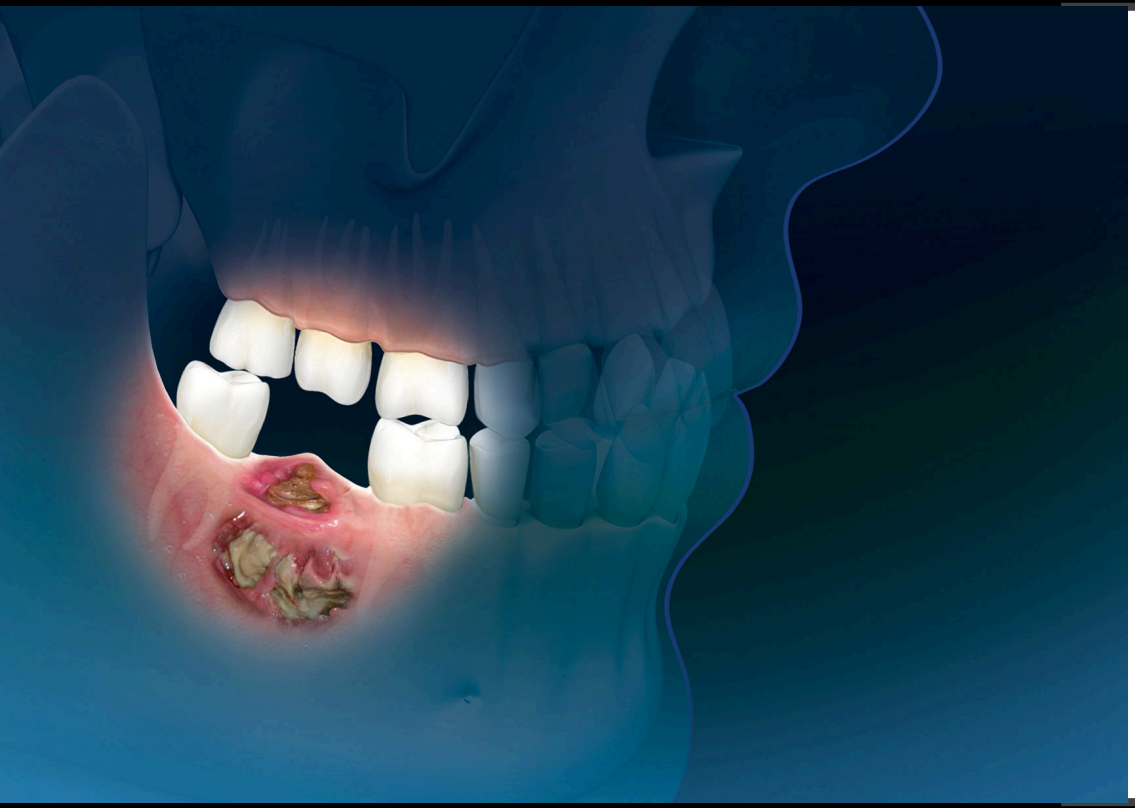


EVIDENCE-BASED ORAL SURGERY CASE

3B-2,
TIMOTHY SEMON, CAMILA NEGRON GARCIA, NICK POLITIS AND THERAN SEMRAD
NOV. 11TH 2020

https://www.endocrinologyadvisor.com/home/topics/bone-metabolism/oral-bisphosphonates-linked-to-6-fold-increase-in-risk-for-osteonecrosis-of-the-jaw/

ROUNDS TEAM

- **Group Leader: Dr. Grady**
- **Specialty Leader: Dr. Reiger**
- **Project Team Leader: Timothy Semon**
- **Project Team Participants:**
- **D1: Theran Semrad**
- **D2: Nicholas Politis**
- **D3: Camila Negron Garcia**

PATIENT BACKGROUND

- 74 y/o
- Caucasian
- Male
- CC: “I want to be able to eat food properly.”

MEDICAL HISTORY

- Sigmoid Removal- 2006
- Tummy Larandscopy- 2015
- L1/L4 laninectomy- 2016
- Osteoporosis- 2016
- Kidney Stone- 2016
- Bowel Complications due to sigmoid- 2017
- Prostate Cancer Radiation until- July 2019
- Xerostomia

MEDICATIONS

- Terazosin 10 mg 1 tab bedtime
- Pantoprazole 40 mg 1/2 tab as needed
- Fluticasone Propionate nasal spray as needed
- Duloxetine 60 mg 1 tab daily
- Pregabalin 200 mg 1 tab daily
- Doxycycline 100 mg 1 tab daily
- Poly Glycol 3350 11 mg daily
- Prolia injections every 6 months

DENTAL HISTORY

- Caries:

  #11 MF
- Resin restorations:

  #4 DO, #5 MODB, #7 DFL, #8 MF, #9 MF,

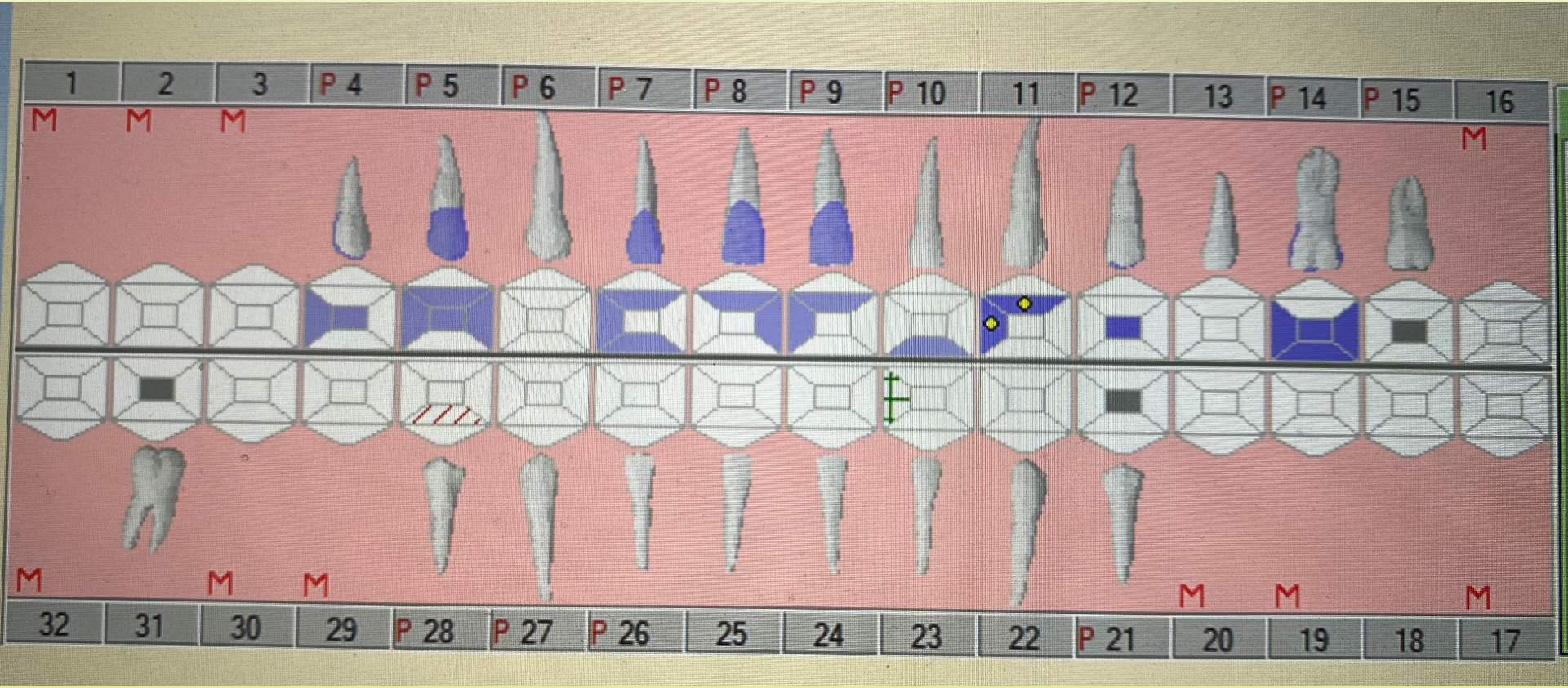
  #10 L, #12 O, #14 MODL
- Amalgam restorations:

  #15 O, #21O and #31 O
- Fracture:

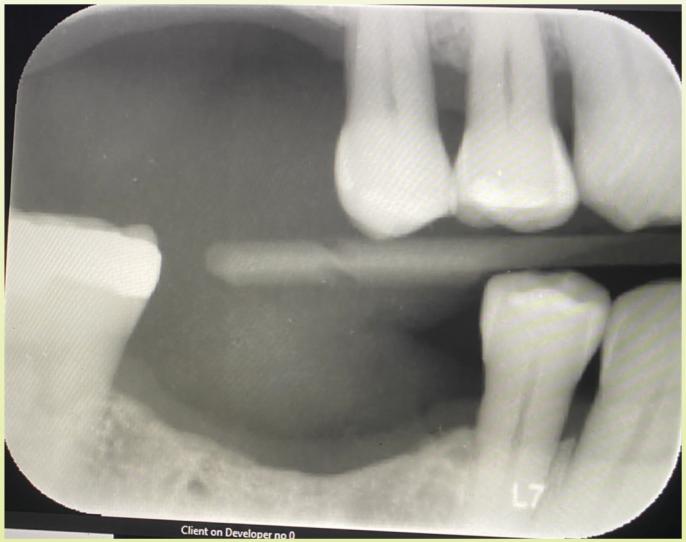
  #23 M
- Abfraction:

  #28 B

ODONTOGRAM


1 2 3 P 4 P 5 P 6 P 7 P 8 P 9 P 10 11 P 12 13 P 14 P 15 16
M M M M
M M M M M M
32 31 30 29 P 28 P 27 P 26 25 24 23 22 P 21 20 19 18 17

BITEWINGS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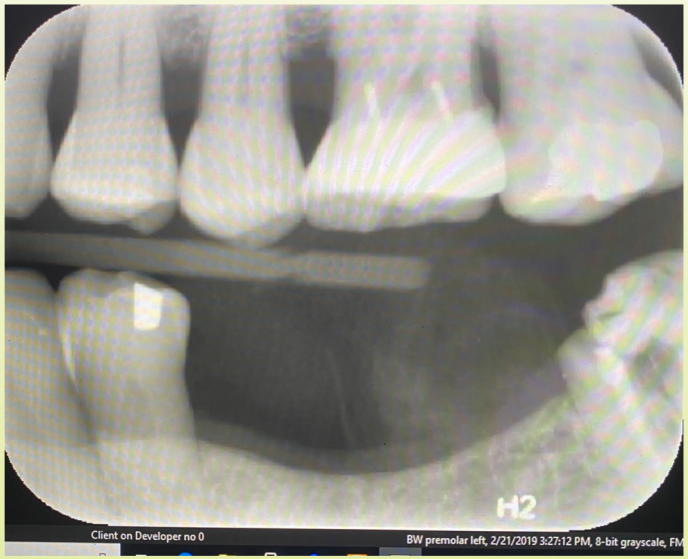
H2
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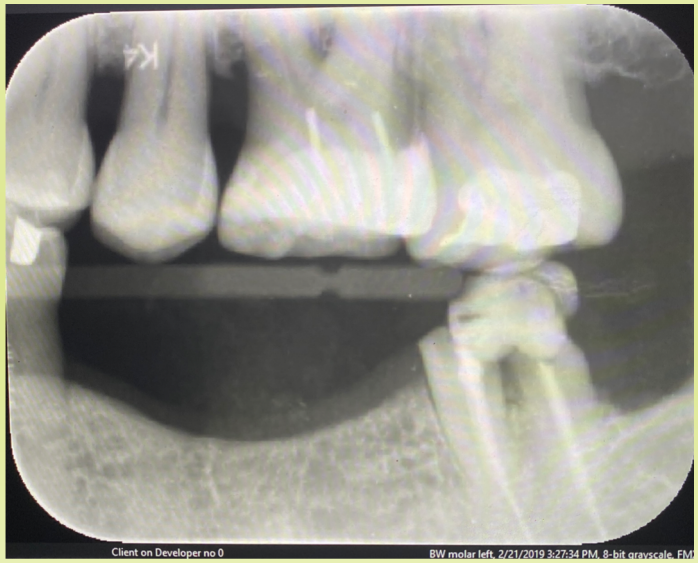
BW premolar left, 2/21/2019 3:27:12 PM, 8-bit grayscale, FM


K4
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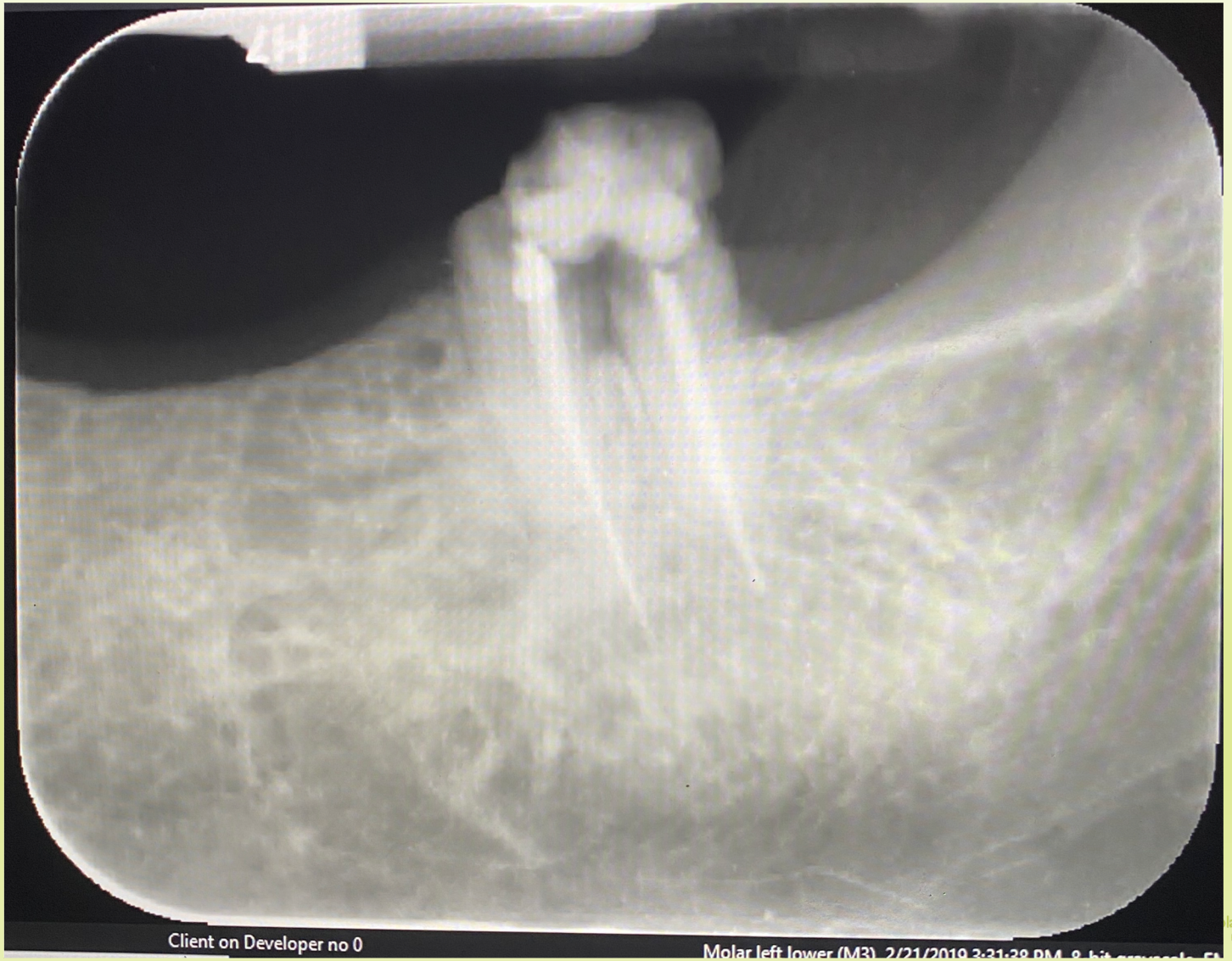
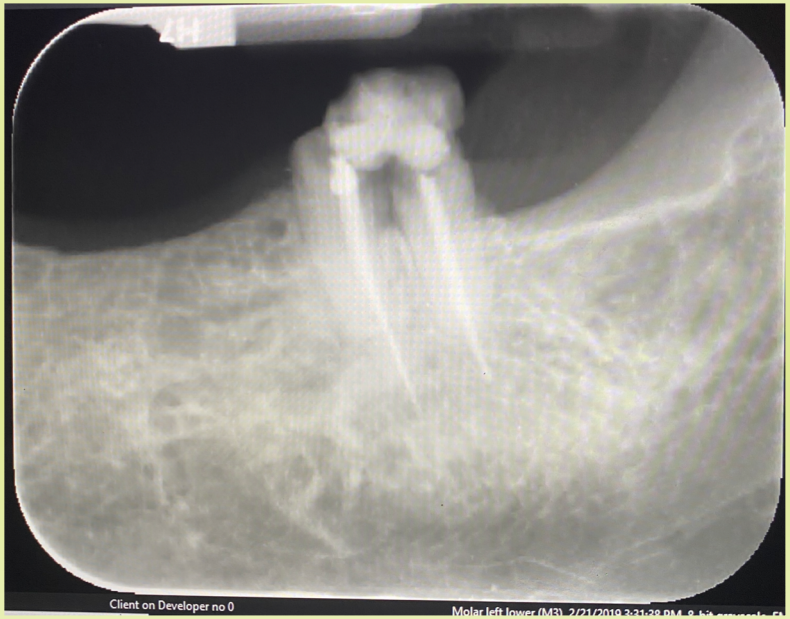
BW molar left, 2/21/2019 3:27:34 PM, 8-bit grayscale, FM

PERIAPICALS

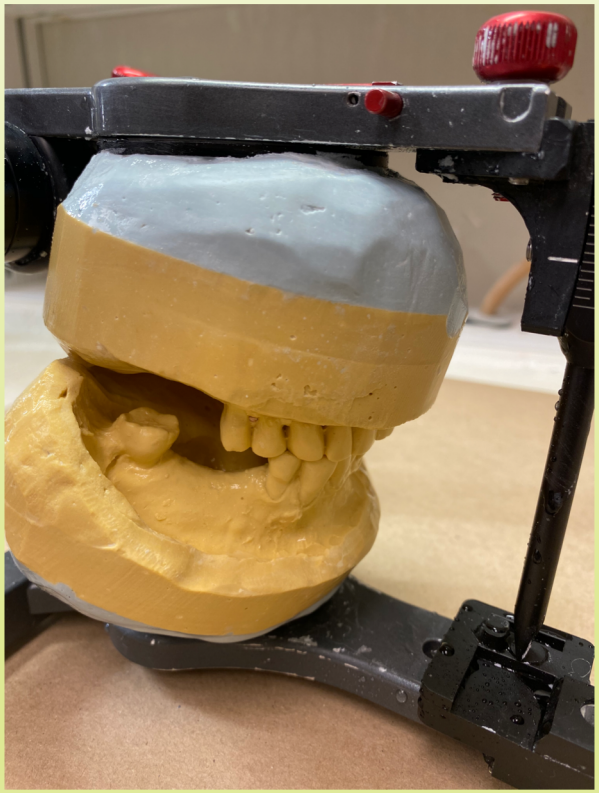


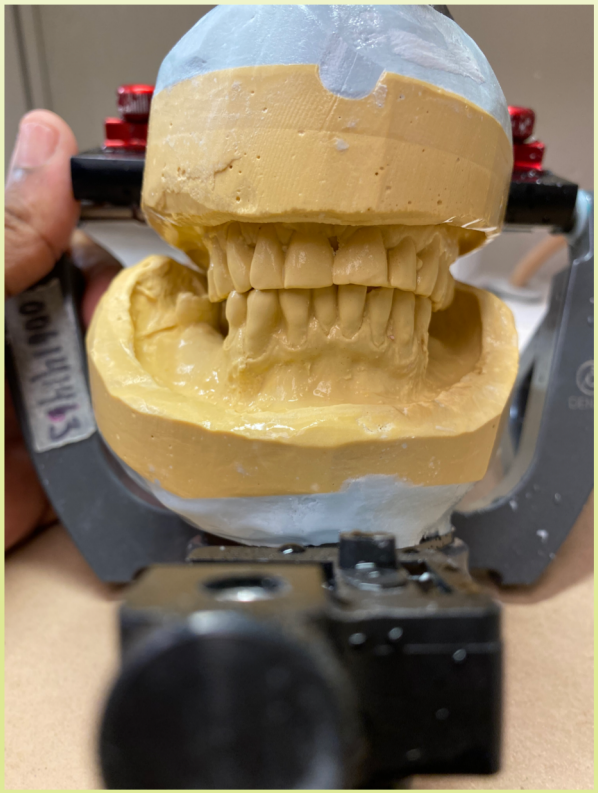
RADIOGRAPHIC FINDINGS

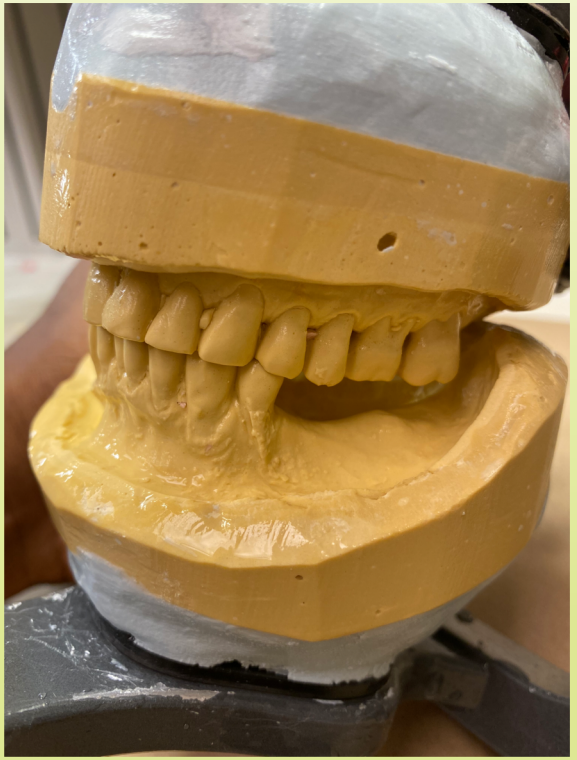
- #18 Previously treated RCT
- Less than half of the clinical crown is present
- Tooth most likely non-restorable



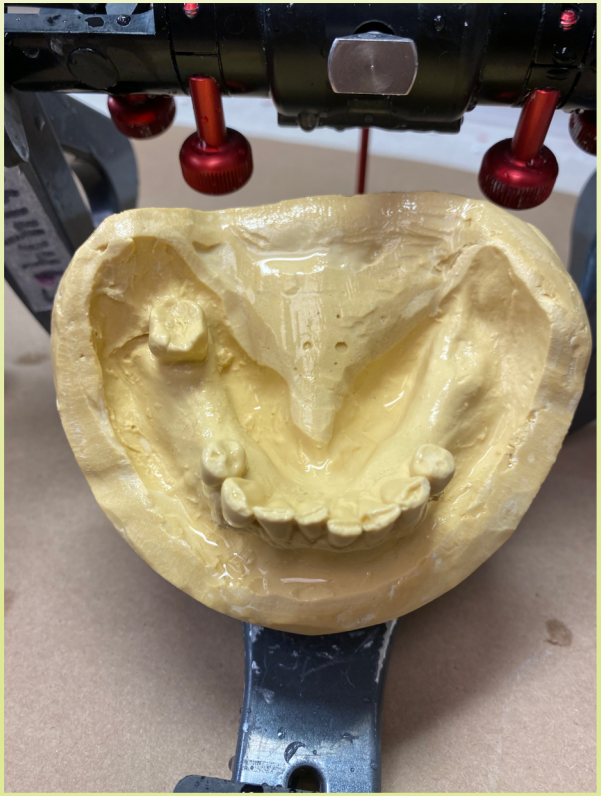
DIAGNOSTIC CASTS

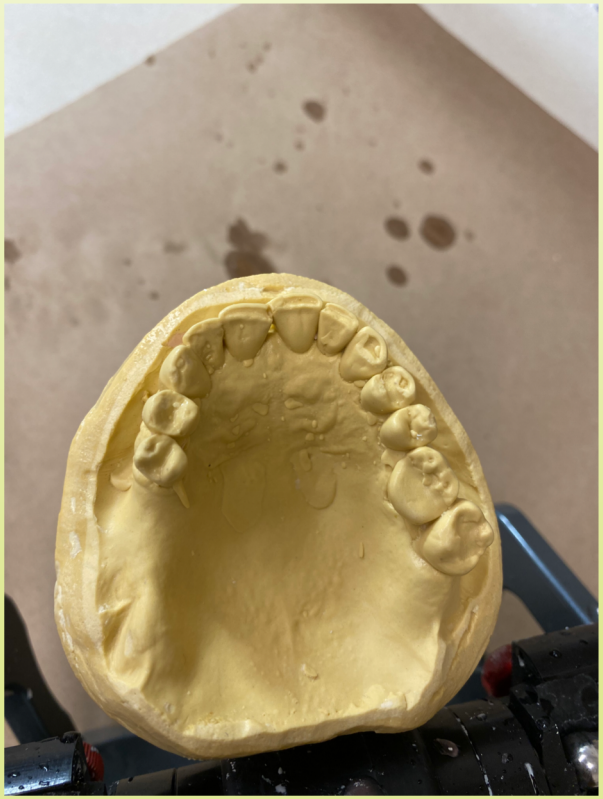


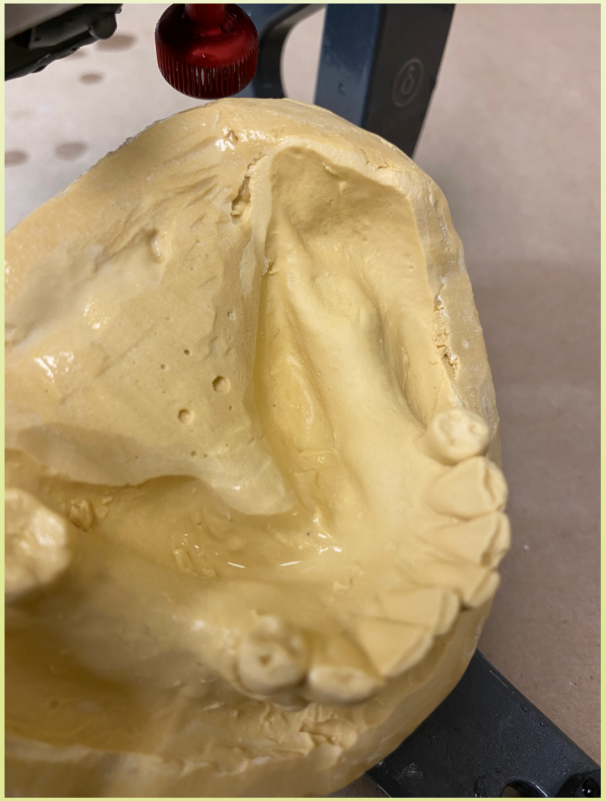




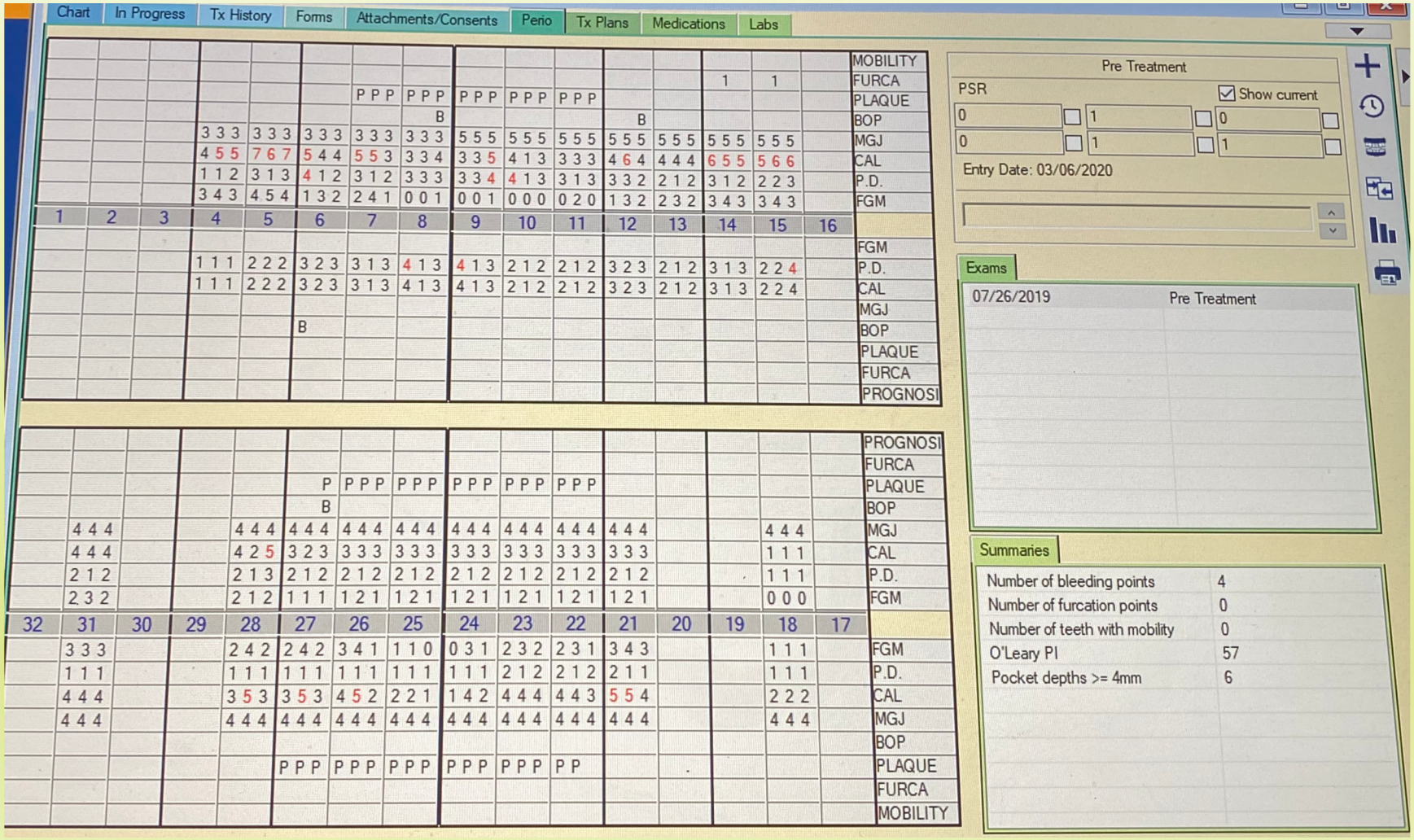
DIAGNOSTIC CASTS







PERIODONTAL CHART



PERIODONTAL FINDINGS/DIAGNOSIS

<u>07/26/19: Periodontal Consultation was conducted</u>

- Dr. Herman deemed tooth #18 hopeless/non-restorable
- Furcations Grade 1: #14 and #15 Facial
- Restorative/Perio Prognosis:

  Good
- D1110 (Prophy)

ORAL SURGERY CONSULTATION

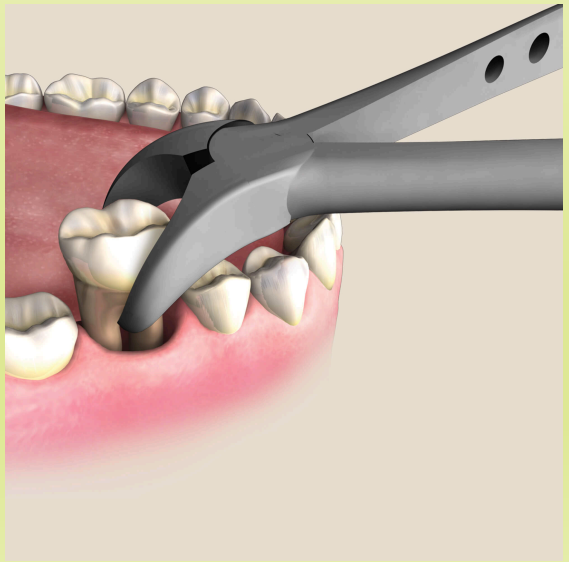
09/03/19: Oral Surgery Consultation was conducted

- Chief Complaint (CC): "Get the tooth out of there."
- History of Present Illness (HPI): The tooth started hurting about 1 year ago when the crown fell off. Chewing causes more pain but soft tissue bother patient constantly.
- Past Medical History (PMH): Patient underwent prostate radiation July 2019. Patient is using Prolia (bisphosphonate) for osteoporosis. took Fosamax prior. Last shot of Prolia was on May 2019
- Vital Signs: BP __133___/__85___ Pulse___68_____ Temp __98.8_____

https://www.stethoscope.com/adc-603-copper-general-diagnostic-stethoscope/

DIAGNOSIS

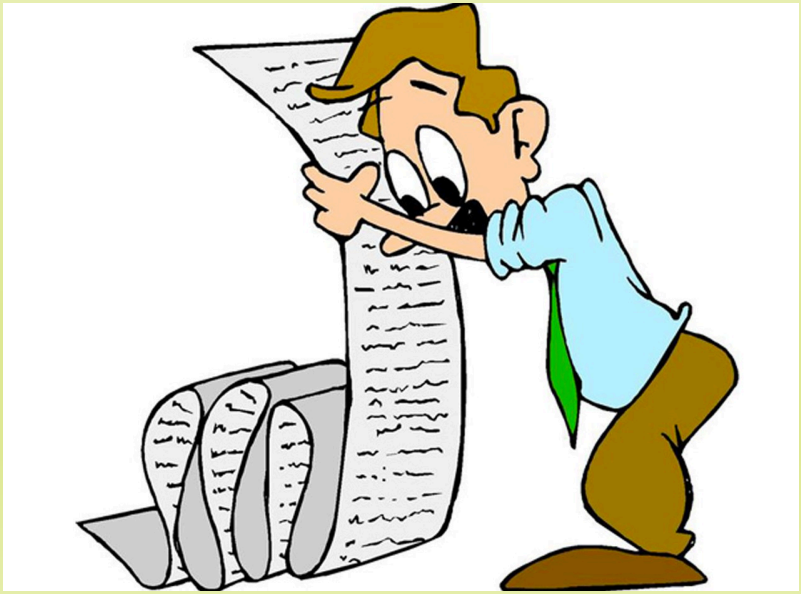
- Oral/Facial Examination (PE): #18 is non-restorable. Untreated decay on maxillary anteriors. Missing teeth #1, 2, 3, 16, 17, 19, 20, 29, 30, and 32.
- Diagnosis: Non-restorable #18.
- Treatment Plan: Surgical ext #18
- Prescriptions Written (Rx): none - OTC prn



https://www.hu-friedy.com/surgical/forceps/atraumair/23-cowhorn-forceps-lower-molars-atraumair

PROBLEMS LIST

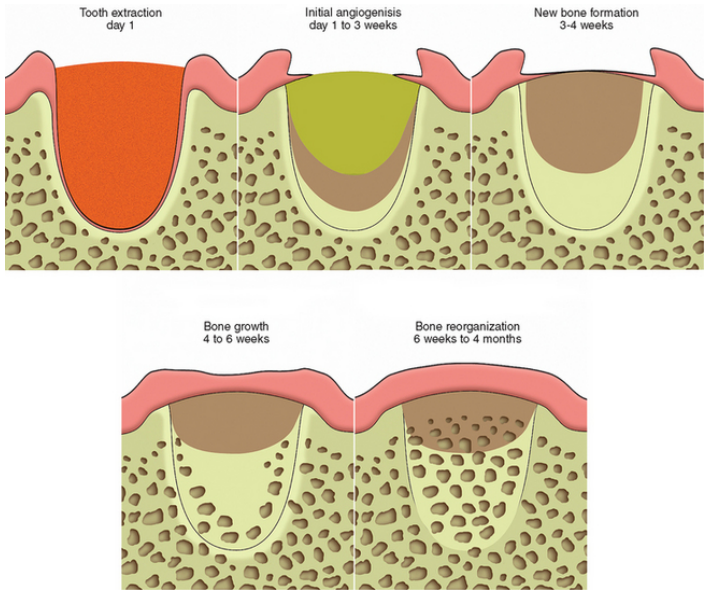
- Fractured tooth
- Caries
- Defective Restoration
- Missing Teeth



https://rixtrema.com/blog/a-list-of-issues-found-in-403b-plans/

D1 BASIC SCIENCE

- ***D1 Basic Science Question: What is the healing process of an extraction site?***

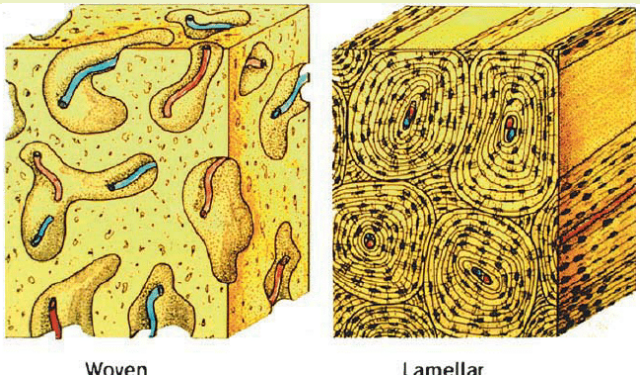


- ***Discussion:***
  - ***Three phases to healing***
    - ***Inflammatory phase***
    - ***Proliferative phase***
    - ***Bone modeling and remodeling***
  - ***Timeline variable***
    - ***Months to years***
    - ***Most people will complete healing in several months***

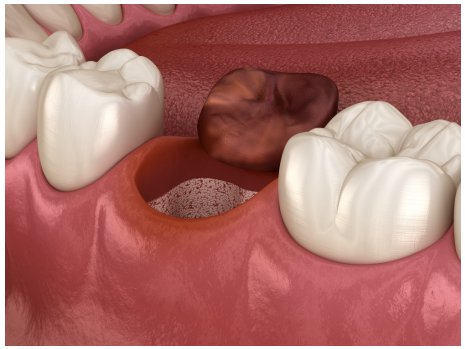
Works Cited for Image 1: Themes, UFO. "37: Tooth Extraction, Socket Grafting, and Barrier Membrane Bone Regeneration." *Pocket Dentistry*, 5 Jan. 2015, pocketdentistry.com/37-tooth-extraction-socket-grafting-and-barrier-membrane-bone-regeneration/.

D1 BASIC SCIENCE

- ***Phase 1***
  - ***Clotting***
  - ***Migration of immune cells***
  - ***Formation of granulation tissue***
- ***Phase 2***
  - ***Fibroplasia***
  - ***Woven bone formation***
- ***Phase 3***
  - ***Bone modeling and remodeling***
  - ***Woven bone replaced with lamellar bone***
- ***Complications***
  - ***Dry Socket***



Safadi, Fayez F., et al. "Bone Structure, Development and Bone Biology." *Bone Pathology*, 2009, pp. 1–50., doi:10.1007/978-1-59745-347-9_1



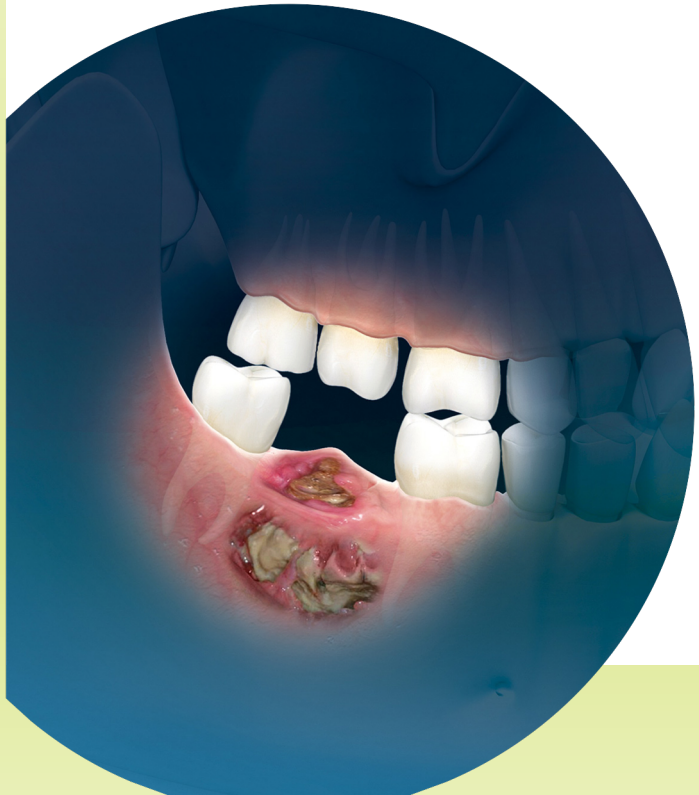
"How to Identify and Deal with a Dry Socket?" *Oral & Dental Surgery Specialist in OKC*, www.drwooten.com/how-to-identify-and-deal-with-a-dry-socket/.

Reference citation(s):

Araújo, Mauricio G., et al. "Alveolar Socket Healing: What Can We Learn?" *Periodontology 2000*, vol. 68, no. 1, 2015, pp. 122–134., doi:10.1111/prd.12082.
Dr. Judy Maloney lecture slides "Bone"

D2 PATHOLOGY: WHAT IS OSTEONECROSIS?

- Osteonecrosis- "coronary disease" of the bone

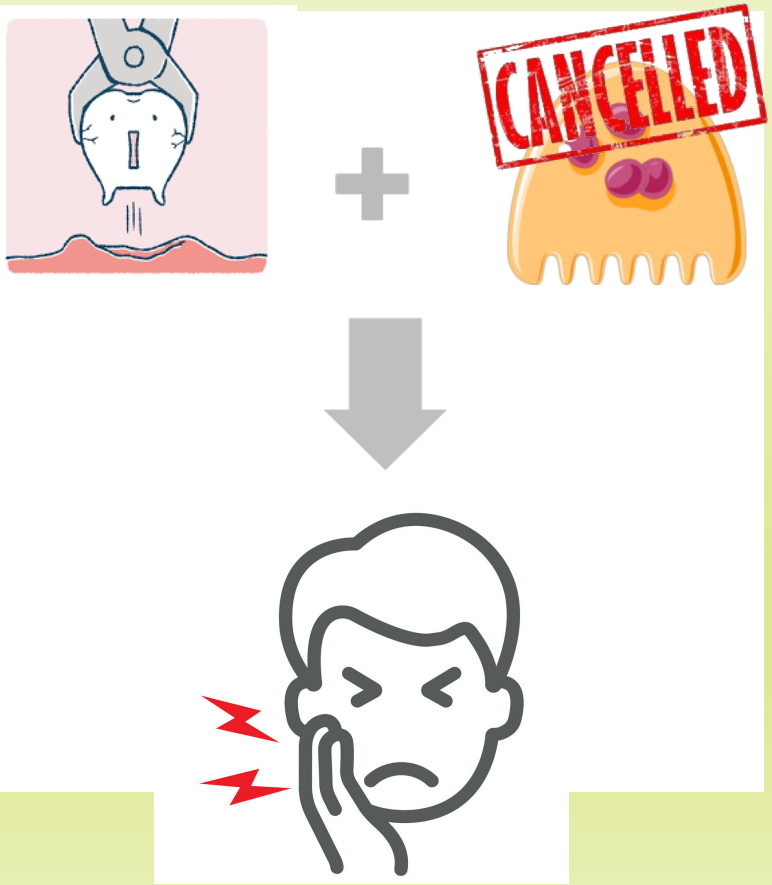


OSTEO – NECROSIS: "BONE" – "DEATH"

- In response to ischemia
- Skeletally most common in femur with steroids
- Orally most common in **mandible** with medications
  - Antiresorptives
  - Antiangiogenics
  - Imunomodulators

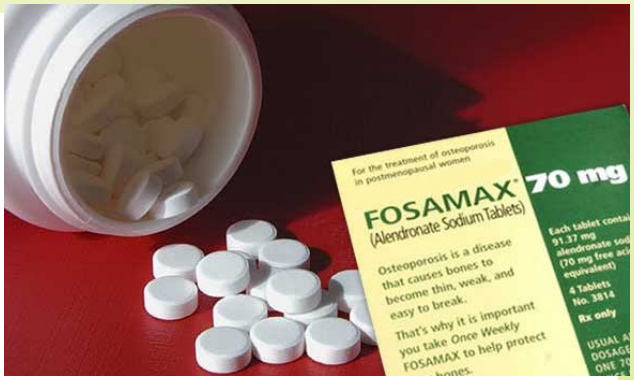
THE PERFECT BREW! FOR FAILURE . . .

- Trauma
  - Tooth extraction
  - Implant placement
  - Aberrant denture pressure
- Compromised biologic setting
  - **MED-INDUCED**
  - Diabetes
  - Inflammatory joint pathology

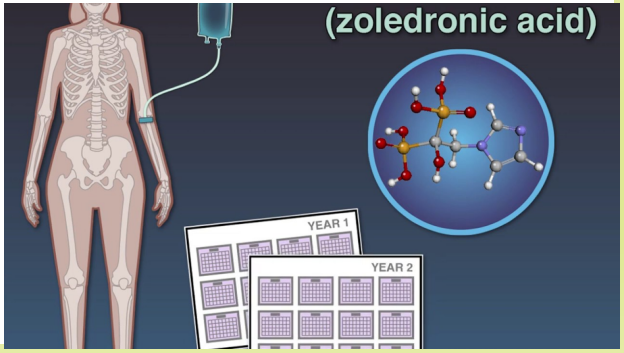


BISPHOSPHONATES (ANTIRESORPTIVE TX)

- Deposit within bone matrix
- Low doses taken orally for osteoporosis
- High doses administered IV for certain cancers
- **Associated with ONJ!!!**



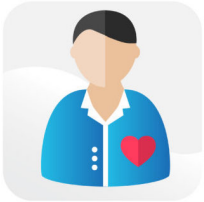
Alendronate: PO for osteoporosis



Zoledronate: IV for cancer

PREVENTION, PREVENTION, PREVENTION

- Currently no effective Tx
- Routine dental work safe (woohoo!)
- Extensive/Invasive/Prolonged dental work needs M.D. consult



D3 PICO

Clinical Question:

How can the risk of osteonecrosis be reduced in patients requiring extractions after bisphosphonate use and current RANK-L inhibitor use?

PICO FORMAT

P: Patient with gross decay on tooth with previous bisphosphonates use and current RANK-L inhibitor use

I: Extraction of tooth with delayed treatment

C: versus extraction of tooth during treatment

O: decreases the likelihood of osteonecrosis

PICO FORMATTED QUESTION

- In patients with previous bisphosphonate use and current RANK-L inhibitor use, will the delayed treatment increase the prognosis vs. continued treatment while proceeding with extraction?

CLINICAL BOTTOM LINE

- Patient needs to have non-restorable #18 treated while being on Denosumab (Prolia) injections

SEARCH BACKGROUND

- **Date(s) of Search:** 10.20.2020
- **Database(s) Used: PubMed**
- **Keywords:** Bisphosphonates, dental extractions, osteonecrosis, denosumab

SEARCH BACKGROUND

- **MESH terms used:**
  Osteonecrosis/chemically induced, Osteonecrosis/ prevention & control, Bisphosphonate-Associated Osteonecrosis of the Jaw, drug holiday, Denosumab, Dental Extractions

DENOSUMAB (PROLIA) VS. ALENDRONATE (FOSAMAX)

Feature	Alendrolate (Fosamax)	Denosumab (Prolia)
Drug Class	Bisphosphonate- nitrogen containing	Monoclonal antibody
Molecular Target	Cellular metabolic enzymes	Binds and inhibits RANKL
Site of Action	Tightly bound to mineral in the bone matrix; internalized by osteoclasts	Extracellular milieu; not associated with bone tissue
Effect on osteoclast	Induce apoptosis; bone associated osteoclasts that survive may remain in bone with low resorptive activity	Inhibits osteoclast formation, function, and survival
Onset of action	Slow	Rapid
Elimination Half Life	~ exceeds 10 yrs.	~6 months

ARTICLE 1

- Citation: Ruggiero S, Et. Al , American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw, J Oral Maxillofac Surg, 2014, Volume: 72, Page Numbers: 1938-2956
- Study Design: Expert Opinion
- Evidence Level: 6

ARTICLE 1 SYNOPSIS

- The purpose of this updated position paper is to provide: Risk estimates of developing MRONJ, Comparisons of the risks and benefits of medications related to osteonecrosis of the jaw (ONJ) to facilitate medical decision making for the treating physician, dentist, dental specialist, and patients. Guidance to clinicians regarding: The differential diagnosis of MRONJ in patients with a history of exposure to antiresorptive or antiangiogenic agents MRONJ prevention measures and management strategies for patients with MRONJ based on disease stage. The receptor activator of nuclear factor kB ligand (RANKL) inhibitor (denosumab) is an antiresorptive agent that exists as a fully humanized antibody against RANKL and inhibits osteoclast function and associated bone resorption. When denosumab (Prolia; Amgen,Thousand Oaks, CA) is administered subcutaneously every 6 months, there is a decrease in the risk of vertebral, nonvertebral, and hip fractures in osteoporotic patients. Risk for ONJ in osteoporotic patients exposed to oral BPs: In a survey study of more than 13,000 Kaiser Permanente members, the prevalence of MRONJ in patients receiving long-term oral BP therapy was reported at 0.1% (10 cases per 10,000), which increased to 0.21% (21 cases per 10,000) in patients with longer than 4 years of oral BP exposure. MRONJ risk in osteoporotic patients exposed to IV BP or RANKL inhibitors: A study analyzing patients with osteoporosis exposed to yearly zoledronate therapy for 3 years reported a risk for MRONJ of 0.017% (1.7 cases per 10,000 patients). An extension of this study through 6 years did not show a change in frequency of MRONJ. In recent reports studying patients exposed to denosumab, the risk for MRONJ was 0.04% (4 cases per 10,000 patients). For patients receiving oral BP therapy to manage osteoporosis, the prevalence of ONJ increases over time, from nearly 0% at baseline to 0.21% after at least 4 years of BP exposure

ARTICLE 1 SELECTION

Reason for selection:

This is the most recent position paper from the AAOMS that can be used to guide a provider, along with their own clinical judgement on how to manage MRONJ

1. This is the most recent position paper from the AAOMS that can be used to guide a provider, along with their own clinical judgement on how to manage MRONJ
2. This article is specific to denosumab, and treatment outcomes can be predicted based on this case study.

ARTICLE 2 CITATION, INTRODUCTION

- Citation:

S. Aljohani et al., Osteonecrosis of the jaw in patients treated with denosumab: A multicenter case series, Journal of Cranio-Maxillo-Facial Surgery, 2018, Volume: 46 Page Numbers: 1515-1525

- Study Design: Case Series

- Evidence Level: 5

ARTICLE 2 SYNOPSIS

Method:

- A retrospective medical chart review was carried out at two German institutions: the Department of Oral and Maxillofacial Surgery, Ludwig-Maximilians-University, Munich, and the Department of Oral and Maxillofacial Surgery and University Medical Center Hamburg-Eppendorf, Hamburg. All patients diagnosed and treated for DRONJ between July 2011 and April 2017 were identified. This study included all patients diagnosed with DRONJ based on the following criteria: 1) MRONJ diagnosis based on AAOMS criteria in patients receiving denosumab with or without history of bisphosphonates intake; and 2) a minimum period of 3 months between the last administration of bisphosphonates and DRONJ onset. The exclusion criteria were: a history of head and neck radiation, obvious metastasis to jaw bones and a history of bisphosphonates within the 3 months preceding the onset of DRONJ. A total of 63 patients were identified and fulfilled the entry criteria.

ARTICLE 2 SYNOPSIS

Results:

- Statistical significance between prior bisphosphonate therapy and outcomes of treatment was not observed. There wasn't an association between a denosumab holiday and DRONJ healing. However, a positive effect of denosumab cessation on DRONJ can be assumed, given its short half-life. It is very important to know that pausing denosumab even for short intervals can result in remarkable rebound in bone remodeling and bone mineral density (BMD) and might lead to increased fracture risk.

ARTICLE 2 SYNOPSIS

Conclusions:

- Within the limitations of this retrospective study, characteristics of DRONJ were investigated. DRONJ tends to develop after administration of 16.4 doses. The previous use of bisphosphonates does not appear to affect DRONJ severity or treatment response. Based on the findings, we recommend surgical treatment, particularly fluorescence-guided surgery, to allow complete removal of necrotic bone and to prevent ONJ progression.

ARTICLE 2 SYNOPSIS

Lmitations:

- First, the retrospective nature of this study did not allow to draw final conclusions regarding the treatment modalities and the effect of denosumab discontinuation. Second, results are based on analysis of a small sample size due to the rarity of DRONJ. Third, information on some clinical variables was missing.

ARTICLE 2 SELECTION

Reason for selection:

- This article is specific to denosumab, and treatment outcomes can be predicted based on this case study.

LEVEL OF EVIDENCE

- ☐ **1a** – Clinical Practice Guideline, Meta-Analysis, Systematic Review of Randomized Control Trials (RCTs)
- ☐ **1b** – Individual RCT
- ☐ **2a** – Systematic Review of Cohort Studies
- ☐ **2b** – Individual Cohort Study
- ☐ **3** – Cross-sectional Studies, Ecologic Studies, "Outcomes" Research
- ☐ **4a** – Systematic Review of Case Control Studies
- ☐ **4b** – Individual Case Control Study
- ☑ **5** – Case Series, Case Reports
- ☑ **6** – Expert Opinion without explicit critical appraisal, Narrative Review
- ☐ **7** – Animal Research
- ☐ **8** – In Vitro Research

STRENGTH OF RECOMMENDATION TAXONOMY (SORT)

☐	**A** – Consistent, good quality patient oriented evidence
☐	**B** – Inconsistent or limited quality patient oriented evidence
☒	**C** – Consensus, disease oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening

CONCLUSIONS

D3: How does the evidence apply to this patient?

- This patient receives corticosteroid injections in the hip and shoulder 2-3x a year, in addition to having been on an oral bisphosphonate (Fosamax). Because of this, the prescribing provider should be contacted to consider discontinuation of the antiresorptive for at least 2 months before oral surgery and not restarted until osseous healing has occurred.
- Specialist recommended 2-month hiatus

- D4: how will you advise the patient?
  - I would advise the patient to discontinue the antiresorptive for at least 2 months to follow the oral surgeons recommendation at the consultation.

DISCUSSION QUESTIONS

- For patients that may need bisphosphonates for eg. osteoporosis, what are other treatment options that would reduce risk of osteonecrosis?
- How long before an extraction should the patient begin hyperbaric oxygen therapy?
- Are there particular populations that are more susceptible to developing osteonecrosis with bisphosphate use than others?
- Are there any localized treatment options to prevent osteonecrosis for patients on bisphosphonates?
- How does the difference in prevalence between the mandible and the maxilla in developing ORN change the course of treatment?

DISCUSSION QUESTIONS

- How long after cessation of bisphosphonate therapy are patients at higher risk of osteonecrosis?
- Have oxygen therapies before extractions proven affective?
- Does the form of bisphosphonate IV vs oral determine the extend of osteoradionecrosis?
- During bisphosphonate use, is there a way to determine whether or not it is safe to perform the extraction, or is it necessary to discontinue bisphosphonate use?

DISCUSSION QUESTIONS

- Besides hyperbaric oxygen therapy, are there any other treatment approaches to help reduce the risk of developing osteoradionecrosis?
- For what types of invasive dental procedures has medicationassociated osteonecrosis of the jaw been documented, and which invasive procedures should a drug holiday be considered?
- Are there other therapies that could be coupled with bisphosphonate to limit its disruption of bone remodeling?
- How can one tell clinically the difference between osteoradionecrosis and bisphosphonate related osteonecrosis of the jaw?