

RANK-L Inhibitors and Drug Induced Osteonecrosis of the Jaw

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Disclosure

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The following potential conflict of interest relationships are germane to my presentation.

Equipment: None
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Consultant: None

Status of FDA devices used for the material being presented

NA/Non-Clinical

Status of off-label use of devices, drugs or other materials that constitute the subject of this presentation

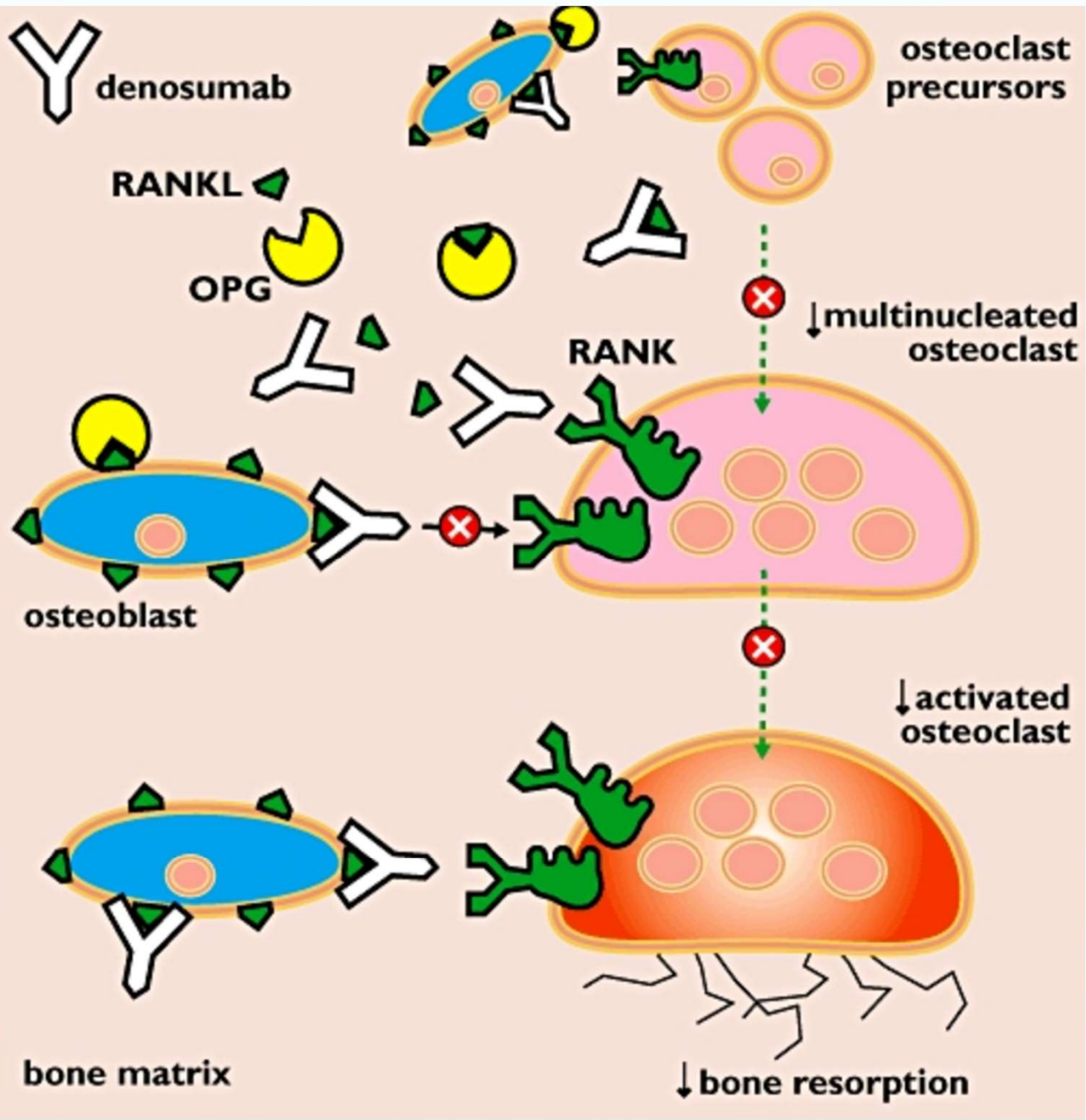
NA/Non-Clinical

Goals

- Review drugs and their clinical use
- Mechanism of Denosumab
- Drug Induced Osteonecrosis of the Jaw
- Prevention
- Treatment Options
- JMH/UMH Experience

What is Denosumab?

- Human monoclonal antibody to the receptor activator of nuclear factor kappa-B ligand (RANKL)
- Inhibits osteoclast formation
- Decreases bone resorption and renewal
- Increases bone mineral density
- Reduces risk of fracture



Denosumab (Low Dose) Indications

- Osteoporosis
 - Post-menopausal women
 - Men with increased risk of fractures
- Bone loss in men treated for prostate cancer
- Bone loss in adults with increased risk of fractures treated with 6 months use of corticosteroids (oral and IV)

Denosumab (Low Dose)

How it is Used

- Solution for injection
 - Prefilled syringe containing 60 mg denosumab
- Given once every 6 months (60 mg injection) subcutaneously in the thigh, abdomen, or arm
- Ensure calcium and vitamin D supplementation

Denosumab (High Dose) Indications

- Prevention of skeletal-related injuries in patients with multiple myeloma or bone metastases from solid tumors
- Adults and skeletally-mature adolescents with giant cell tumors of bone that are unresectable or where resection would incur significant morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonates

Denosumab (High Dose)

How it is Used

- Solution for injection
- Given once every 4 weeks (120 mg injection) subcutaneously
- Correct pre-existing hypocalcemia prior to therapy

Denosumab - Risks

- Osteonecrosis of the jaw
- Hypocalcemia
- Hypersensitivity reactions
- Atypical femoral fractures
- Musculoskeletal pain (bone, joint, muscle)
- Hypercalcemia following discontinuation in patients with Giant Cell Tumor of Bone and skeletally immature patients
- Multiple vertebral fractures following discontinuation

High vs Low Dose Denosumab

- The low dose is similar to alendronate and the high dose similar to IV bisphosphonates – due to increased potency

Denosumab vs Bisphosphonates

- Denosumab site of action → mature osteoclasts and precursors at all sites
 - Half-life 26 days in bone
- Bisphosphonates site of action → osteoclasts at resorbing bone sites and potentially bone marrow precursors
 - Half-life 11+ years in bone

Drug Induced Osteonecrosis of the Jaw

- Non-healing bone which has been exposed in the mandible or maxilla that persists for >8 weeks in the setting of a systemic drug such as bisphosphonates, **denosumab**, or anti-angiogenic drugs

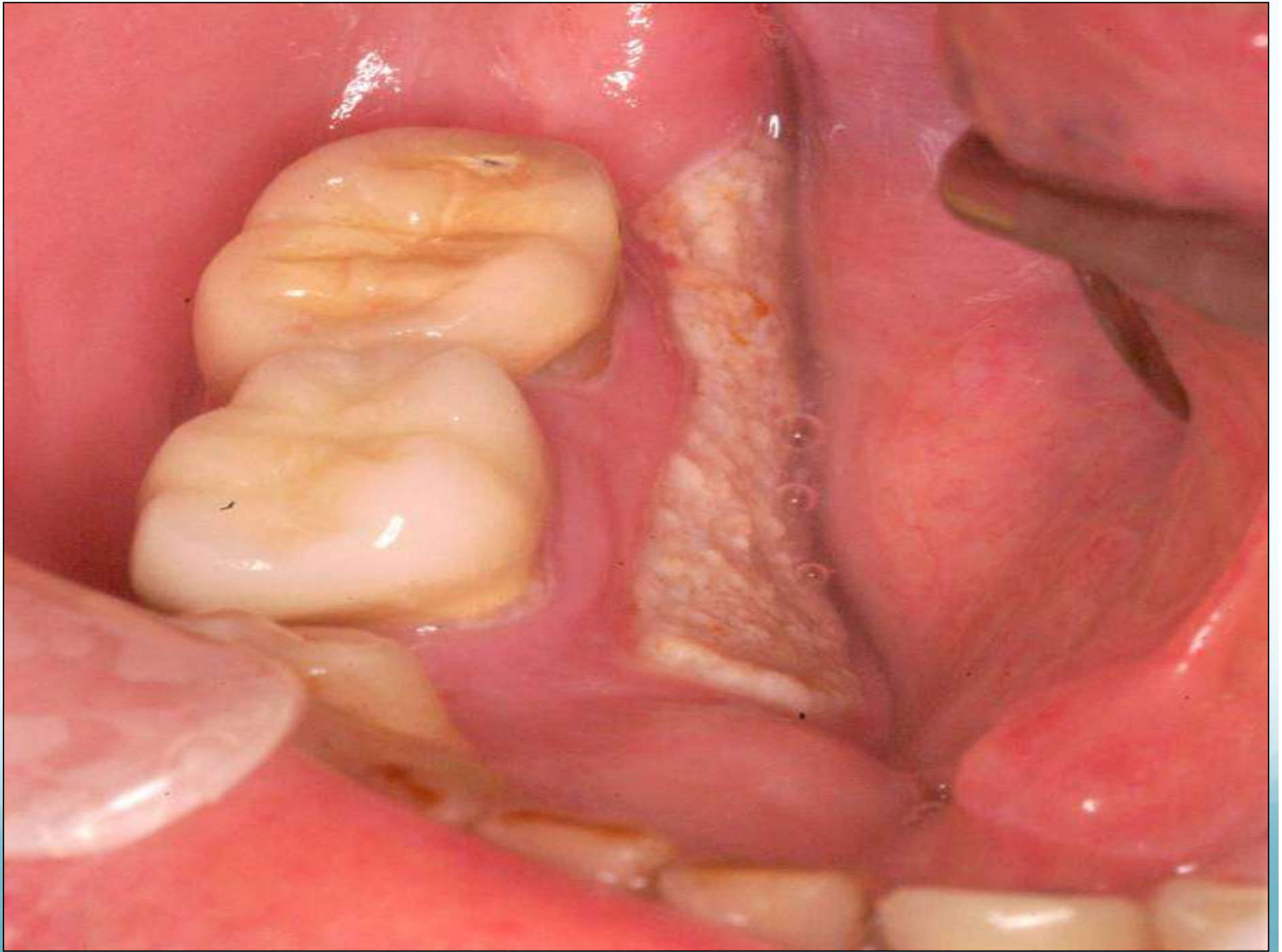
DIONJ Staging

- Stage 0: Radiographic evidence of osteolysis
- Stage I: Exposed bone in one quadrant
- Stage II: Exposed bone in two quadrants
- Stage III:
 - Exposed bone in three or four quadrants
 - Extension of osteolysis into the maxillary sinus and/or nasal cavity
 - Pathologic fracture

Initiating Factors

- Extractions
- Traumatic occlusion
- Dental implants
- Osseous periodontal surgery
- Spontaneous







Risk Factors

- Steroids
- Methotrexate
- Diabetes
- Smoking
- Cancer
- Periodontitis

Prior to Denosumab Therapy

- Extraction of non-restorable dentition
- Treat caries
- Treat periodontitis
- Prophylaxis

Recommendations During Denosumab Therapy

- Avoid invasive procedures
 - Extractions, osseous periodontal surgery, dental implants
- Scaling and prophylaxis
- Splinting of mobile teeth as last resort
- Treat caries with restorations, root canal therapy, coronectomy + RCT

Alternatives to Surgical Treatment

- Non-invasive procedures are safe
- Restorative dental procedures
- Dentures
- Root canal therapy
- Non-osseous periodontal surgery

Drug Holiday

- Prior to surgical procedures if patient is already on denosumab
- 3 month drug holiday
- Continue drug holiday for 3 months after surgical treatment has been completed

C-terminal Telopeptide

- CTX serum biomarker to measure rate of bone turnover
- Cross-linked peptide fragment of type 1 collagen cleaved by osteoclast during resorption
- Predict treatment risk related to bisphosphonate and denosumab use
 - $\text{CTX} \leq 100\text{pg/ml} \rightarrow$ high risk
 - $\text{CTX } 101\text{-}150\text{pg/ml} \rightarrow$ moderate risk
 - $\text{CTX} \geq 151\text{pg/ml} \rightarrow$ Minimal risk

CTX Limitations

- Patients on methotrexate
 - Value lower than expected
- Patients on corticosteroids
 - Value lower than expected
- Cancer patients
 - Value higher than expected

Common Clinical Findings

- Mobile teeth
- Suppuration
- Edema
- Oral-cutaneous fistula
- Pathologic fracture
- Asymptomatic exposed bone vs painful exposed bone

Ineffective Therapies

- Hyperbaric oxygen
- Ozone
- Laser
- Clindamycin

Clindamycin and Common Microorganisms

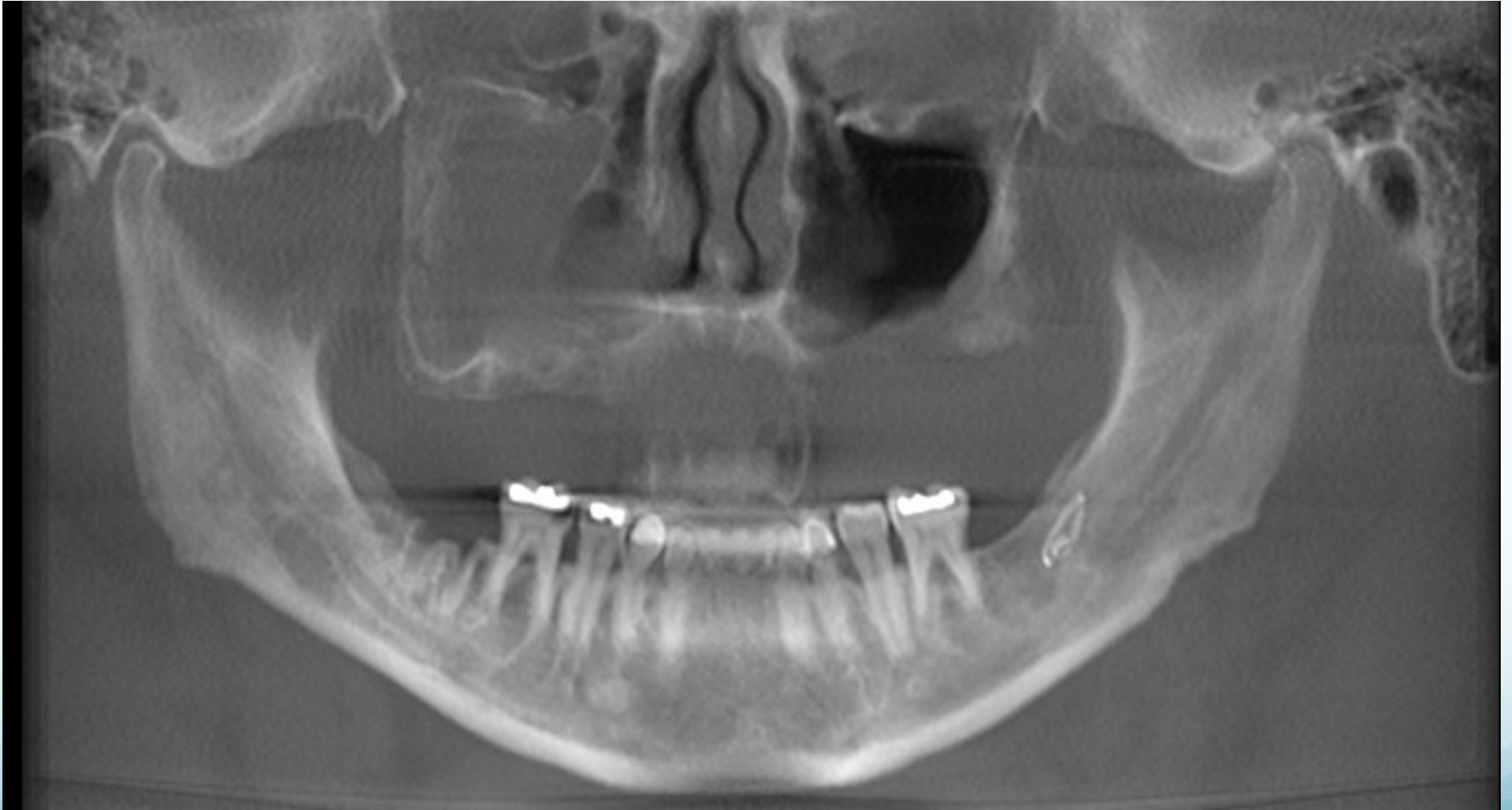
- Moraxella – resistance
- Veillonella – resistance
- Eikenella – resistance
- Actinomyces – minimal sensitivity

General Treatment Principles

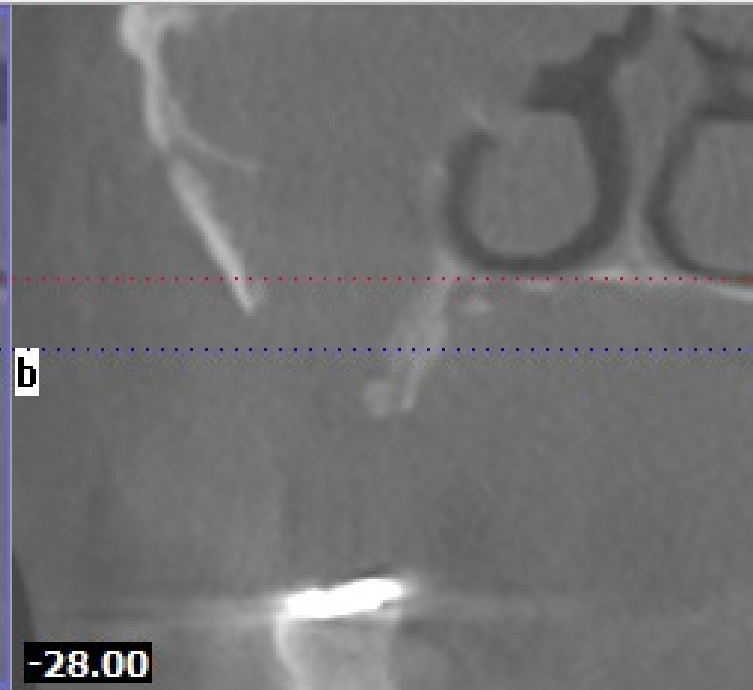
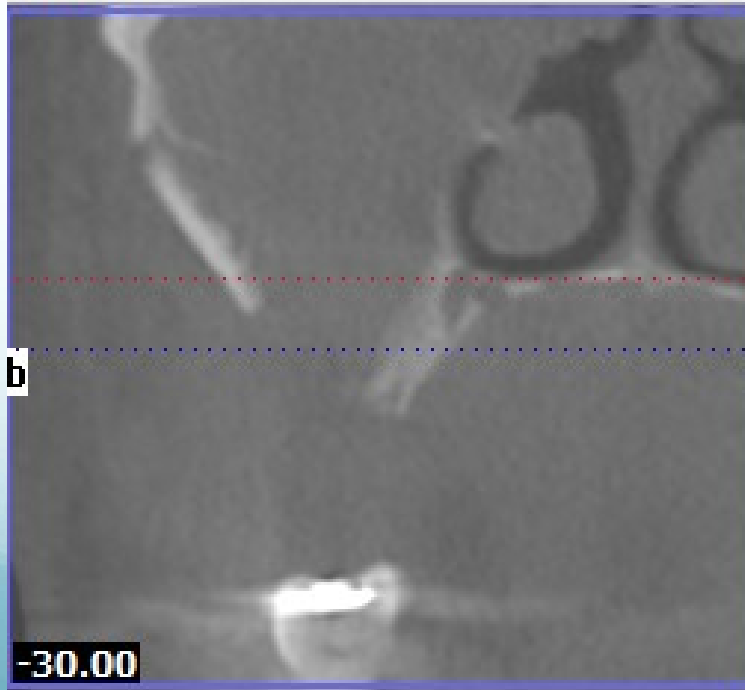
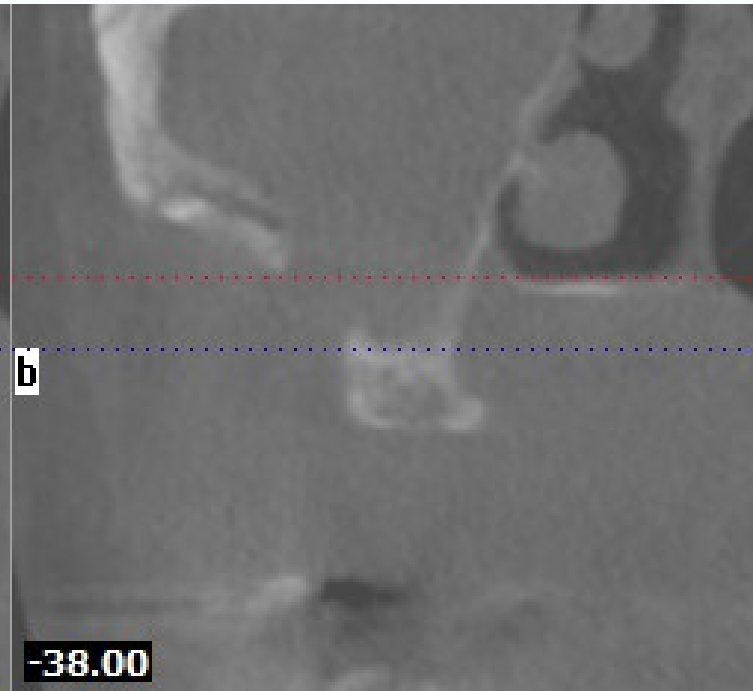
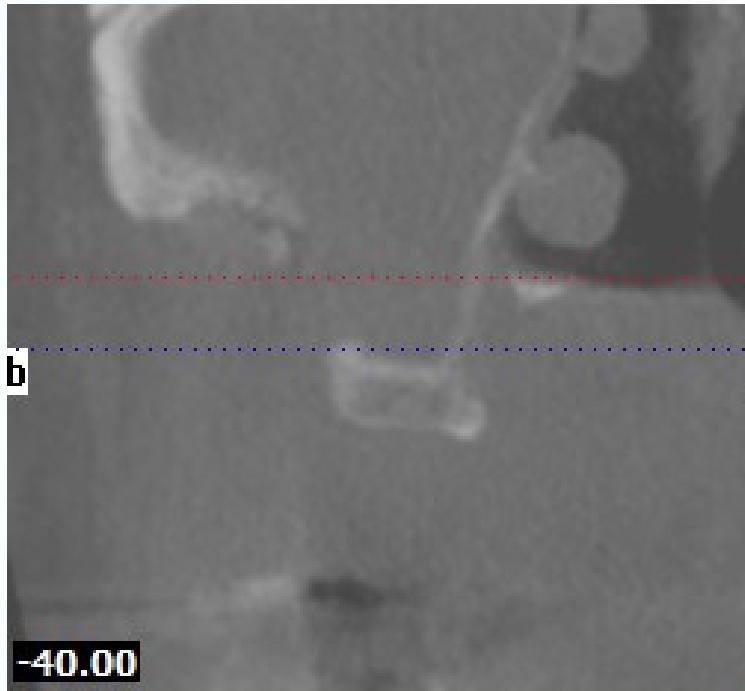
- Avoid surgical treatment until drug holiday is completed
- Initial non-surgical treatment with Penicillin VK 500mg Q6H or doxycycline 100mg daily
- Chlorhexidine TID
- Metronidazole 500mg Q8H x 10 days in refractory cases

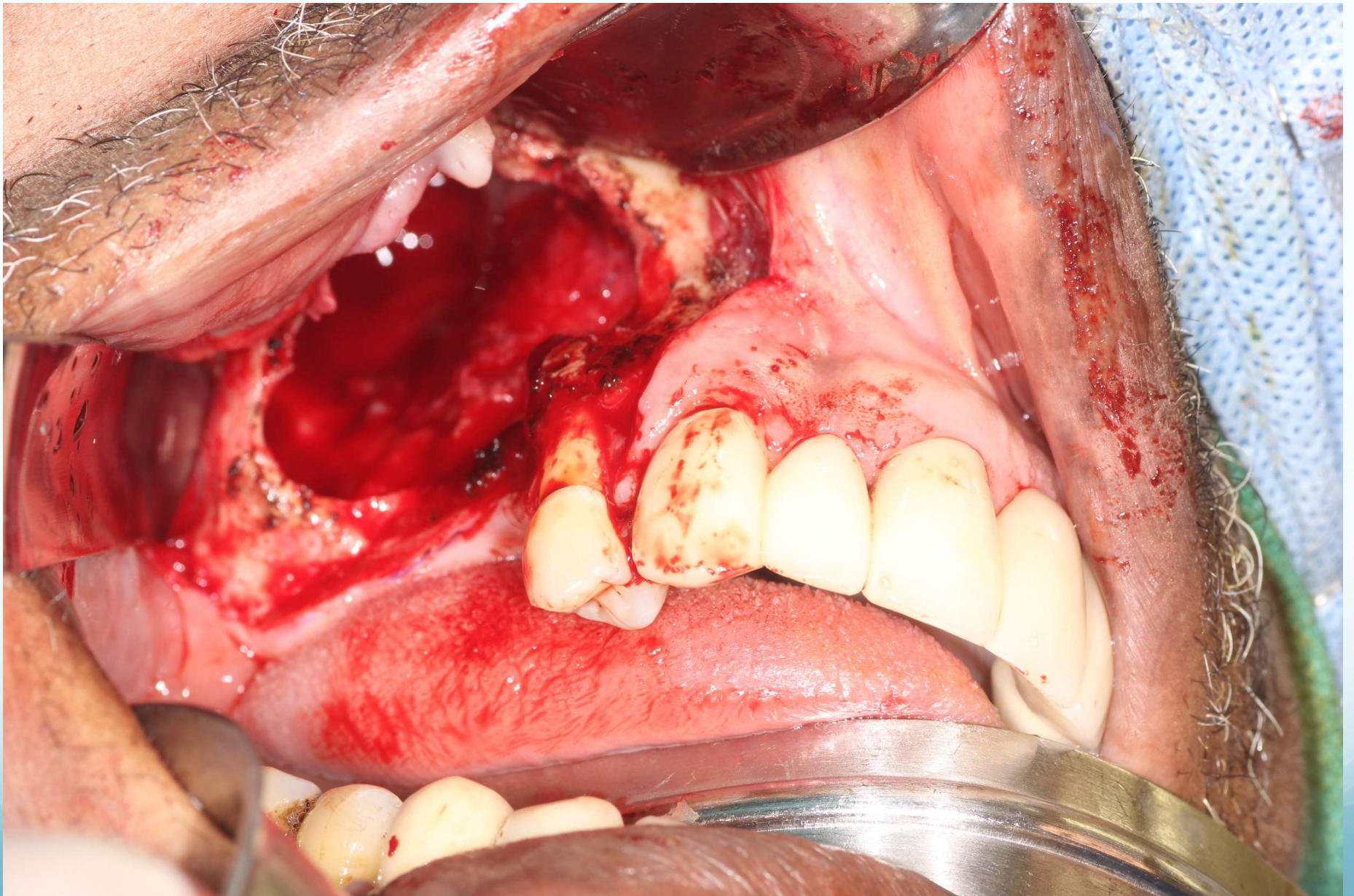
Symptomatic DIONJ

- Debridement → Alveolectomy → Continuity resection
- Sharp edges should be smoothed and rounded



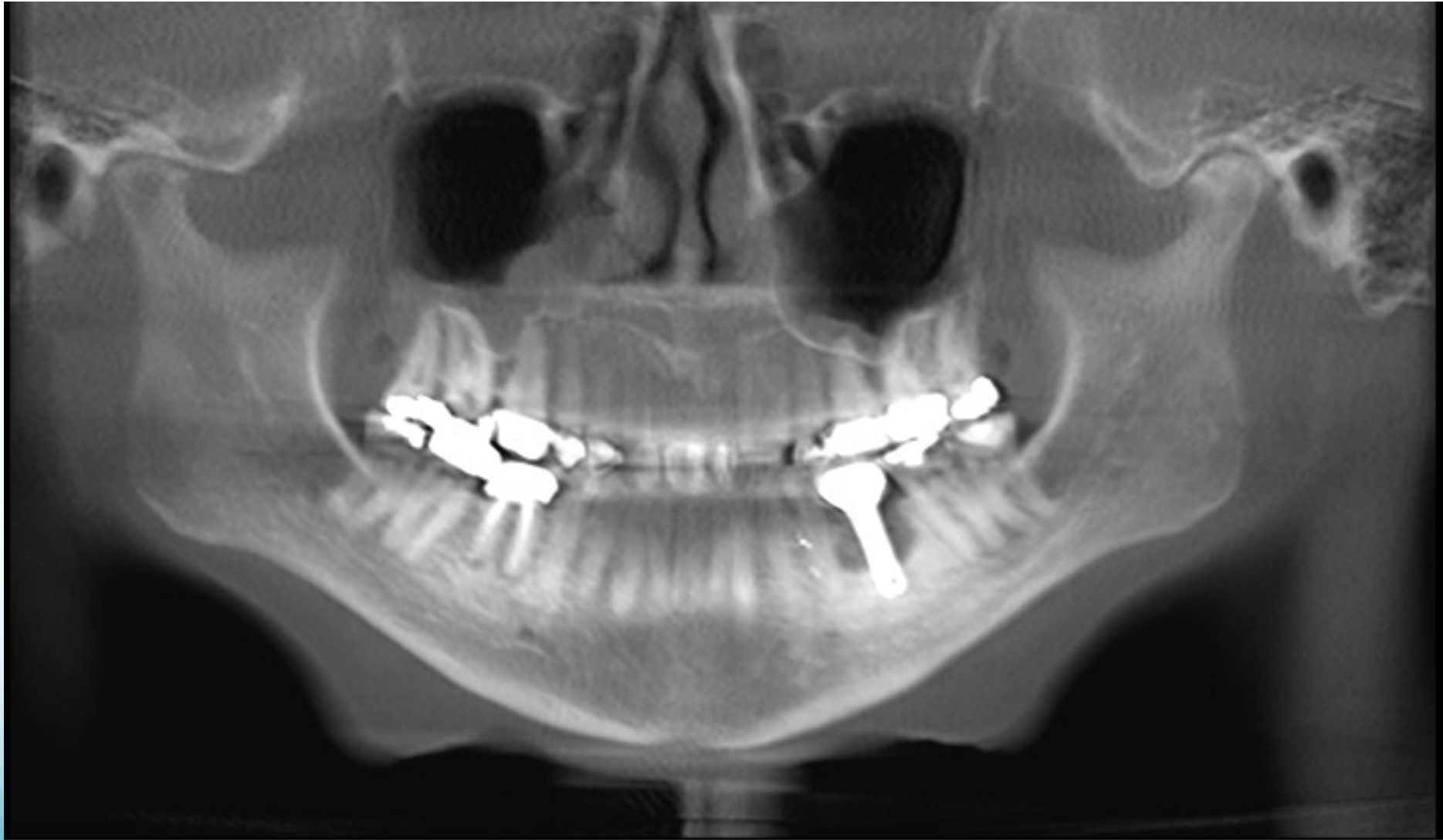
1. The mandible is the lower jawbone, and the maxilla is the upper jawbone. The nasal cavity is the space inside the nose. The sinuses are the air-filled spaces in the skull.

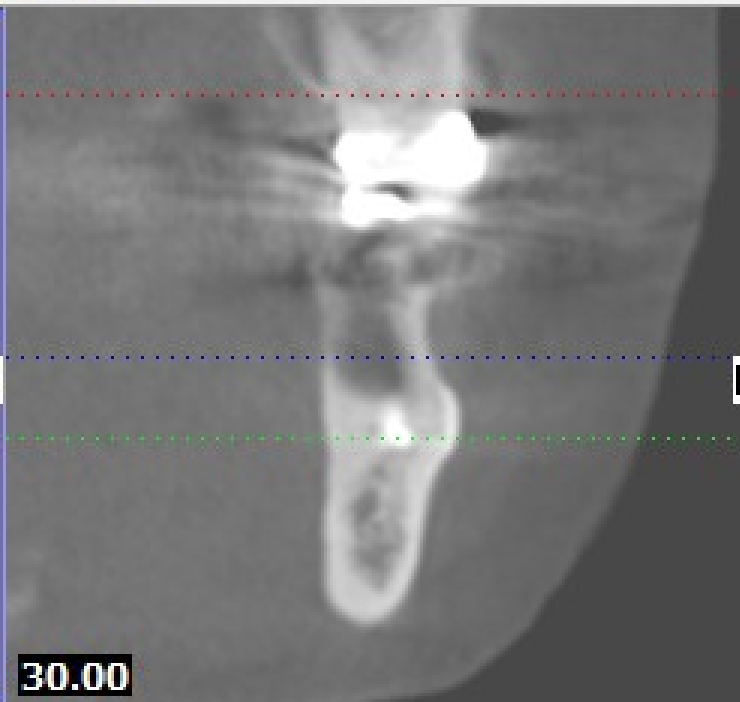
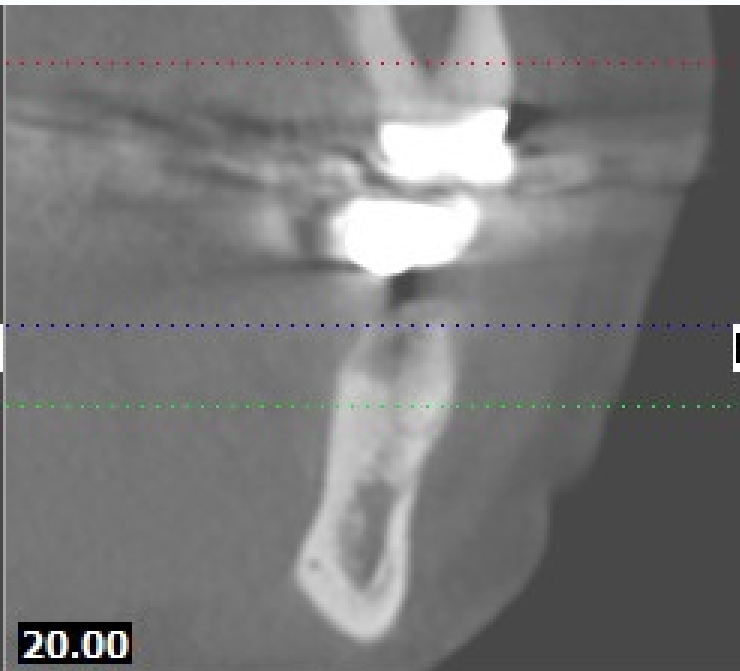




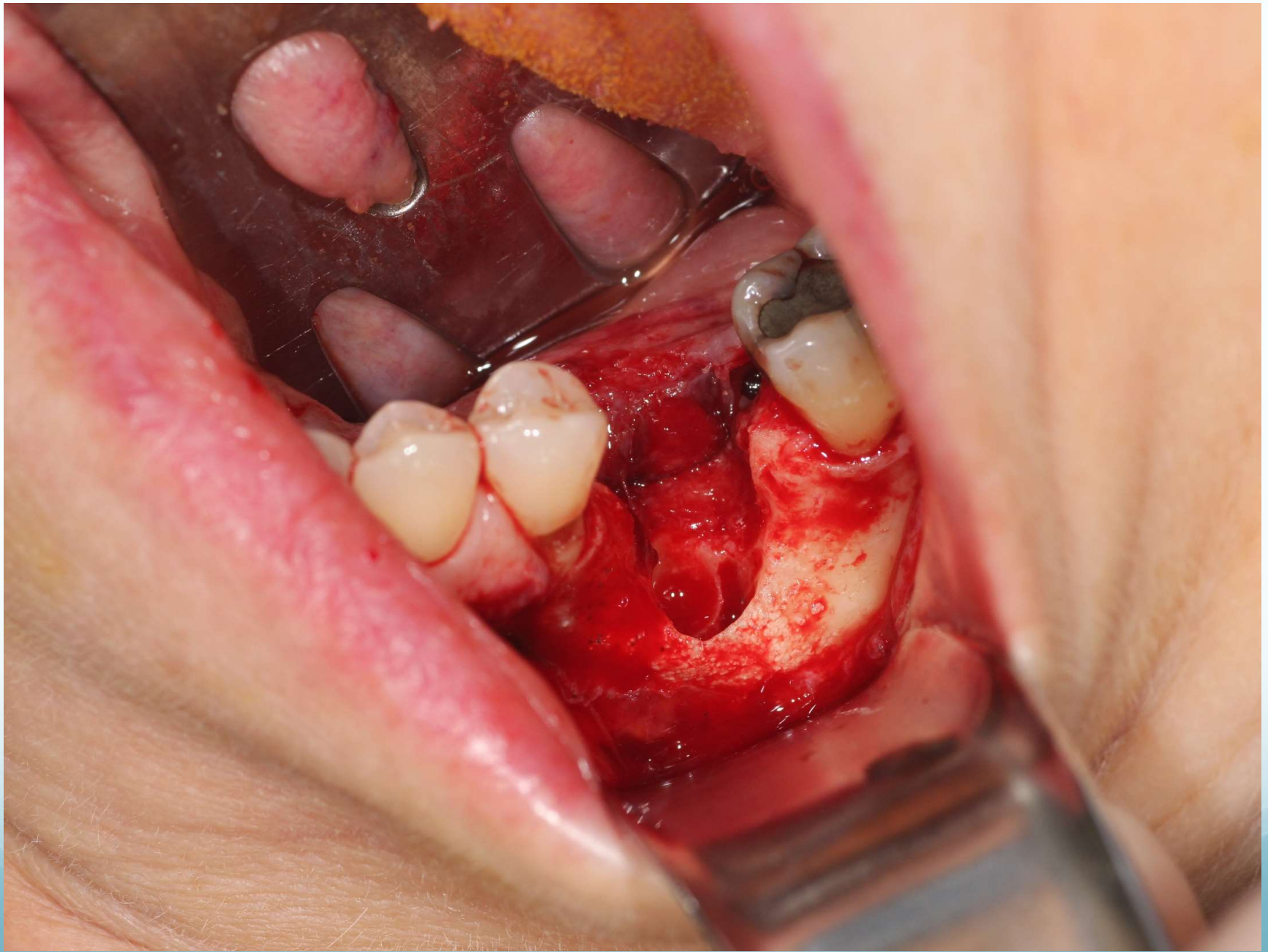
The 4 P's for Considering Resection

- Purulence
- Pain
- Pathologic fracture
- Progression – sinus/nasal communication, inferior border, continued worsening









Denosumab Use Following Bisphosphonates

- Scarce data
- Bisphosphonates still found in bone for multiple years following cessation of treatment
- Adding another drug which inhibits osteoclast activity may accelerate ONJ onset
- Results in more severe ONJ

Average Duration of Drug Use Before DIONJ Diagnosis

- Zoledronate– 9 doses
- Pamidronate –14 doses
- Alendronate– 3 years of weekly doses
- **Bisphosphonate → Denosumab – 4.5 doses**



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