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Presentation Outline

- **1. Review of metastatic disease and osteoporosis**
- **2. Introduction to bisphosphonate drugs**
- **3. BRONJ- Clinical and radiographic features**
- **4. Risk factors and comorbidities**
- **5. Treatment stratagies for IV and oral bisphosphonate therapy**
- **6. Office protocols**
- **7. 2014 AAOMS position paper update**

Discovery of a new disease

- **"If you think you've discovered a new disease, you probably haven't reviewed the literature thoroughly enough"- Anonymous**

The 3 stages of scientific theory

- **1. It is scoffed at and met with disbelief.**
- **2. It is accepted as true, but insignificant and trivial.**
- **3. It is thought to be correct and even revolutionary. In fact, those who criticized it most now claim that they invented it and are the experts.**

"Phossy Jaw"

Goodbye BRONJ, Hello MRONJ

Metastatic Disease

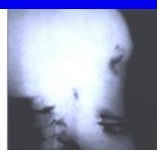
- Metastatic bone lesions produce a number of cytokines that stimulate excess osteoclastic activation disrupting the blast/clast balance
- This osteoclasis decreases bone volume and strength, and increases the chance of bone fracture
- Common findings in patients with metastatic bone lesions:
  - Pain
  - Fractures
  - Spinal cord compression
  - Hypercalcemia

Metastatic Disease

- 350,000 patients in the U.S. die from metastatic disease annually
- Metastatic bone disease is most commonly a result of one of the following:
  - Multiple myeloma
  - Breast cancer
  - Prostate cancer

Other Processes with Abnormal Osteoclastic Activity

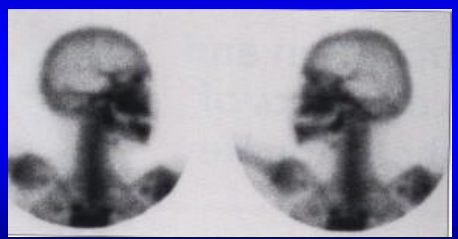
- Osteopetrosis (Albers-Schonberg disease, marble bone disease)-genetic loss of osteoclasts
- Paget's disease
- Fibrous dysplasia
- Osteoporosis



Bone Remodeling Facts

- The entire skeleton remodels every 150 days
- Due to the constant stresses of biting forces the remodeling rate of the alveolus is 10 fold that of long bones (5 fold at the canal, and 3 fold at the inferior border)

Tc99 Bone Scan Demonstrating High Bone Turnover in Jaws



Enter the Bisphosphonates

- Non-metabolized analogues of pyrophosphate
- Avidly bind to bone mineral around resorbing osteoclasts and inhibit their function
- Not metabolized, so high concentrations are maintained in bone for long periods of time, disrupting osteoclastic mediated bone resorption
- The terminal phase of elimination half life may be up to 10 years

The Bisphosphonates

- IV Preparations
  - Pamidronate (Aredia)
  - Zoledronate (Zometa)
- Oral Preparations
  - Etidronate (Didronel)
  - Tiludronate (Skelid)
  - Alendronate (Fosamax)
  - Risedronate (Actonel)
  - Ibandronate (Boniva)
- Didronel and Skelid only used for Paget's

Aredia/Zometa

- American Society of Clinical Oncology promotes the use of bisphosphonates as the standard of care
- 85% in U.S. on Aredia (35%) or Zometa (65%)
- 5/2/89-11/30/04-1,880,000 patients treated worldwide
- Decrease SREs (skeletal related events) by up to one third
- A hip fracture in the elderly is equivalent to a stroke, and 20% die
- If tolerated, the patient may be maintained on the drug indefinitely
- One source estimates that there are 3 million patients on IV bisphosphonate therapy in the U.S. today

Oral Preparations

- Commonly used for the osteoporosis associated with menopause
- Estimated to being used by 14 million women in the U.S.
- Not as potent as the IV preparations
- In 2003 17 million prescriptions were written for Fosamax and 6 million for Actonel; 190 million prescriptions have been written worldwide

Relative Potency

- Didronel (po) 1
- Skelid (po) 50
- Fosamax (po) 1000
- Actonel (po) 1000
- Boniva (po) 1000
- Aredia (IV) 1000-5000
- Zometa (IV) 10,000

The Problem

- In 2003, 36 patients in a study by Marx in Miami, and 63 patients in a study by Ruggerio at LIJ in New York were identified as having avascular necrosis of one or both jaws.
- The common denominator in these cases was bisphosphonate therapy

Black Box Warning

- A dental examination with appropriate preventive dentistry should be considered before starting treatment with IV bisphosphonates. This is particularly important if you:
- Have poor dental health
- Have cancer
- Are receiving chemotherapy
- Are taking corticosteroids

Bisphosphonate Related Osteonecrosis of the Jaws (BRONJ)

- Cause-vascular insufficiency from excessive inhibition of osteoclastic activity
- Bisphosphonates directly inhibit endothelial cell function, depress bone blood flow, and display potent antiangiogenic properties
- The inflammatory and infectious potential associated with the dentition provides the reason for only the jaws being affected by the process

Clinical Presentation of BRONJ

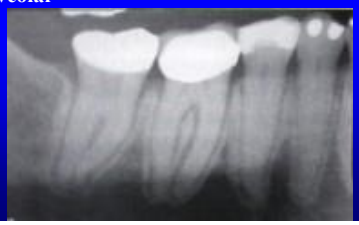
- Bisphosphonate induced osteonecrosis of the jaws refers to a condition of exposed necrotic bone in the mandible or maxilla that persists for more than 8 weeks in a patient who has taken or currently is taking a bisphosphonate and who has no history of radiation therapy to the jaws
- The process may begin following an invasive procedure or spontaneously (75%/25%)
- May remain asymptomatic and painless for weeks or months, unless secondarily infected or traumatized
- Progression to sequestrum formation is common
- Unlike ORN, the maxilla is commonly affected

Clinical Presentation of BRONJ contd

- Early x-rays show widening of the perio ligament space and sclerosis of the lamina dura, later films show regions of mottled bone and sequestrum formation
- Cultures reveal normal oral flora (commonly Actinomyces, Eikenella, and Moraxella), and microscopy shows dead bone with bacterial debris and granulation tissue
- Tooth mobility and deep bone pain may present before bone exposure

Early X-Ray Features

- Widened PDL/sclerosed trabecular alveolar bone



X-Ray Features

Clinical Presentation of BRON contd

- **Dead bone is painless; pain indicates infection**
- **Process always begins in the alveolus (usually in the molar region)**

Clinical Presentation of BRONJ




Risk Factors

- **Drug related risk factors:**
  - Potency
  - Duration of therapy
    - Over 3 years with the oral preparations
    - About 1 year with the IV preparations
- **Local risk factors**
  - Dentalveolar surgery
    - 7 times the risk of developing BRONJ in the IV patient

Risk Factors contd.

- **Local risk factors contd.**
  - Local anatomy
    - More common in the mandible, and more common over bony prominences where mucosa is thin
  - Concomitant oral disease
    - History of inflammatory dental disease increases risk of BRONJ at least 7 fold
  - Demographic and systemic factors
    - Age- each passing decade increases risk of BRONJ 9% in the multiple myeloma patient

Risk Factors contd.

- **Demographic and systemic factors contd**
  - Race-Caucasian
  - Cancer diagnosis-risk> with multiple myeloma patients than breast cancer, and risk> with breast cancer than other cancers
  - Osteopenia/osteoporosis diagnosis concurrent with cancer diagnosis

Other BRONJ Risk Factors

- **1. Corticosteroid therapy**
- **2. Diabetes**
- **3. Smoking**
- **4. Alcohol use**
- **5. Poor oral hygiene**
- **6. Chemotherapeutic drugs**

Dental Comorbidities

- Perio disease
- Caries
- Abscessed teeth
- Failing endo
- Mandibular tori

Clinical Management

- Frustrating, ineffective, and difficult
- Antibiotics have little impact other than helping to keep process in check
- HBO therapy of no help
- Surgery is difficult due to inability to identify a surgical margin of viable bone
- Stopping the offending IV drug once the process has begun does not stop its progress

Staging

- Stage 0 (at risk)- taking a bisphosphonate with no exposed bone or symptoms
- Stage I-exposed bone, no pain or infection
- Stage II-exposed bone with infection and pain
- Stage III-pathological fracture, large volume of necrotic bone, no response to antibiotics

Stage 0 Treatment Strategies

- No treatment required other than maintenance of excellent oral hygiene
- Patients need to be informed of risks for developing BRONJ, as well as signs and symptoms of the process
- Invasive procedures should be avoided in IV bisphosphonate patients

Stage 1 Treatment Strategies

- Avoid surgical treatment
- Chlorhexidine rinses

Stage 2 Treatment Strategies

- Antimicrobial rinses
- Antibiotic therapy
  - Penicillin often works well
  - Quinolones, metronidazole, clindamycin, doxycycline, erythromycin for the penicillin allergic
  - Refractory cases may require combination antibiotic therapy, long-term antibiotic maintenance, or intravenous therapy

Stage 3 Treatment Strategies

- Pain impacts quality of life; analgesic therapy important
- Surgical debridement/resection in combination with antibiotic therapy may offer long-term palliation with resolution of acute infection and pain
- Mobile segments should be removed without exposing uninvolved bone
- Extraction of teeth within exposed necrotic bone should be considered

Discontinuation of IV Bisphosphonates

- Offers no short-term benefits
- If systemic conditions permit, long-term discontinuation may stabilize established sites and reduce risk of new site development

Discontinuation of Oral Bisphosphonates

- May lead to gradual disease improvement
- After 6-12 months either spontaneous sequestration or resolution following debridement surgery may occur
- Consult with managing physician concerning patient's condition and whether discontinuation is a viable option

Treatment of the Patient Taking IV Bisphosphonates

- Occurrence of symptoms takes an average of 10 months with Zometa, and 14 months with Aredia
- 3-8% of IV bisphosphonate patients develop BRONJ (twice as common in the mandible)
- It takes 5-6 doses of chemo before all the bone is compromised
- Therapy should be directed toward decreasing pain, managing infection, and preventing additional exposure
- 75% of BRONJ cases develop in response to dental trauma or invasive procedures

Dental Treatment Prior to IV Bisphosphonate Therapy

- Extraction of suspect teeth
- Evaluate denture fit
- Treatment of caries and perio
- Prophylaxis and aggressive home care eduction
- Impactions with no oral communication and total bony coverage may be left
- May be wise to remove tori that may be irritating
- Defer therapy until things have healed for 2-3 months

Dental Treatment for Patients Already Taking IV Bisphosphonates

- Avoid all invasive procedures
- Limit scaling to supragingival
- Treat caries
- Avoid extractions by using endo and crown removal
- Splint perio involved teeth vice extraction

Treatment of Patients Receiving IV Bisphosphonate Therapy

- Maintain highest level of oral hygiene
- Removeable appliances should be frequently checked and adjusted to avoid soft tissue injury
- Avoid soft tissue injury during cleaning procedures
- Manage dental infections aggressively, while keeping surgical intervention minimal
- Dental exams should be at 3-4 month intervals, and a brief inspection by the oncologist at every follow-up visit

IV Bisphosphonate Patient with Exposed Bone

- Don't debride; treat symptoms with anitbiotics/peridex
- Conservative smoothing of sharp edges
- Rx-PenVK 500mg QID for infection exacerbations (add Flagyl for 10 days for refractory cases); Levaquin for patients with PCN allergy
- Don't use clindamycin due to resistance in Actinomyces and Eikenella
- Patient may be kept on maintenance dose of PenVK 500mg BID indefinitely
- Intractable pain or pathological fx may force alveolectomy or resection (5% require resection)
- In Marx' study of 119 patients, 87% were kept pain free with exposed bone

Oral Bisphosphonates

- Etidronate (Didronel)
- Tiludronate (Skelid)
- Alendronate (Fosamax)
- Risedronate (Actonel)
- Ibandronate (Boniva)
- Zoledronic Acid (Zometa IV monthly for metastatic bone disease, Reclast IV annually for osteoporosis)

Reclast (new use for zoledronate)

- Approved 4/16/07 for use in Paget's disease of bone (first new Paget's drug approved in 10 years)
- Now also approved for osteoporosis
- Given IV over a time span of at least 15 minutes; one injection annually
- Same dental precautions as other bisphosphonates used orally for osteoporosis

Oral Bisphosphonates

- Not as potent as injectables
- Accumulate much more slowly
- .01%-.04% of spontaneous BRONJ; .09%-.34% following invasive procedure
- No bone exposure documented until after 3 yrs of taking drug; bone exposure more likely with each year over 3 (comorbidities may make for exposed bone in <3yrs)
- Comorbidity of steroid use seen frequently in patients with RA, SLE, etc.

Oral Bisphosphonates

- If bone is exposed it is less severe, may be reversible, and debridement is more predictable
- Some question as to whether there is any benefit to taking Fosamax longer than 3yrs
- There is a simple serum lab test that can guide you concerning the patient's risk for developing BRONJ (only for oral preparations)- CTX

CTX (C-Terminal Cross-Linking Telopeptide)

- Correlates to the systemic suppression of bone renewal caused by oral bisposphonates
- The CTX test provided by Quest Diagnostics, it uses an AM fasting serum sample, costs $140, and takes a week to get results
- Results lower than 100pg/ml are associated with high risk of BRONJ, 101-150 moderate risk, and > 150 minimal risk for BRONJ

Exposed Bone After 3yrs of Therapy

- Stop drug if possible, treat palliatively, monitor CTX
- In 50% of Marx' patients the dead bone sequestered and soft tissue healed without surgery in 4-9mos
- You can expect the CTX to go up ~20-25 units/mo for each month off the drug

Office Protocols

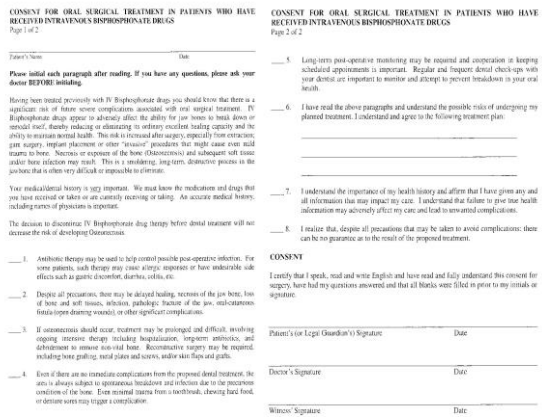
- Health History Questions
  - Are you now, or have you ever been txd for cancer? when, for how long, what drugs
  - Are you now, or have you ever been treated for osteoporosis? when, for how long, what drugs
  - Be cognizant of drugs and disease processes that may be comorbidities

Office Protocols

- Have a special consent form for invasive procedures performed on the oral bisphosphonate patient (especially implants, since the risk for problems increases with each year after the first 3yrs of drug therapy)
- Offer them the option of getting a CTX to see where they are from a risk standpoint, and then if you feel it necessary to improve things check with physician about a "drug holiday"
- You may think about getting a CTX even in patients with <3yrs of therapy for big cases, or for the patient's peace of mind

Risk Management

- All patients that have received these drugs must sign an informed consent disclosing options and the potential risk associated with bisphosphonate drugs prior to any treatment or non-treatment
- Your progress note must document the discussion of the treatment options and the potential risk of and significance of BRONJ



CONSENT FOR ORAL SURGICAL TREATMENT IN PATIENTS WHO HAVE RECEIVED INTRAVENOUS BISPHOSPHONATE DRUGS
Page 1 of 2

Patient's Name _____ Date _____

Please initial each paragraph after reading. If you have any questions, please ask your doctor BEFORE initialing.

Having been treated previously with IV Bisphosphonate drugs you should know that there is a significant risk of future severe complications associated with oral surgical treatment. IV Bisphosphonate drugs appear to adversely affect the ability for jaw bones to break down or remodel itself, thereby reducing or eliminating its ordinary excellent healing capacity and the ability to maintain normal health. This risk is increased after surgery, especially from extraction, gum surgery, implant placement or other "invasive" procedures that might cause even mild trauma to bone. Necrosis or exposure of the bone (Osteonecrosis) and subsequent soft tissue and/or bone infection may result. This is a smoldering, long-term, destructive process in the jaw bone that is often very difficult or impossible to eliminate.

Your medical/dental history is very important. We must know the medications and drugs that you have received or taken or are currently receiving or taking. An accurate medical history, including names of physicians is important.

The decision to discontinue IV Bisphosphonate drug therapy before dental treatment will not decrease the risk of developing Osteonecrosis.

___1. Antibiotic therapy may be used to help control possible post-operative infection. For some patients, such therapy may cause allergic responses or have undesirable side effects such as gastric discomfort, diarrhea, colitis, etc.

___2. Despite all precautions, there may be delayed healing, necrosis of the jaw bone, loss of bone and soft tissues, infection, pathologic fracture of the jaw, oral-cutaneous fistula (open draining wounds), or other significant complications.

___3. If osteonecrosis should occur, treatment may be prolonged and difficult, involving ongoing intensive therapy including hospitalization, long-term antibiotics, and debridement to remove non-vital bone. Reconstructive surgery may be required, including bone grafting, metal plates and screws, and/or skin flaps and grafts.

___4. Even if there are no immediate complications from the proposed dental treatment, the area is always subject to spontaneous breakdown and infection due to the precarious condition of the bone. Even minimal trauma from a toothbrush, chewing hard food, or denture sores may trigger a complication.

CONSENT FOR ORAL SURGICAL TREATMENT IN PATIENTS WHO HAVE RECEIVED INTRAVENOUS BISPHOSPHONATE DRUGS
Page 2 of 2

___5. Long-term post-operative monitoring may be required and cooperation in keeping scheduled appointments is important. Regular and frequent dental check-ups with your dentist are important to monitor and attempt to prevent breakdown in your oral health.

___6. I have read the above paragraphs and understand the possible risks of undergoing my planned treatment. I understand and agree to the following treatment plan:

_____

_____

_____

___7. I understand the importance of my health history and affirm that I have given any and all information that may impact my care. I understand that failure to give true health information may adversely affect my care and lead to unwanted complications.

___8. I realize that, despite all precautions that may be taken to avoid complications: there can be no guarantee as to the result of the proposed treatment.

CONSENT

I certify that I speak, read and write English and have read and fully understand this consent for surgery, have had my questions answered and that all blanks were filled in prior to my initials or signature.

Patient's (or Legal Guardian's) Signature _____ Date _____

Doctor's Signature _____ Date _____

Witness' Signature _____ Date _____

CONSENT FOR ORAL SURGICAL TREATMENT IN PATIENTS WHO HAVE RECEIVED ORAL BISPHOSPHONATE DRUGS
Page 1 of 2

Patient's Name Date

Please initial each paragraph after reading. If you have any questions, please ask your doctor BEFORE initialing.

Having been treated previously with oral Bisphosphonate drugs you should know that there is a very small, but real risk of future complications associated with dental treatment. This risk is currently estimated to be less than 1/10 of one percent. Bisphosphonate drugs appear to adversely affect the health of jaw bones, thereby reducing or eliminating the jaw bones ordinary excellent healing capacity. This risk is increased after surgery, especially from extraction, implant placement or other "invasive" procedures that might cause even mild trauma to the bone. Spontaneous exposure of the jaw bone (Osteonecrosis) may result. This is a smoldering, long-term, destructive process in the jawbone that is often very difficult or impossible to eliminate.

Your medical/dental history is very important. We must know the medications and drugs that you have received or taken or are currently receiving or taking. An accurate medical history, including names of physicians is important.

The decision to discontinue oral Bisphosphonate drug therapy before dental treatment should be made by you in consultation with your medical doctor.

___1. If a complication occurs, antibiotic therapy may be used to help control infection. For some patients, such therapy may cause allergic responses or have undesirable side effects such as gastric discomfort, diarrhea, colitis, etc.

___2. Despite all precautions, there may be delayed healing, osteonecrosis, loss of bone and soft tissues, pathologic fracture of the jaw, oral-cutaneous fistula (open draining wound), or other significant complications.

___3. If osteonecrosis should occur, treatment may be prolonged and difficult, involving ongoing intensive therapy including hospitalization, long-term antibiotics, and debridement to remove non-vital bone. Reconstructive surgery may be required, including bone grafting, metal plates and screws, and/or skin flaps and grafts.

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CONSENT FOR ORAL SURGICAL TREATMENT IN PATIENTS WHO HAVE RECEIVED ORAL BISPHOSPHONATE DRUGS
Page 2 of 2

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CONSENT

I certify that I speak, read and write English and have read and fully understand this consent for surgery, have had my questions answered and that all blanks were filled in prior to my initials or signature.

_____ _____
Patient's (or Legal Guardian's) Signature Date

_____ _____
Doctor's Signature Date

_____ _____
Witness' Signature Date

Re: _____

I am currently seeing your patient, _____. Your patient informs me that she/he has been taking an oral bisphosphonate (Fosamax, Actonel, Boniva, Didronel, or Skelid). As you know, a number of patients have developed osteonecrosis of the jaws (ONJ) after taking bisphosphonates, particularly IV bisphosphonates (Zometa or Aredia).

The American Association of Oral and Maxillofacial Surgeons has recently issued a "Position Paper" on "Bisphosphonate-Related Osteonecrosis of the Jaws". While oral bisphosphonates are associated with only a small number of osteonecrosis cases at this time, it appears that the risk of developing Bisphosphonate-Related Osteonecrosis of the Jaws (BRON) associated with oral bisphosphonates may be increased when duration of therapy exceeds three years, or when oral bisphosphonates are given concomitantly with long-term corticosteroids or chemotherapy, the patient has diabetes, smokes, uses excessive alcohol, or has poor oral hygiene. Your patient meets one of these criteria.

For patients who have been on oral bisphosphonates more that 3 years, or have taken oral bisphosphonates and have one of the additional risk factors listed above, the AAOMS Position Paper recommends the following for patient management prior to any elective dentoalveolar surgery:

"…the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least three months prior to oral surgery, *if systemic conditions permit.* The bisphosphonate should not be restarted until osseous healing has occurred (approximately three more months)."

Please advise our office by return fax (_____) or phone (_____) if you would:

1. recommend a drug holiday as described above YES _____
2. not recommend a drug holiday as discussed above YES _____

Signature_____

Once we have your recommendation, we will contact your patient with your recommendation and schedule our surgery in compliance with it. Thank you for your help with this patient. Working together, we can provide the best care for your patient.

Cordially,

LETTER TO DENTISTS

Dear Dr. _____

As we all know, a number of patients have developed osteonecrosis of the jaws after taking bisphosphonates, particularly IV bisphosphonates. We also see attorneys advertising for patients with osteonecrosis of the jaw (ONJ) to contact them for legal help to "get the settlement that they deserve".

While initially dentists saw the bisphosphonate issue as "someone else's problem", unfortunately it appears that dentists will also have malpractice claims as plaintiff's attorneys start looking for someone to "blame" for their client's misfortunes. Patients who are on IV bisphosphonates are usually being treated for multiple myeloma , metastatic breast, lung or prostate cancer. Many of these patients will likely die because of their disease, but have been spared several years of debilitating bone pain that many times goes along with these diseases. Unfortunately, a small percentage of these patients will be reading off the bone destruction and pain associated with their disease for ONJ. Oncologists appear to be continuing to use IV bisphosphonates in spite of the potential for the development of ONJ saying that the benefits outweigh the risks.

While it is obvious that ONJ is NOT a condition that dentists are responsible for creating, it is important that dentists look at every patient who walks into their office with metastatic bone cancer as a potential "claim". We have seen that many patients on IV bisphosphonates DO NOT DISCLOSE to the dentist that they are on them. Rather, they will disclose that they are on "chemotherapy", NOT LISTING which specific drugs they are taking. It is important for the dentist to be suspicious that patients with metastatic disease MAY be on bisphosphonates, and question the patient and their oncologist as to which specific drugs they are taking.

As always, claims defense is much easier if the cardinal principles of risk management are followed:

1. Disclose …patients need to be advised of potential bad outcomes from surgical treatment while on bisphosphonates.
2. Document …a documented informed consent discussion, along with the use of a consent form for patients on oral or IV bisphosphonates really helps with claims defense. We have copies of consent forms for patients taking both forms of the drug, oral and intravenous. If you would like a copy of these forms, please contact our office.
3. Follow Guidelines for Treatment as announced by the company producing IV bisphosphonates (Novartis). In the letter to dentists on May 05, 2005, Novartis indicates that "prescribing information recommends that cancer patients:
   - receive a dental examination prior to initiating therapy with intravenous bisphosphonates; and,
   - avoid invasive dental procedures while receiving bisphosphonate treatment. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. Clinical judgment by the treating physician should guide the management plan of each patient based on individual benefit/risk assessment."
4. The American Dental Association convened an Expert Panel and developed recommendations for dental management of patients on bisphosphonates and published them in June, 2006. The recommendations can be found at http://www.ada.org/prof/res/ecp/osteonecrosis.
5. The American Association of Oral and Maxillofacial Surgeons has recently issued a "Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws (September 25, 2006) available at http://www.aaoms.org/docs/position_papers/bisphosphonate_osteonecrosis.pdf. This paper defines Bisphosphonate-Related Osteonecrosis of the Jaws ("BRON") and provides current management/treatment strategies for patients undergoing either oral or IV bisphosphonate therapy. These recommendations are somewhat more involved than the recommendations issued by the ADA. For patients taking oral bisphosphonates for longer than three years prior to any invasive surgery, the current recommendation is a "drug holiday" of three months before surgery and three months after surgery. These recommendations are based on anecdotal evidence that may be of benefit, not on any long-term clinical studies. We have enclosed a summary of the AAOMS "Treatment" and "Management" recommendations for you to use as a guide for treatment if you want. These summaries can be kept in your desk for reference. In addition, we have included a current listing of all bisphosphonate drugs currently available, both oral and intravenous.

It is important that we as a dental community do what is best for our patients. With regard to treatment of those patients on bisphosphonates, it is important to keep current with the latest information and suggestions. A little bit of additional time on the initial consultation will be beneficial in allowing the doctor to provide excellent care to patients taking bisphosphonates.

Cordially,

_____, DDS
Oral and Maxillofacial Surgery

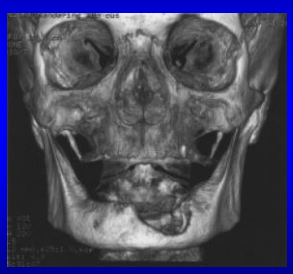
Alternative Drugs for Osteoporosis

- Evista-works as well as fosamax and costs about the same
- Forteo-expensive and requires daily injection
- Salmon calcitonin-expensive, comes as a nasal spray

Final Thoughts

- These drugs will continue to be used, and probably with greater frequency
- We are going to see more patients with the problem or at risk for it
- We must be aggressive in educating our patients and dental and medical colleagues
- We must be vigilant in our follow-up and treatment of both patients with or at risk for BRONJ

Hello, MRONJ



AAOMS Position Paper Update

- Original paper 2009; before the advent of non-bisphosphonate antiresorptives and other antiangiogenics
- New 2014 position paper revises:
  - 1. Diagnosis
  - 2. Staging
  - 3. Management
  - 4. Highlights current research status

Position Paper Purpose

- Risk estimates of developing MRONJ
- Comparison of risks and benefits related to MRONJ
- Guidance regarding:
  - 1. Differential diagnosis
  - 2. MRONJ prevention measures
  - 3. Management strategies based on disease stage

IV Bisphosphonates pamidronate (Aredia) zoledronate (Zometa)

- Hypercalcemia of malignancy
- Skeletal related events (SRE) associated with solid tumors (breast, prostate, lung), and the lytic lesions of multiple myeloma
- Once yearly zoledronate (Reclast), once quarterly banidronate (Boniva) for osteoporosis

Oral Bisphosphonates alendronate (Fosamax) risedronate (Actonel)

- Used for osteopenia and osteoporosis
- Far less likely to cause MRONJ than the injectables

RANK Ligand Inhibitors

- Osteoblasts secrete RANKL which activates osteoclast precursors and subsequent osteolysis
- RANKL inhibitors block the interaction between RANK, the receptor on the osteoclast, and RANKL has no activity, leading to no resorption and greater bone density

RANK ligand inhibitor denosumab (Prolia, Xgeva)

- A fully humanized antibody that inhibits osteoclast function and associated bone resorption
- Prolia- subcutaneous injection every 6 months decreases SREs in osteoporosis patients
- Xgeva- decreases SREs in metastatic bone disease from solid tumors

Bisphosphonates vs RANK ligand inhibitors

- The inhibitors do not bind to bone, so their effects on bone remodeling are mostly diminished within 6 months of treatment cessation.

Antiangiogenic Medications bevacizumab (Avastin)

- Inhibit formation of new blood vessels by disrupting the angiogenesis signaling cascade
- Used in treatment of GI tumors, renal cell carcinomas, and neuroendocrine tumors
- Potential for significant oral manifestations

MRONJ Case Definition

- 1. Current or previous treatment with antiresorptive or antiangiogenic agents
- 2. Exposed bone or bone that can be probed through an intra- or extraoral fistula in the maxilolfacial region that has persisted for more than 8 weeks
- 3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

Pathophysiology

- I. Inhibition of osteoclastic bone resorption and remodeling (the normal bone turnover in the jaws is much higher than other bones)
- II. Inflammation/infection (oral bacteria, existence of the perio ligament)
- III. Inhibition of angiogenesis

Risk Factors for MRONJ

- Medication related risk factors
  - Risk of ONJ is 50-100 times higher in cancer patients taking Zometa or denosumab than in cancer patients not taking these drugs
- Much less preliminary evidence concerning the antiangiogenic agents, but these agents used in consort with BPs have shown to significantly increase risk

MRONJ Risk in Osteoporosis Patients Taking Oral BPs

- 10 cases per 10,000 (.1%) patients, which increases to 21 (.2%) cases in patients with more than 4 years drug exposure

MRONJ Risks in Osteoporosis Patients Taking IV BPs or RANK Inhibitors

- **The risk of ONJ in patients treated with yearly Zometa for 3 yrs- 1.7 cases per 10,000 patients, extending the study 6 years did not impact frequency**
- **Frequency for patients exposed to denosumab was 4 cases per 10,000 patients**
- **Ironically, placebo group patients had similar ONJ risk numbers as above**

Duration of Therapy as a Risk Factor for MRONJ

- **IV BPs or Denosumab**
  - 0.6% incidence of developing ONJ at 1 yr
  - 1.1% at 2 yrs
  - 1.2% at 3 yrs
- **Oral BP Therapy**
  - 0.21% after at least 4 yrs exposure
  - The risk is about 100 times smaller for the osteoporosis patient compared to cancer patients

Local Factors

- **Tooth Extraction or Other Dentoalveolar Surgery- 0.5% occurrence in oral BP patients; 1.6-14.8% in IV BP patients**
- **Anatomic Factors- MRONJ is 73% more likely to occur in the mandible.**
- **MRONJ is twice as likely to occur in denture wearers**
- **Pre-existing inflammatory dental disease increases the MRONJ risk by 50%**

Demographic, Systemic, and Other Medication Factors

- **Corticosteroid therapy in consort with BPs and antiangiogenic agents increase risk**
- **Systemic illnesses (DM, anemia, cancer) increase risk**
- **Uncertain if tobacco is a risk**

Management Strategies

- **Prevention of MRONJ**
  - 50% decrease in patients who are screened and receive dental care prior to initiating drug therapy
  - Drug Holiday- a 2 month holiday for the osteoporosis patient prior to an invasive procedure makes sense physiologically, but there is no substantial data to support this

Management Strategies

- **Cancer patients receiving monthly IV BPs**
  - All invasive dental therapies should be avoided
  - If ONJ develops the oncologist may opt to discontinue the antiresorptive therapy until soft tissue closure has occured

Before Starting IV Cancer Therapies

- Optimize oral health
- Extract nonrestorable teeth, remove tori/exostoses; wait 14-21 days after surgery to begin drug therapy
- Make sure dentures and partials fit well, and take special note of the lingual flange
- Make certain the patient understands the import of immaculate oral hygiene and frequent oral evaluations

Patients About to Begin Osteoporosis Therapy

- Make certain the patient understands the potential risks of ONJ
- Since the therapy is likely to last years it is important that they understand the need for life long attention to their oral health

Asymptomatic Patients Receiving IV Cancer Tx

- Avoid all procedures that involve direct osseous injury (remove the crowns of nonrestorable teeth and do endo on the remaining roots to avoid extractions)
- Dental implants should not be considered

Asymptomatic Patients Being Treated for Osteoporosis

- Regular dental care may be provided, but patient should know that they may have altered healing, especially if they have been taking the BP over 4 years. They should also understand the impact of comorbidities
- If possible a drug holiday 2 months before the invasive procedure and 3 months following is suggested

Patients with Established MRONJ

- Eliminate pain, control infection, minimize progression of bone necrosis
- Avoid elective surgeries
- Minimal procedures to remove sharp bone
- Symptomatic teeth may be removed if they are in a region of nonviable bone
- Therapies involving HBO, BMP, PRP require more study

Patients at Risk

- Asymptomatic patients with no apparent necrotic bone who have been treated with IV or oral antiresorptive or antiangiogenic therapy
- Should be informed of the risks of developing MRONJ and of the signs and symptoms of the disease process

Stage 0 (unexposed bone variant)

- No evidence of necrotic bone, but nonspecific symptoms or radiographic findings
- Symptoms- unexplained odontalgia, bone pain, sinus pain, altered neurosensory function
- Loose teeth not explained by perio findings, fistulae not associated with pulpal necrosis

Stage 0 contd.

- Radiographic Findings
  - Alveolar bone loss not attributable to perio
  - Changes is trabecular pattern
  - Regions of osteosclerosis
  - Thickening/obscuring of perio ligament

Stage 0 Treatment

- Provide symptomatic treatment and conservatively manage local factors
- Management may include medications for pain and antibiotics to manage infection
- Monitor patient closely and continue to evaluate radiographically for disease progression

Stage 1

- Asymptomatic exposed and necrotic bone or probeable fistulae that have no evidence of infection
- May have radiographic findings mentioned for stage 0 which are localized to the alveolar bone region

Stage 1 Treatment

- Antimicrobial rinses
- Analgesics
- No immediate operative treatment is required

Stage 2

- Exposed and necrotic bone or fistula that probe to bone with evidence of infection
- Patients are typically symptomatic
- Radiographic findings mentioned for stage 0 localized to the alveolar bone region

Stage 2 Treatment

- **Antimicrobial rinses**
- **Analgesics**
- **Antibiotics**
  - Penicillin, clindamycin, quinolones

Stage 3

- **Exposed necrotic bone or fistulae that probe to bone with evidence of infection and at least one of the following**
  - Exposed necrotic bone extending beyond the alveolar bone
  - Pathologic fracture
  - Extraoral fistula
  - Oral antral/oral nasal communication
  - Osteolysis extending to the inferior border or sinus floor

Stage 3 Treatment

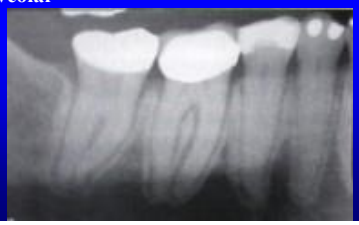
- **Antimicrobial rinses**
- **Analgesics**
- **Antibiotics**
- **Debridement or resection**
- **Reconstruction with a plate is tenuous**
- **Reconstruction with vascularized bone may be successful**

Regardless of the Stage

- **Mobile bony sequestra should be removed to facilitate tissue healing**
- **Extraction of symptomatic teeth in necrotic exposed bone should be considered for extraction**
- **A through histologic analysis of all resected bone should be performed to rule out metastasis in the cancer patient**

Early X-Ray Features

- **Widened PDL/sclerosed trabecular alveolar bone**

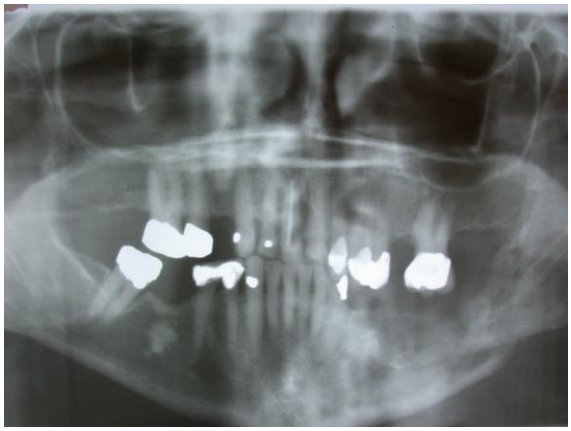


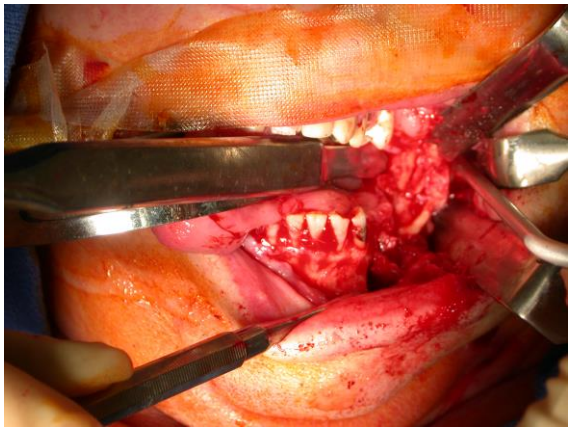
X-Ray Features

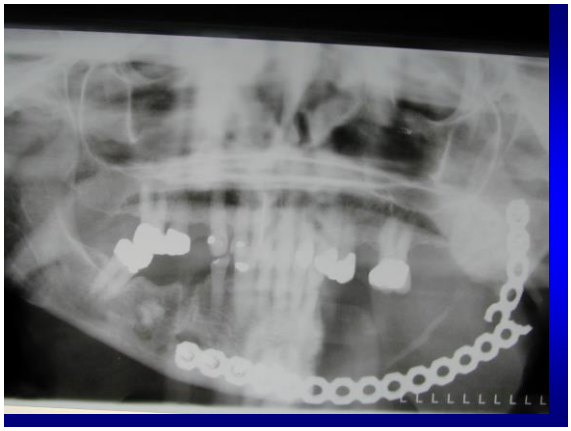
Clinical Presentation of MRONJ contd

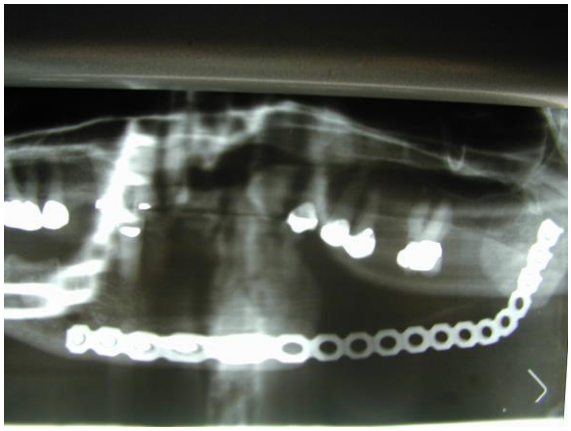
- Dead bone is painless; pain indicates infection
- Process always begins in the alveolus (usually in the molar region)

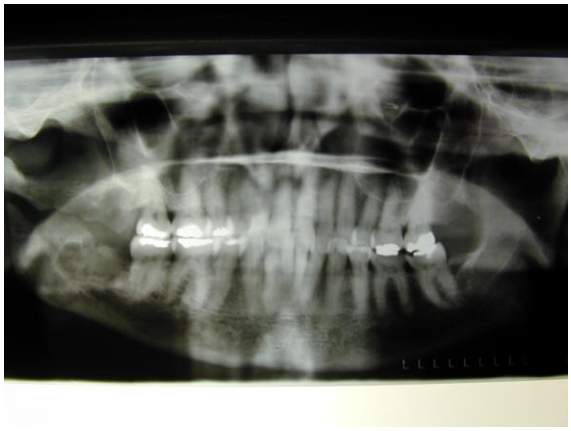
Clinical Presentation of MRONJ

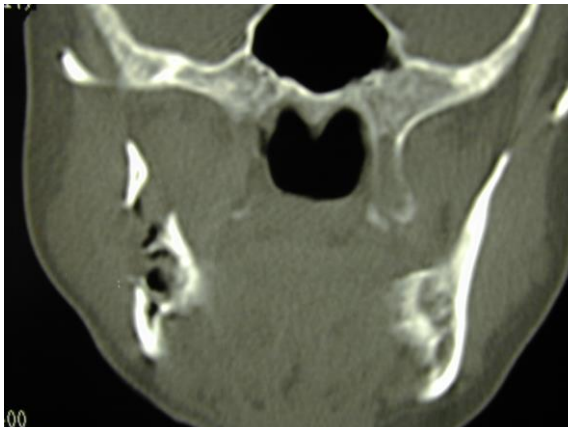


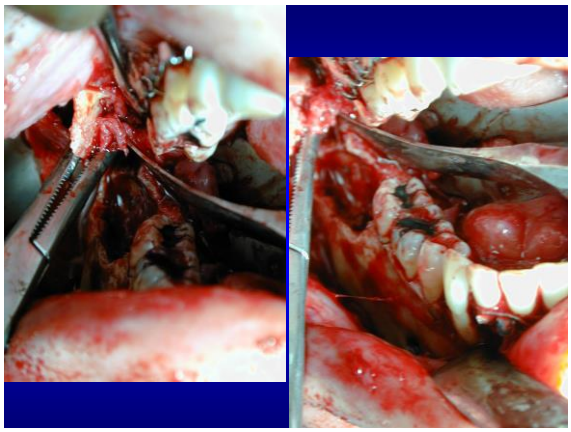


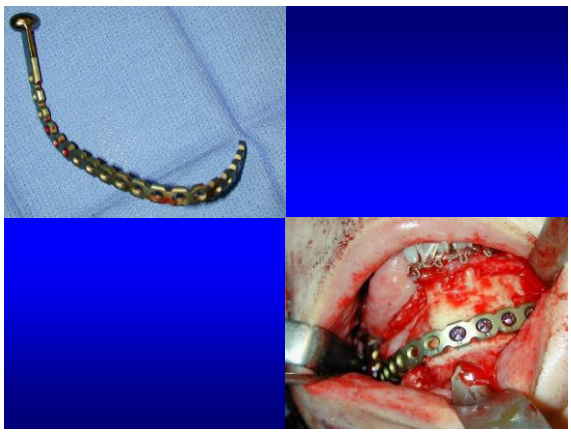












1 Month Postop

Thank You