJ is higher in malignancy group (<5%) compared to osteoporosis group (<0.05%)
- MRONJ risk among cancer patients
  - Risk of MRONJ among cancer patients exposed to zoledronate clusters <5%, ranges from 0-18% (may be explained by varying durations of follow-up)
    - 2-10 times higher than cancer patients treated with placebo
  - Risk of MRONJ with denosumab ranges from 0-6.9% with most studies <5%
    - Risk is comparable to zoledronate
- Numerous other families of medications implicated as risk factors but evidence is level 5 (isolated case reports, mini case series) - identifying single medication as being aetiologic agent for MRONJ unlikely
  - TKIs (sunitinib), monoclonal antibodies (bevacizumab), fusion proteins (aflibercept), mTOR inhibitors (everolimus), selective oestrogen receptor modulators (raloxifene), immunosuppressants (methotrexate and corticosteroids)

MEDICATION-RELATED – OSTEOPOROSIS PATIENTS

- Bisphosphonates
  - Osteoporosis clinical trials - placebo = 0-0.2%; BPs = 0.02-0.05%
  - IV zoledronate risk <0.02% (e.g. 2 per 10,000)
  - Oral bisphosphonates risk <0.05%
- RANK-L inhibitors
  - Denosumab - risk reported to be 0.3% (range 0.04-0.3) after 10 years of follow-up (significantly higher than BPs)
  - Romosuzumab (0.03-0.05%) comparable to aledronate (0.05%) - additional research needed to refine association and risk estimate for MRONJ

NON-MALIGNANT BONE DISEASE

- DMB for management of aggressive giant cell tumours
  - Risk of MRONJ in two studies ranged from 0.7-5%
  - Comparable to risk of MRONJ in DMB for malignancies (0-6.9%)
- Very limited data for MRONJ in paediatric population for osteogenesis imperfecta
  - One SR of 486 subjects found no cases of MRONJ (small sample sizes)

DURATION OF THERAPY

- Duration of therapy
  - Recent SR by Ng et al, risk of MRONJ among cancer patients treated with zoledronate was 1.6-4% after 2 years, and 3.8 to 18% >2 years
    - DMB risk was 1.9% <2 years, and 6.9% >2 years of exposure

RISK FACTORS

- Medication-related
  - Cancer patients
  - Osteoporosis patients
  - Non-malignant bone disease
- Local factors
  - Dento-alveolar operations
  - Anatomic factors
  - Concomitant oral disease
- Demographic and systemic factors

LOCAL FACTORS - DENTO-ALVEOLAR OPERATIONS

- Most common identifiably predisposing factor for MRONJ
  - Tooth extraction cited as predisposing event in 62-82% of patients with MRONJ
- **Current estimates for risk of MRONJ post exo**
  - Osteoporotic patients exposed to BPs 0-0.15%, DMB 1%
  - Cancer patients exposed to BPs 1.6-14.8% - cluster between 1 and 5%, similar to estimates of ORN following extraction in irradiated patients
- Risk of MRONJ for other dentoalveolar operations such as implant placement and endo or perio procedures is unknown
  - AAOMS cautions these procedures in cancer patients exposed to ARs and recommends osteoporosis patients be informed of potential risks, albeit low, including MRONJ, early and late implant failure (described in case reports and clinical trials)
    - Early = implant surgery-triggered
    - Late = implant presence-triggered
      - Reviews show majority of implant-related necrosis were late and often at sites of implants placed prior to BPs - common presentation was an en bloc failure where osseointegration of implant is maintained within sequestrum

LOCAL FACTORS - ANATOMIC FACTORS

- More likely to appear in the mandible (75%) than maxilla (25%) but can appear in both (4.5%)
- Denture use associated with increased risk for MRONJ among cancer patients exposed to zoledronate

LOCAL FACTORS - CONCOMITANT ORAL DISEASE

- Pre-existing inflammatory dental disease (perio/periapical pathology) cited as a significant risk factor
- Among cancer patients with MRONJ, pre-existing dental disease was a risk factor among 50%
- Given common treatment is extraction, pre-existing disease may confound the relationship between exo and risk for MRONJ (did it expose it or was it the precipitating event)

DEMOGRAPHIC/SYSTEMIC FACTORS

- Sex
  - Higher prevalence in females - likely reflection of underlying disease for which agents prescribed for e.g. osteoporosis, breast cancer
- Age
  - <24 treated with ARs for benign bone disease have not demonstrated any risk for MRONJ after extended duration of therapy
    - SR studies had small sample sizes and lack of other MRONJ-related risk factors
- Corticosteroids associated with increased risk, especially when given in conjunction with Ars
- Comorbid conditions inconsistently reported to increase risk (e.g. anaemia, diabetes, cancer type)
- Tobacco use variably reported as risk-factor

RISK FACTOR SUMMARY

- Risk of MRONJ significantly greater in cancer patients compared to OP
- Risk of MRONJ in OP continues to be very low regardless of drug type (BPs, DMB, romoszumab) or dosing schedule

HOW TO ASSESS RISK/WHEN TO REFER

- Risk based on why they're on it, dose and risk, duration of therapy, concomitant drug use, surgical insult (eg number of teeth, perio, mx/md)

MANAGEMENT

- Treatment goals
- Prevention
- Treatment strategies
  - Non-operative
  - Operative

TREATMENT GOALS

- Prevention
- Prioritisation and support of continued oncologic treatment
- Prioritisation and support of continued bone health and prevention of fragility fractures
- Preservation of life through
  - Patient education and reassurance
  - Control of pain
  - Control of secondary infection
  - Prevention of extension of lesion and development of new areas of necrosis

PREVENTION

- Need to recognise importance of coordinated dental care and pretreatment management in minimising risk of MRONJ - emphasis on multidisciplinary approach
- Optimisation of oral health
  - Robust level of support for early screening and initiation of appropriate dental care prior to antiresorptive therapy
  - Treatment planning should include a thorough examination and radiographic assessment
    - Identify both acute infection and sites of potential infection
    - Need to consider patient motivation and education, fluoride application, chx rinses, tooth mobility, perio, root fragments, caries, periapical pathology, edentulism and denture stability (especially posterior lingual flange region)
  - If systemic conditions permit, initiation of antiresorptive therapy should be delayed until dental health is optimised
    - Similarly, if conditions permit, therapy should be delayed until surgical sites have mucosalised or there is adequate osseous healing

PREVENTION

- Cessation of at-risk medication therapy (drug holiday) prior to
  - Practice of drug holidays to mitigate MRONJ risk accepted and recommended by several international professional societies, but evidence to support or refute such positions remains inconclusive
    - Since few events are reported, RCTs provide insufficient data to create sound treatment protocols
  - Concern regarding a drug holiday is the loss of efficacy of antiresorptive therapy with development of skeletal-related events and fragility fractures
    - Need to consider disease-related risk (cancer vs OP), drug frequency, duration of therapy, comorbidities, other medications, degree of underlying dental pathology, extent of surgery
  - Special concern should be considered for suspending RANKL inhibitors in OP patients - several studies demonstrate a rebound increase in bone resorption following cessation, resulting in increased risk of multilevel vertebral fractures
    - Planned surgery can be completed 3-4 months following last dose when level of osteoclast inhibition is waning, then reinstituted 6-8 weeks post surgery
- Bone turnover markers
  - No biomarkers are validated for clinical decision-making

TREATMENT STRATEGIES

- Decision of nonoperative vs operative needs to be patient-specific
  - Risk-benefit ratio (including QOL with current symptomology)
  - Ability to perform good wound care to prevent infection and disease spread
  - Morbidity from major surgical procedure
  - Oral function or dental rehab after marginal or segmental
- Radiographic imaging of utmost importance in evaluation of lesions
  - 3D imaging can identify forming or fully formed sequestra and potentially decrease invasiveness of surgery

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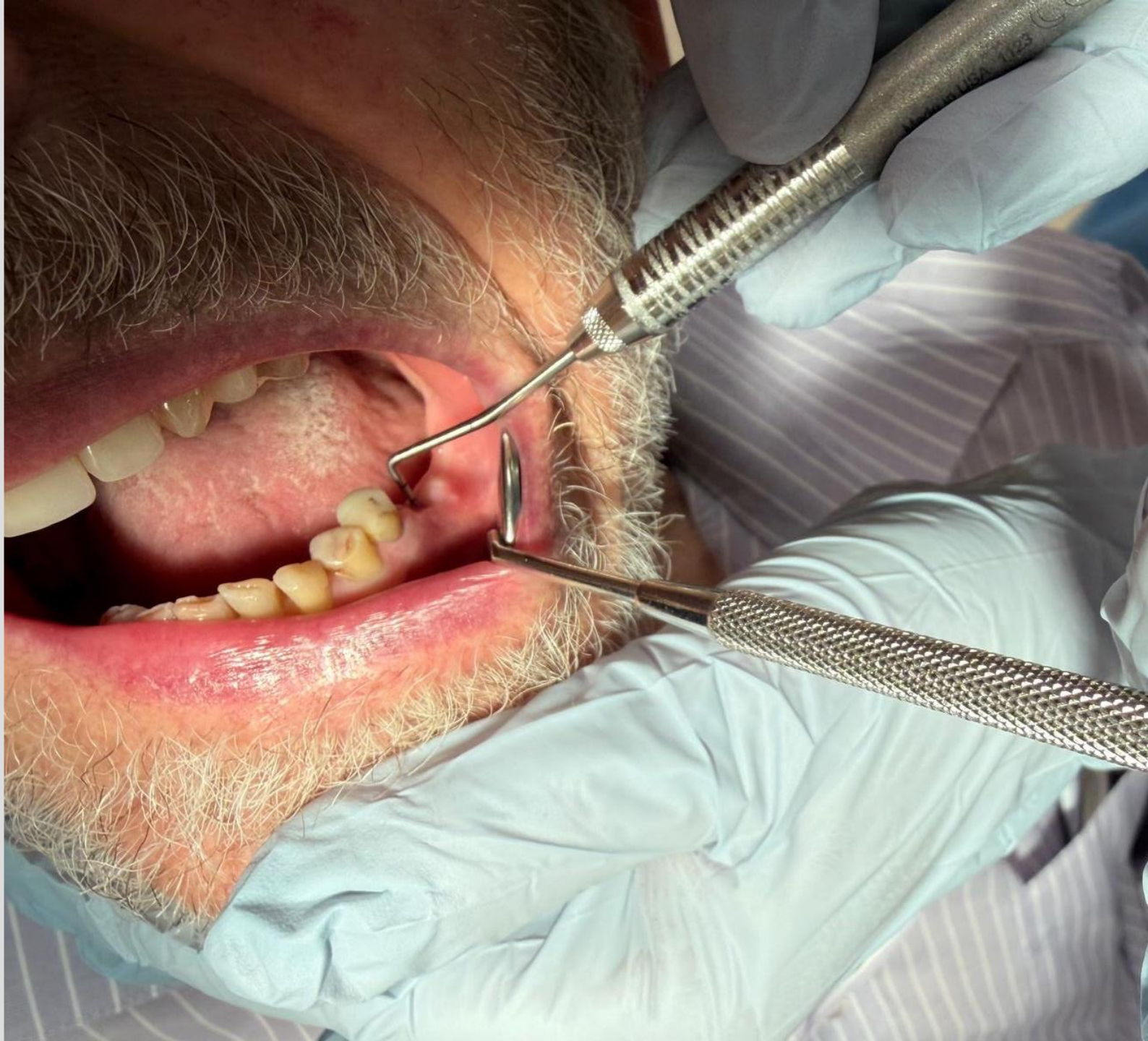
DENOSUMAB FOR
OSTEOPOROSIS



NON-OPERATIVE THERAPY

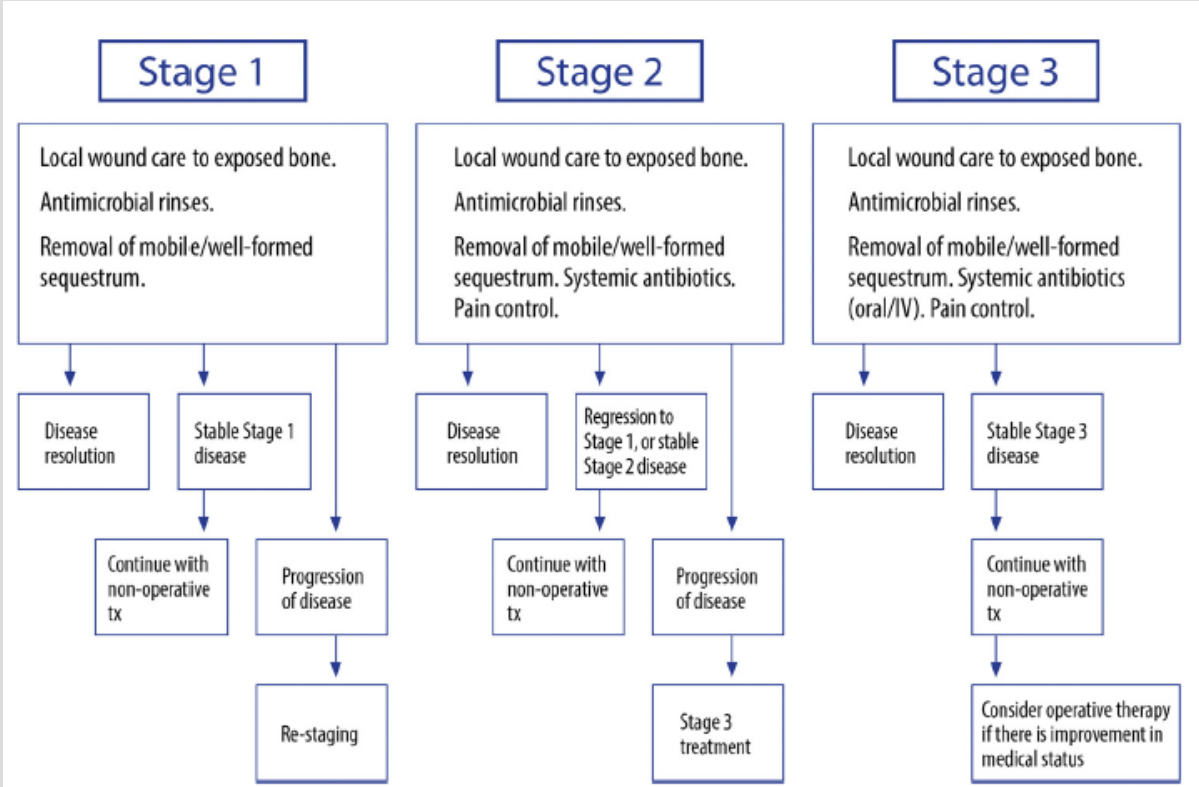


FIGURE 2. Non-operative therapies.

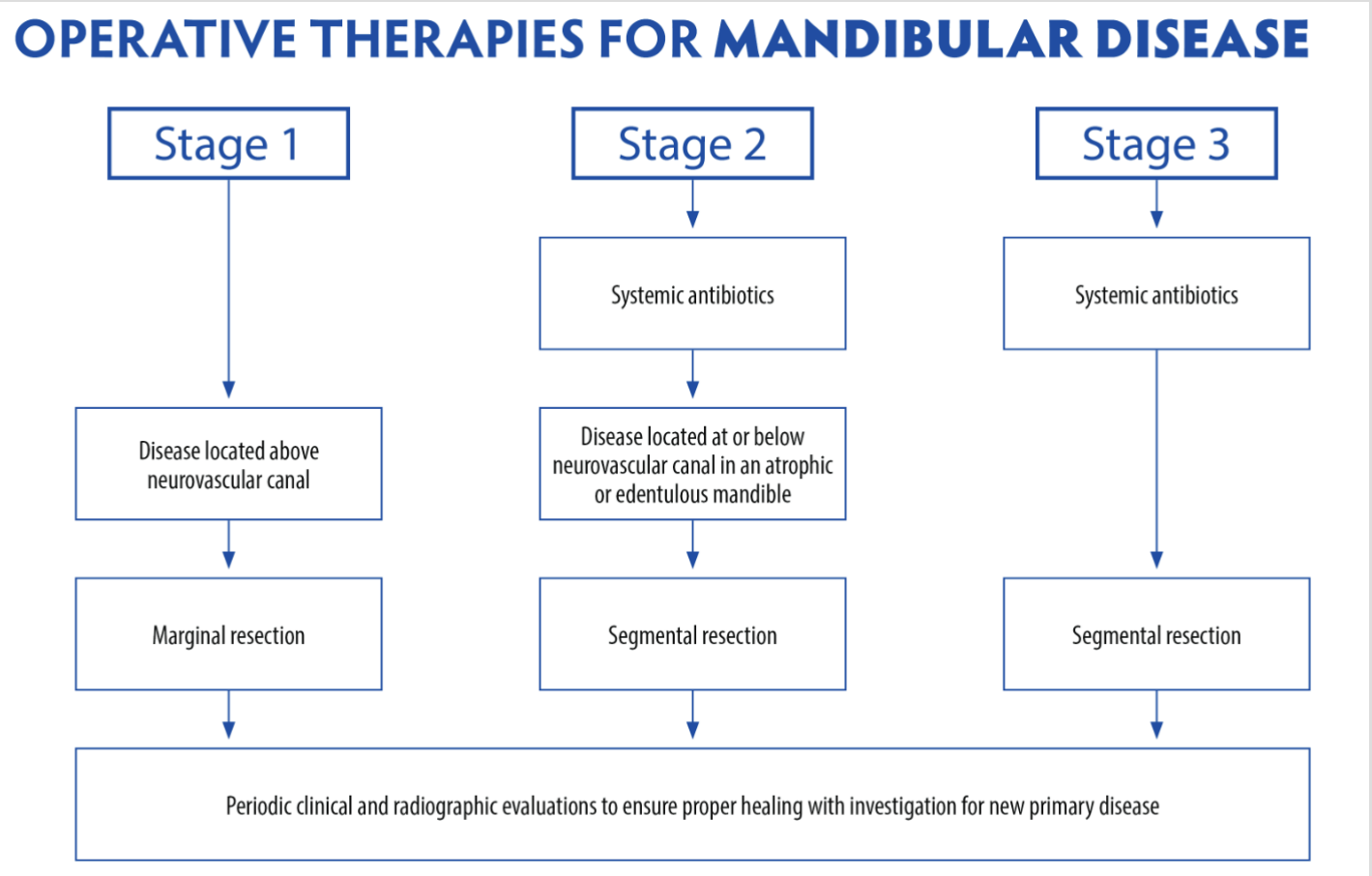
NON-OPERATIVE THERAPY

- Efficacy of nonoperative therapies is well documented in the literature and can be useful in all stages, especially where significant comorbidities preclude operative treatment
- Can result in stabilisation of disease or cure in earlier stages (sequestration and resolution)
- Heavy focus on patient education, reassurance, control of pain, control of secondary infection to allow for sequestration of exposed, necrotic bone
- Stage 1
  - Chlorhexidine wound care and improved OH to remove biofilm from necrotic surface
  - Surgery may not be indicated in absence of progression and adequate QOL
- Stage 2
  - Likely struggle with wound care, may require antibiotics for symptom control
- Little evidence to suggest use of adjunctive therapies, e.g. hyperbaric oxygen or ozone therapy, can lead to resolution
  - Use of vitamin E and pentoxifylline as an adjunct have been reported only in case studies
    - **Randomized, prospective, placebo-controlled trial** is underway
- Active clinical and radiographic surveillance is critical in all stages to monitor for signs of disease progression and offer early operative intervention

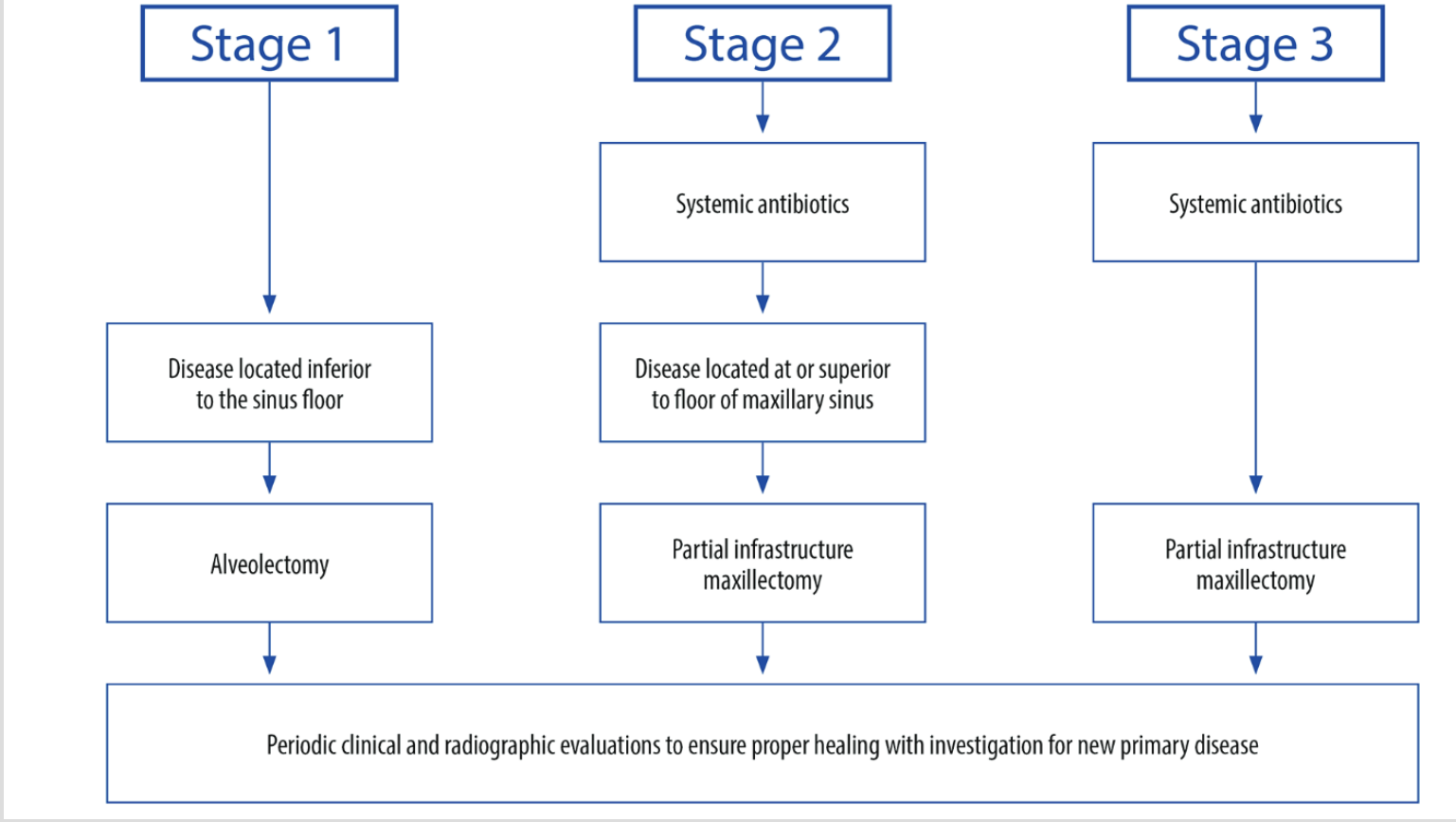
OPERATIVE THERAPY

- Increasingly reported as a viable option with high success rates for all stages of disease
  - Has demonstrated maintenance of mucosal coverage, improved QOL, and expedient resumption of antiresorptive therapy for all stages
  - Patients with progressive clinical or radiographic, r more advance disease at presentation, surgical resection should be performed without instituting prolonged nonoperative measures
- Segmental or marginal resection, and partial maxillectomy can be applied to patients with all stages
  - Require margins beyond the borders of necrotic bone to an area of vital, bleeding bone
- Control of comorbid conditions is paramount - physiologically compromised patients (e.g. distant metastases) may not respond favourably to resection and may develop refractory disease
- Benefit of drug holidays prior to has not been substantiated

OPERATIVE THERAPIES FOR MANDIBULAR DISEASE



OPERATIVE THERAPIES FOR MAXILLARY DISEASE



BREAK

- 15 minutes