Bisphosphonate-Related Osteonecrosis of the Jaws

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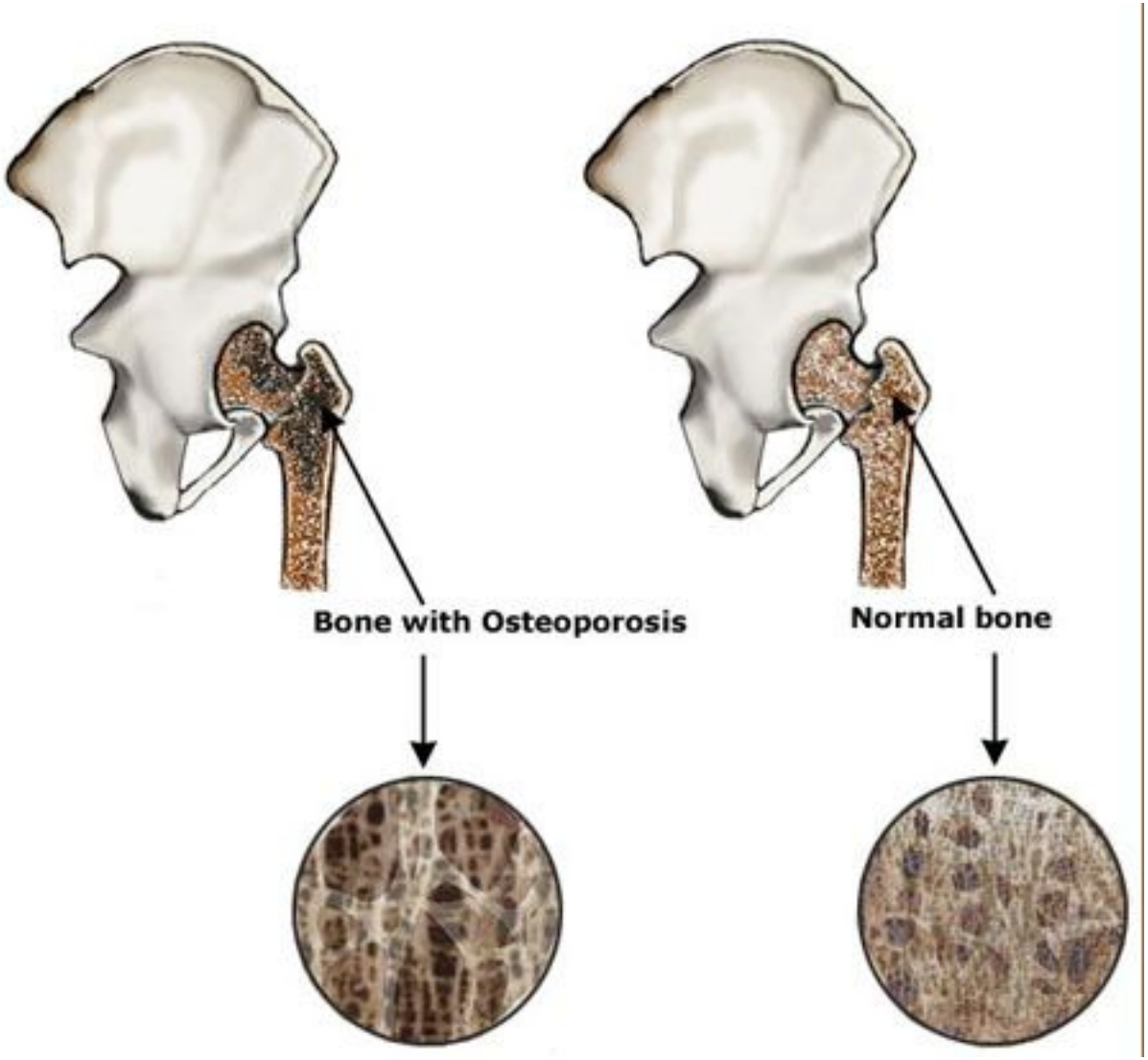
Bisphosphonate Related Osteonecrosis of the Jaw

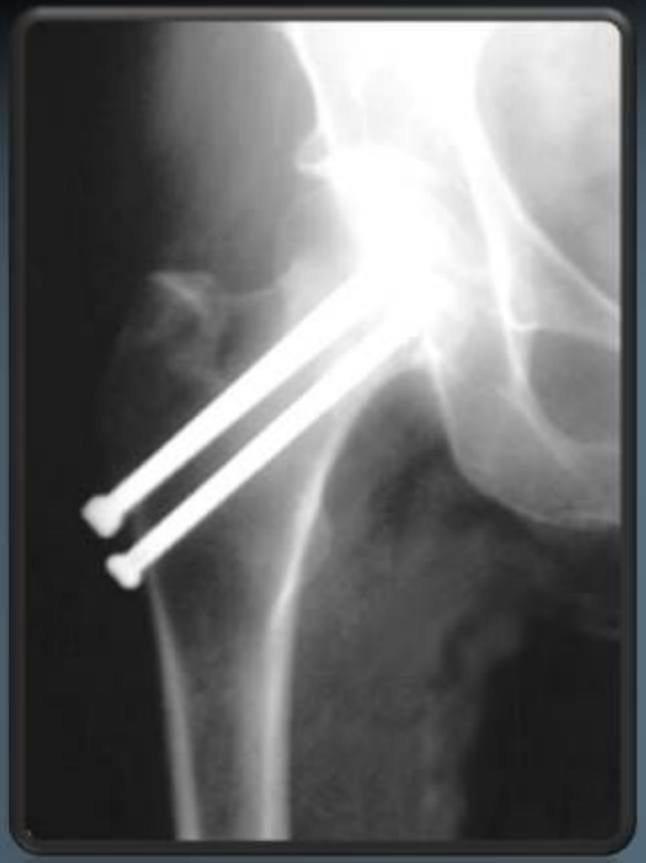
Osteoporosis

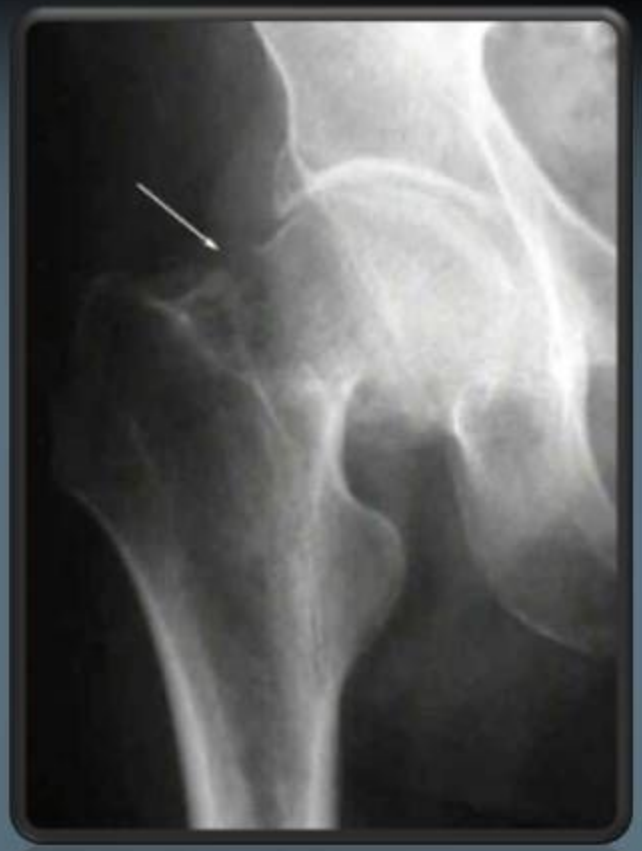
- 15 per cent of females at the age of 50
- 30 per cent of females at the age of 70
- 40 per cent of females at the age of 80

- Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Min Res 1994; 9:1137-41.

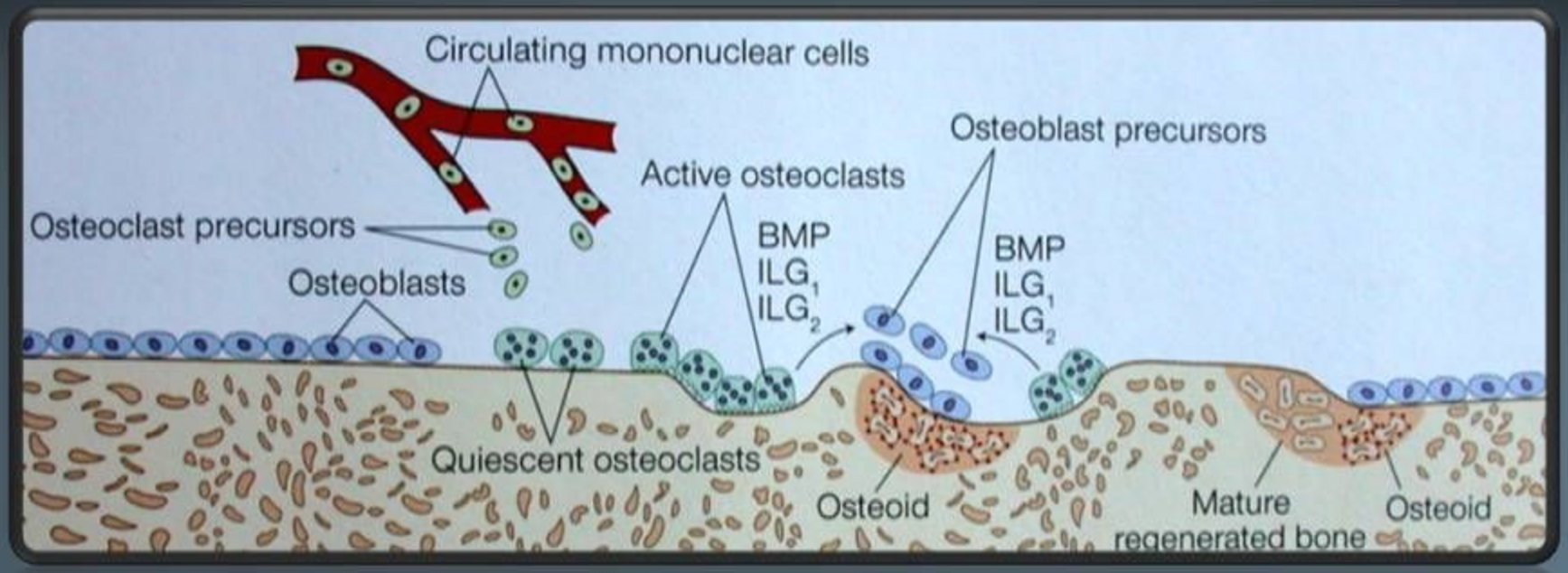

Bone with Osteoporosis
Normal bone

Hip Fracture



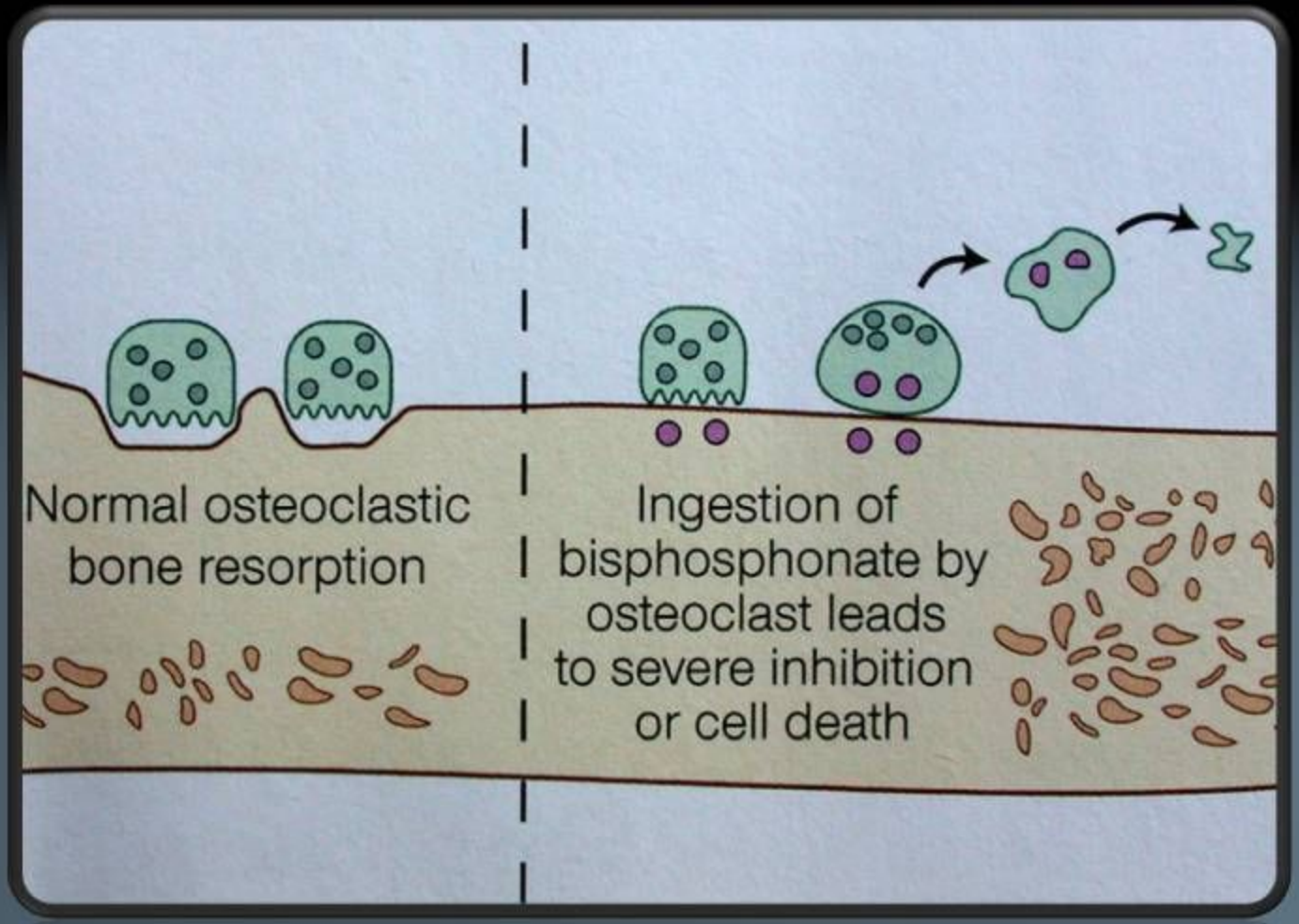


Normal Bone Physiology



1 month | 3 months | 6 months

Time →


Normal osteoclastic bone resorption
Ingestion of bisphosphonate by osteoclast leads to severe inhibition or cell death

Canadian Dental Protective Association

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Ottawa, Ontario

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Clinical PRACTICE

A Review of Bisphosphonate-Associated Osteonecrosis of the Jaws and Its Management

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Howard I. Holmes, *DDS;* **A. Wayne Evans,** *MD;*
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ABSTRACT

Bisphosphonate-associated osteonecrosis (BON) may result in serious oral complications, such as osteomyelitis and chronic exposure of necrotic bone. Dentists must be familiar with this disorder and pay special attention to all patients on bisphosphonate therapy due to their defective osteoclast function and reduced osseous tissue vascularity, leading to impaired wound healing. The purpose of this paper is to review the history and pathogenesis of BON, discuss its differential diagnosis, provide guidance to dentists on possible measures to prevent BON and review the management of patients with BON.

For citation purposes, the electronic version is the definitive version of this article: www.cda-adc.ca/jcda/vol-73/issue-5/417.html

Aledronate – Merck Frosst

Definition

- Oral Cavity lesion characterized by one or more areas of bare or denuded alveolar or palatal bone.
- History of iv or po bisphosphonate treatment
- Absence of local malignancy.
- No history of radiation therapy to the affected area.
- No evidence of healing after 6 weeks of appropriate evaluation.

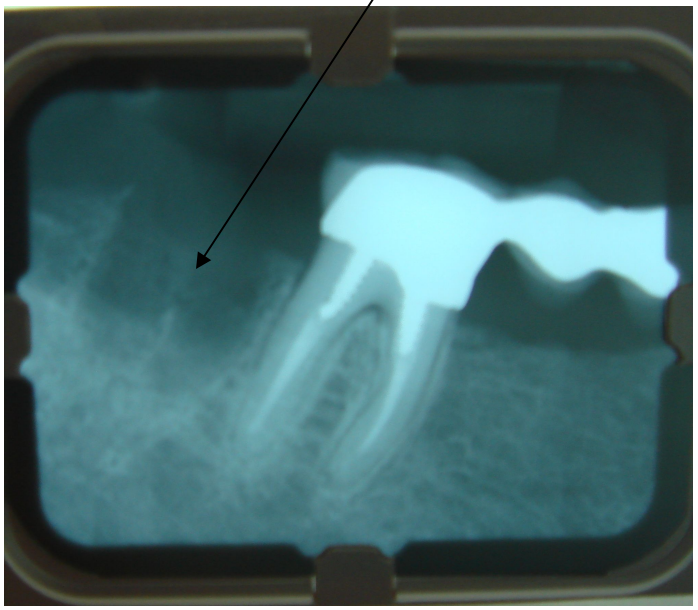
Incidence

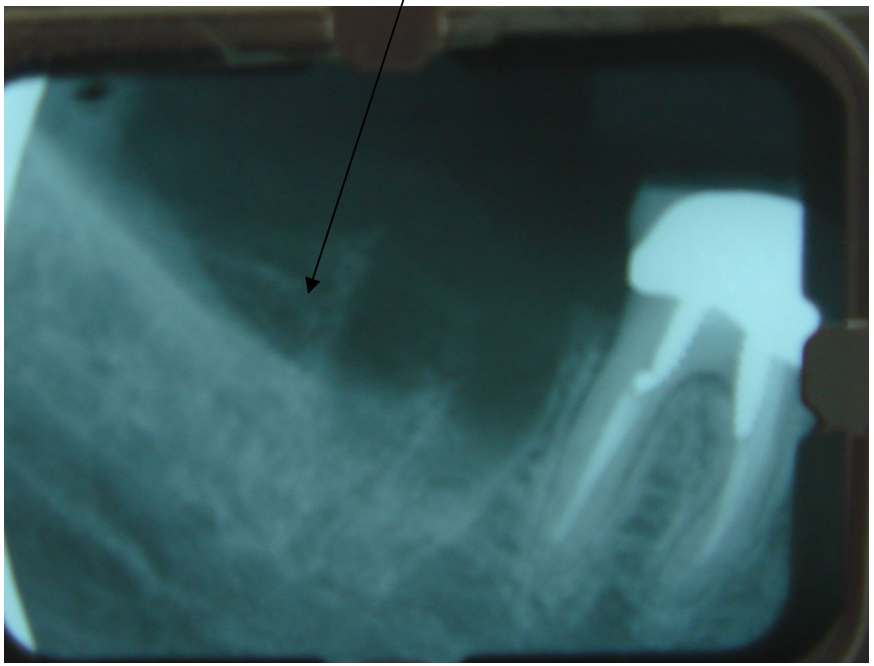
- First reported in 2003.
- Incidence varies by location.
- Over 368 cases reported in the literature to date.
- Has been reported with both oral and iv bisphosphonate administration.
- Has been reported mainly in adults but now in isolated pediatric cases.

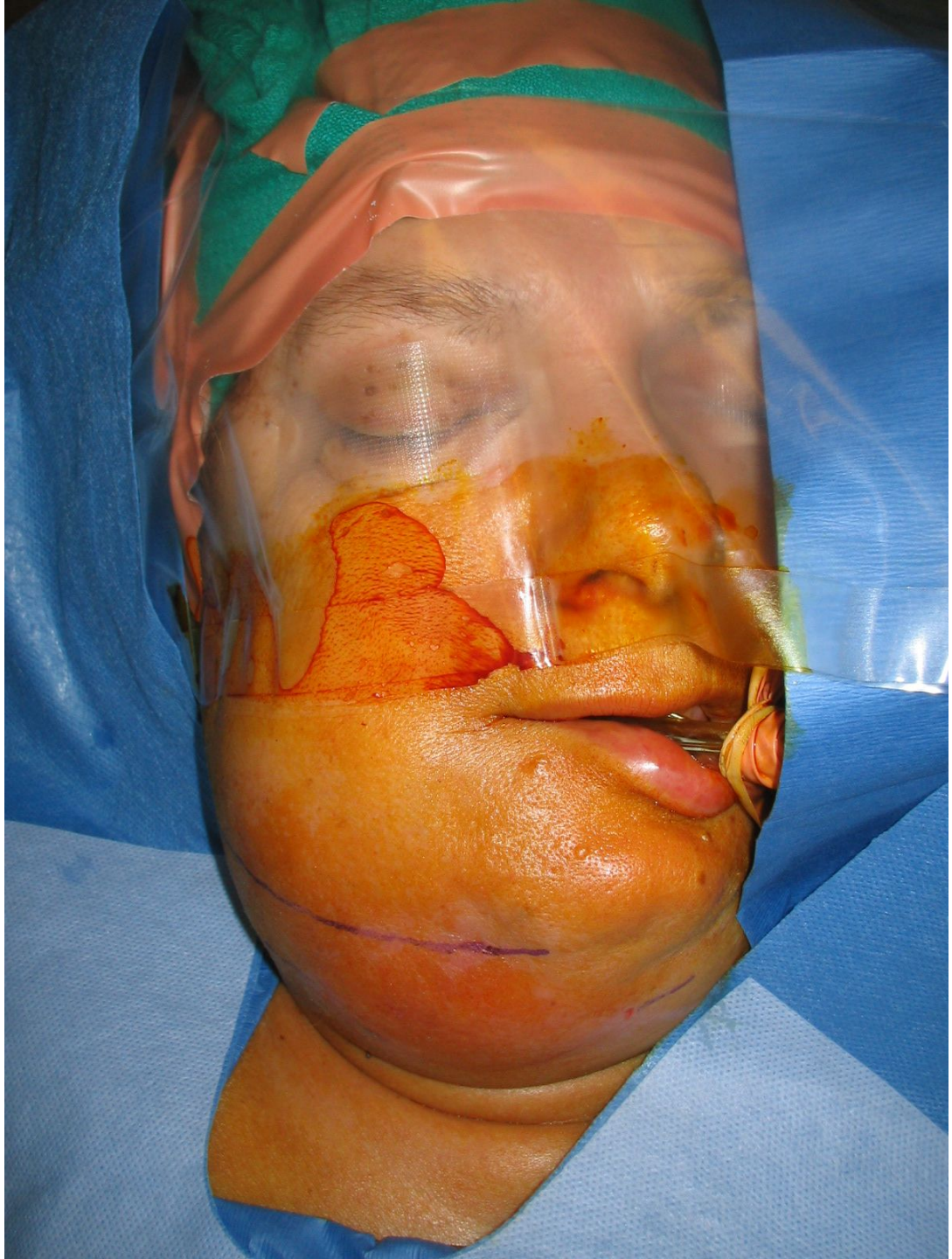
Common Oral Findings

- Poor wound healing.
- Spontaneous or post surgical soft-tissue breakdown leading to intraoral or extraoral bone exposure .
- Bone necrosis.
- Osteomyelitis.

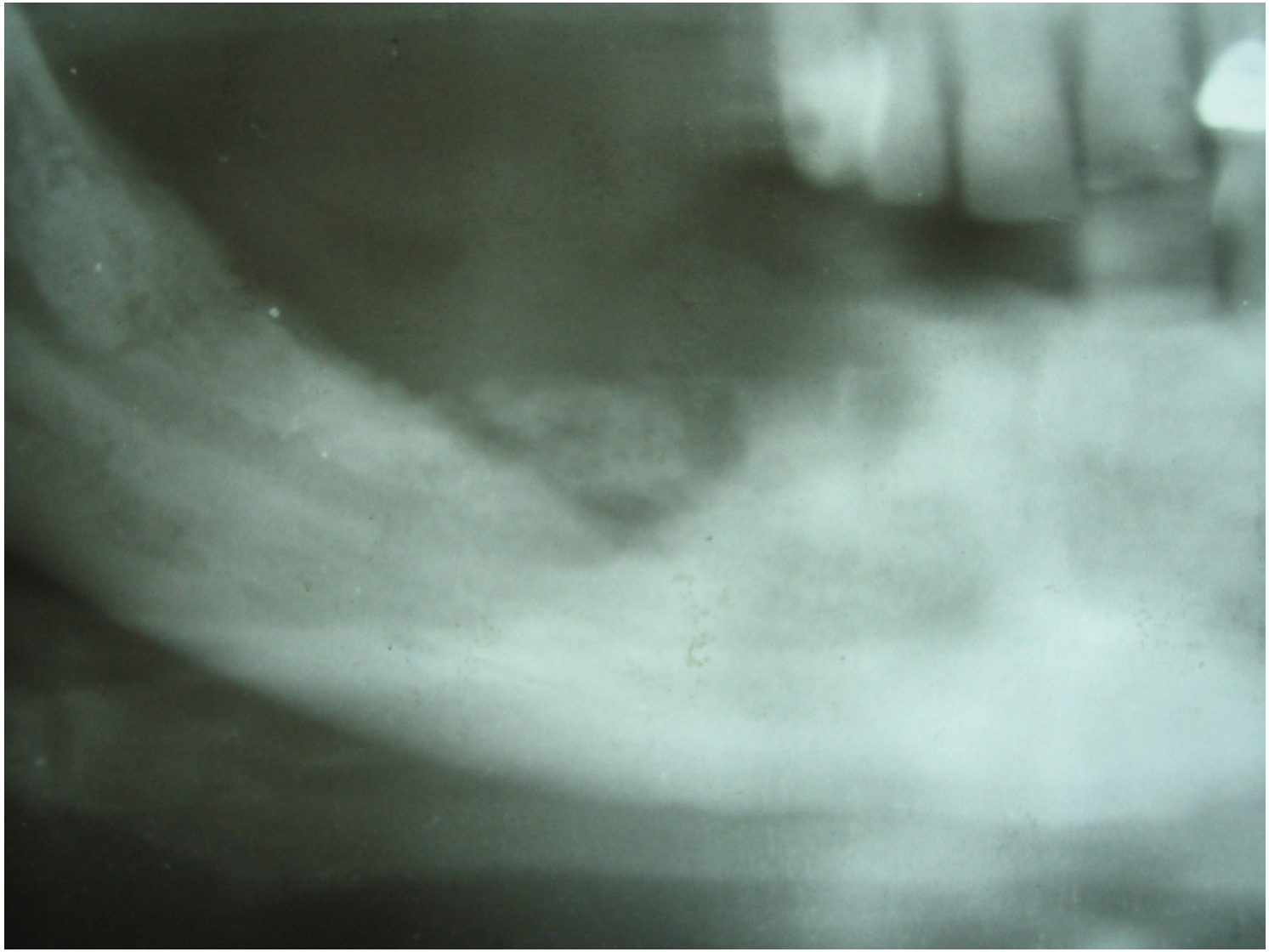
Localized Sequestra Following Extraction



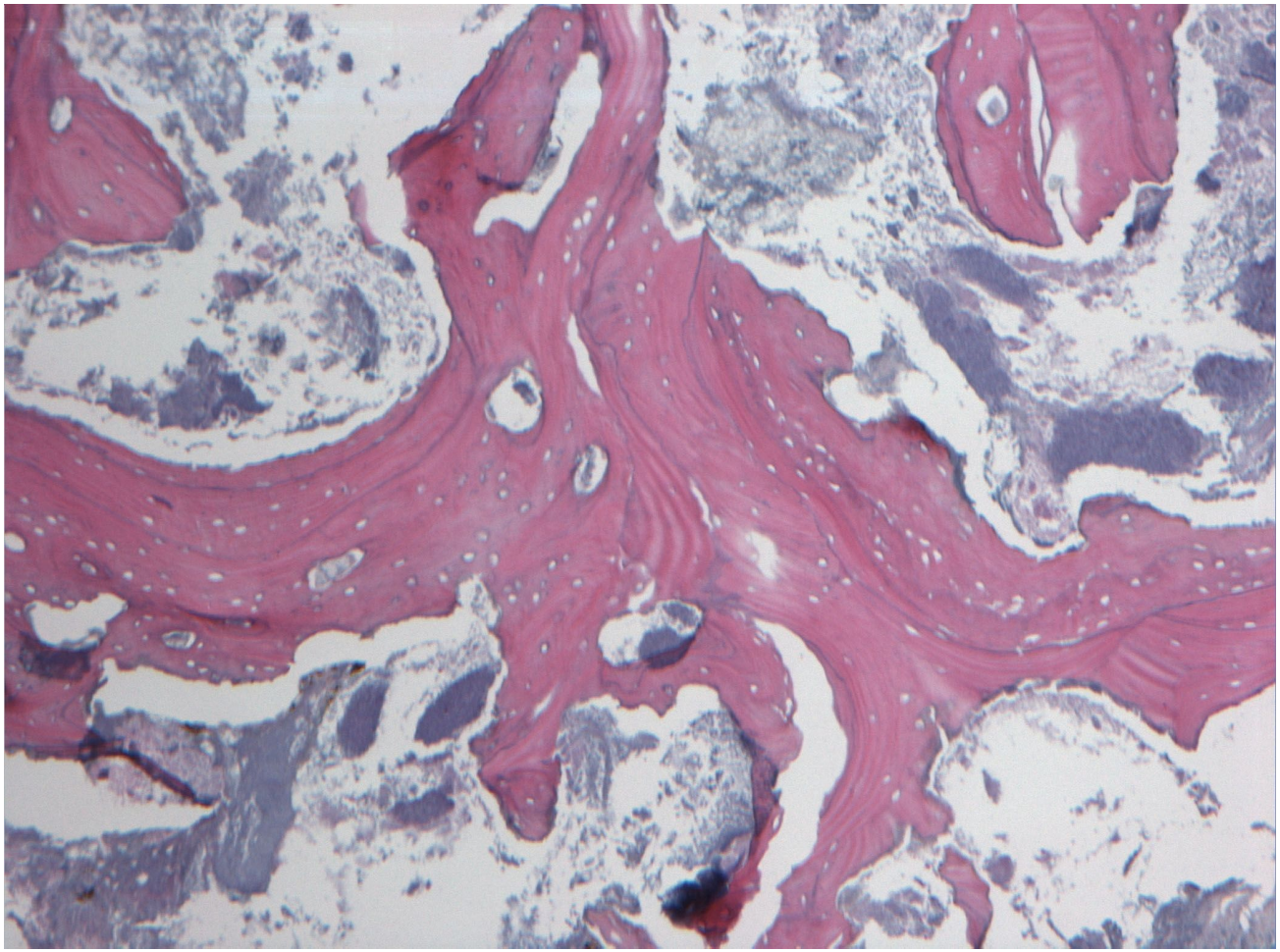




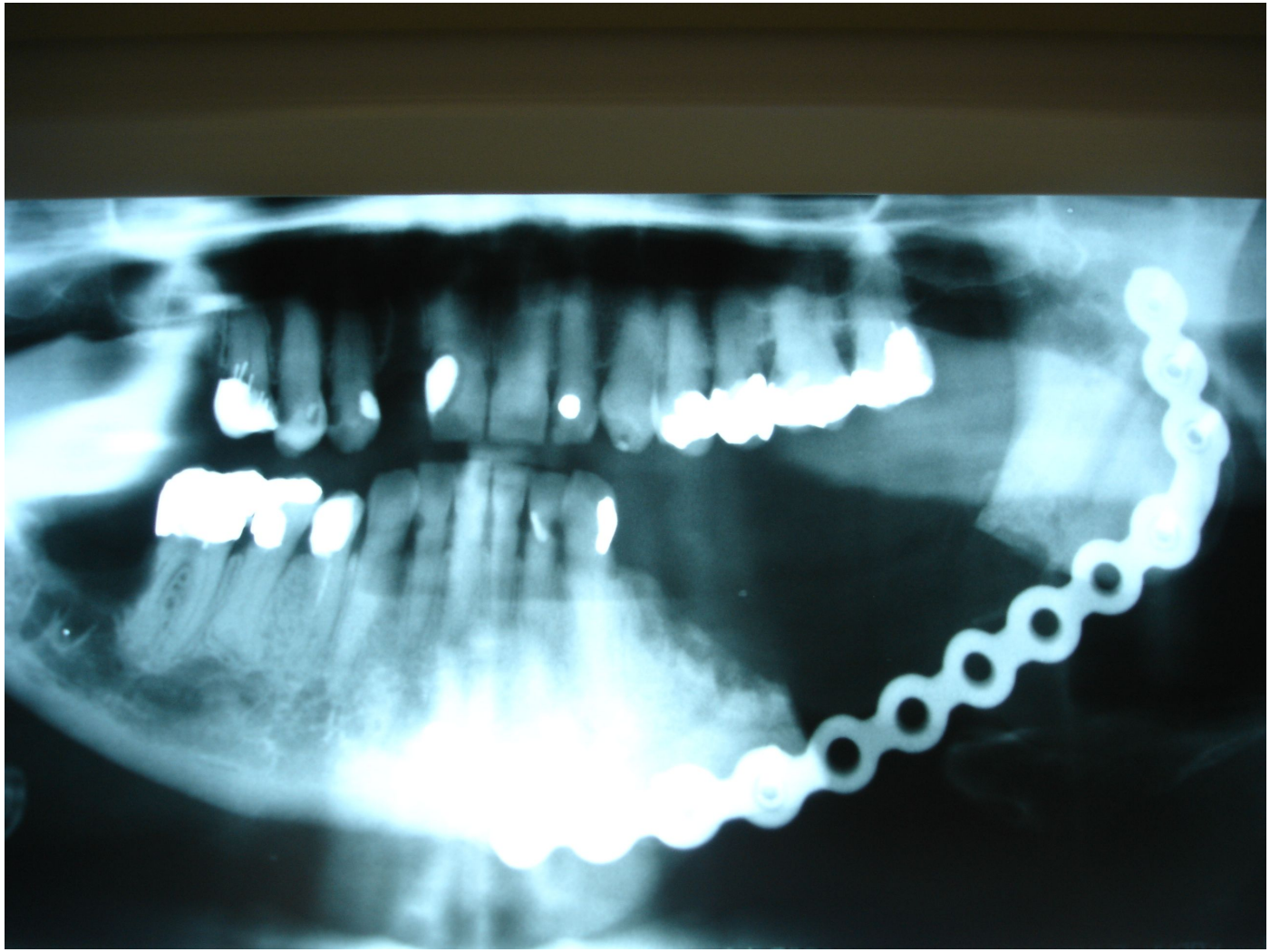
Sequestrum



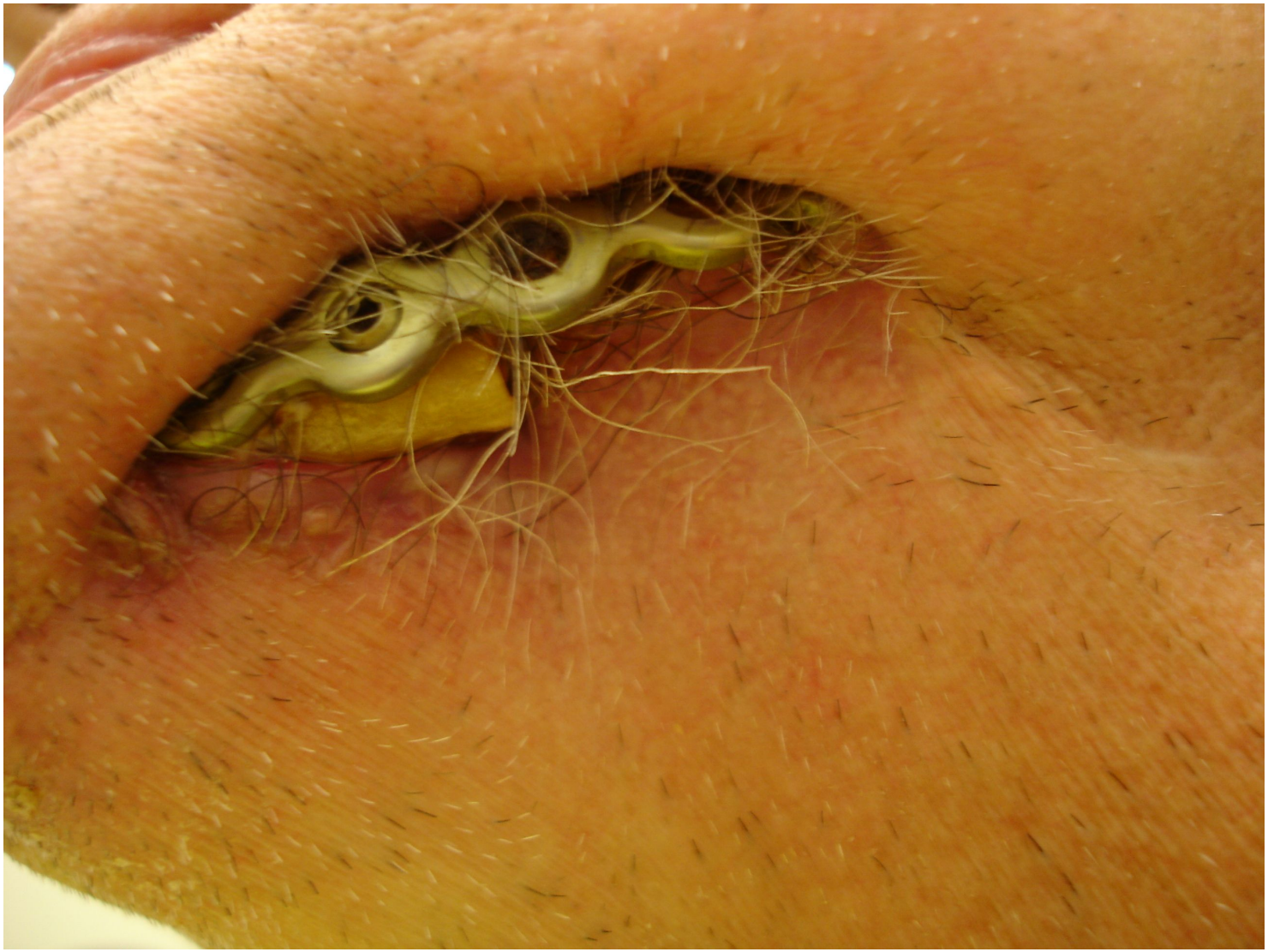
Empty Lacunae



Resection



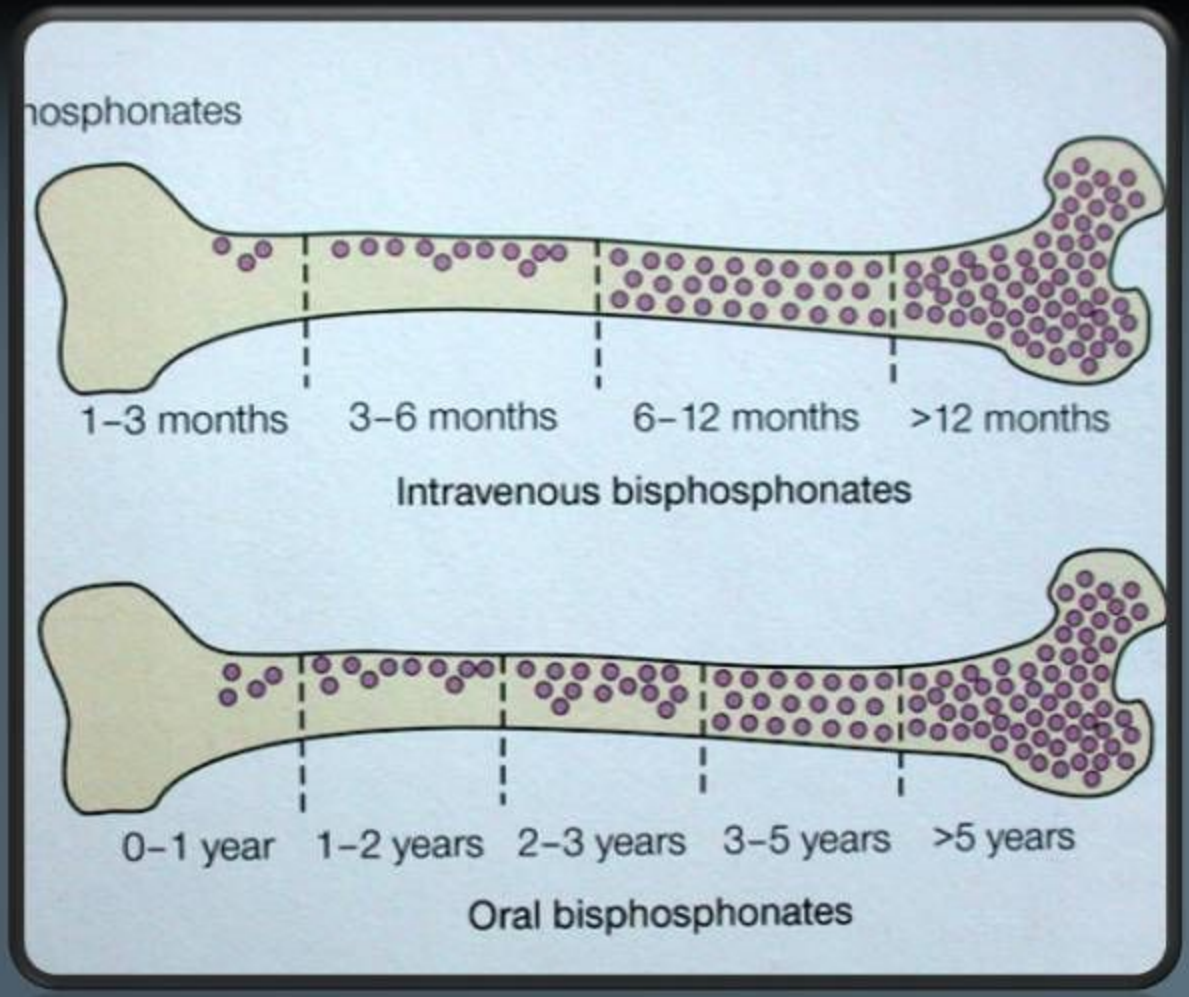
Die-Back of Soft Tissues



Relative Potencies

Relative Potency	Compound	Name
1	Etidronate (no nitro)	Didrocal
50	Tiludronate (no nitro)	Skelid (US)
1000	Alendronate	Fosamax
1000	Residronate	Actonel
1000	Ibandronate	Boniva (US)
1-5000	Pamidronate (iv)	Aredia
10 000	Zolendronate (iv)	Zometa

Intravenous Bisphosphonates



Oral 0.01 - 0.3 %

AAOMS position paper, 2006

IV 0.8 - 12 %

Hoff et al.,
Journal of Clinical Oncology, 2006

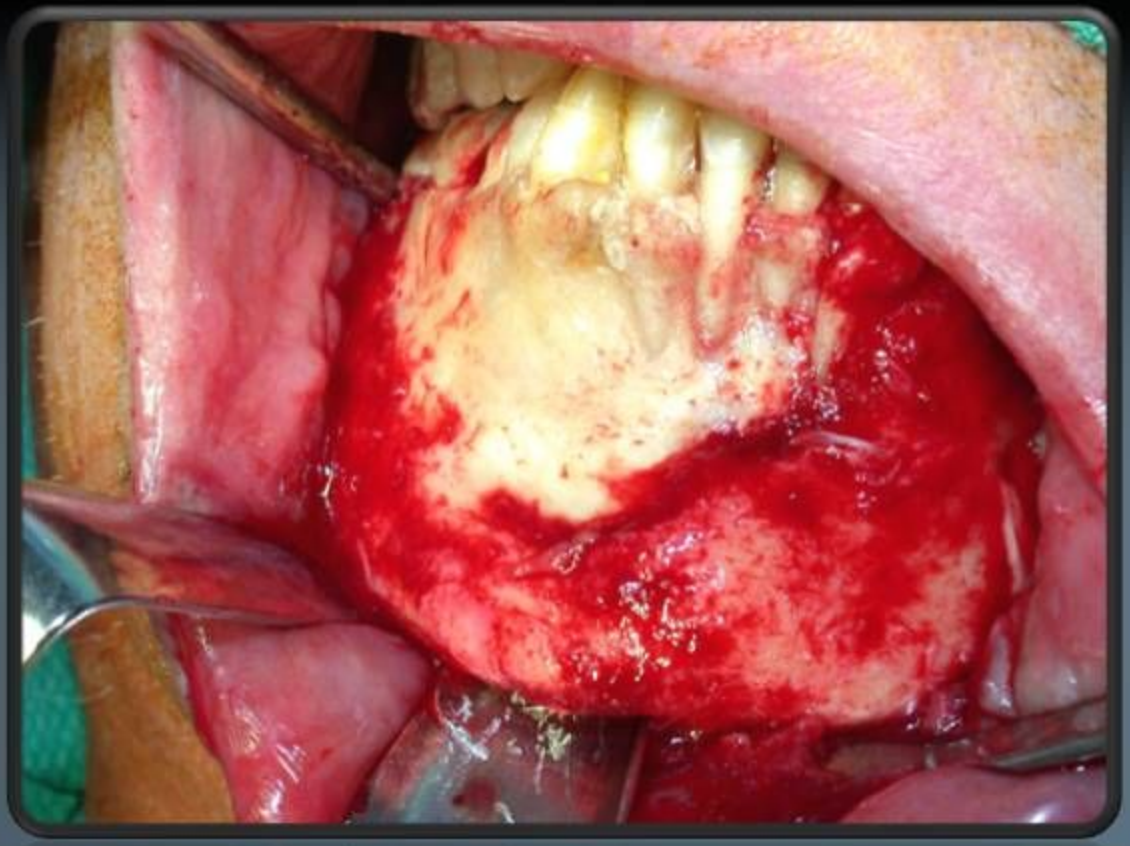
The Alveolar Bone

Remodels 10x that of a tibia
(5x for mand canal, 2.5 inferior border)

Depends on osteoclastic bone
resorption-remodelling more than any other bone

Teeth
(exposure of bone via PDL)

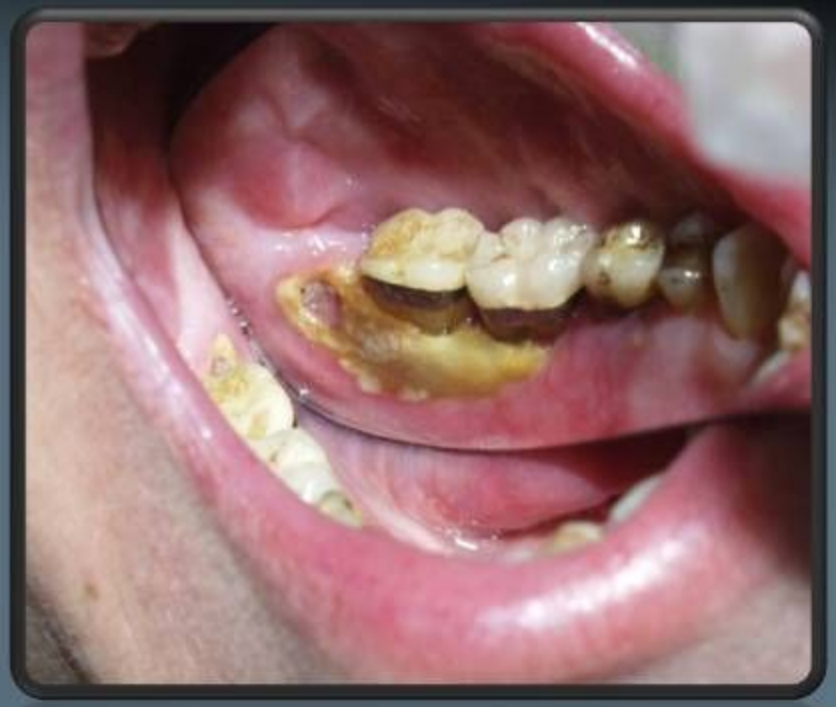
Concurrent dental disease



Stage 1

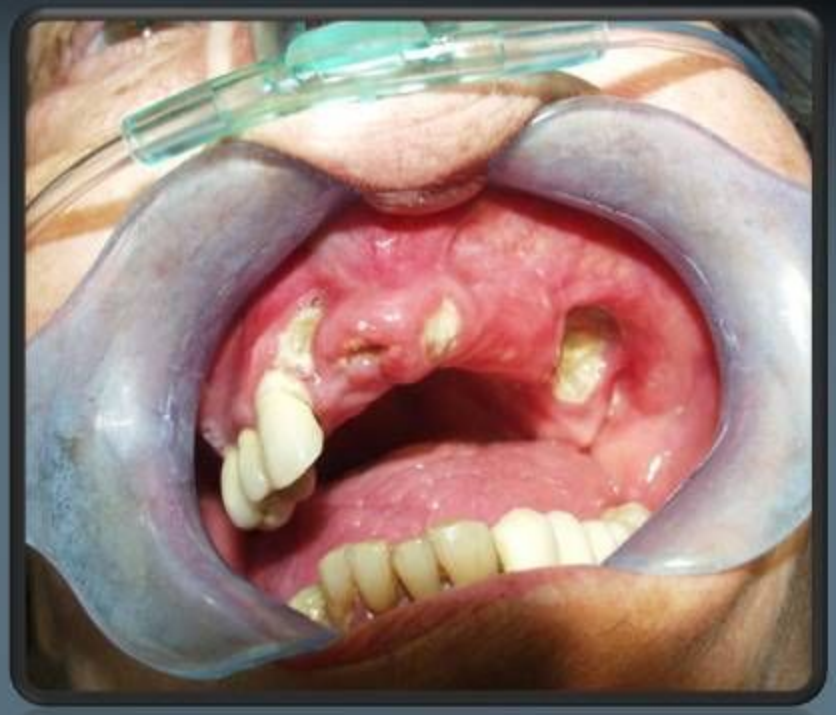
Exposed bone that is asymptomatic

No evidence of significant soft tissue infection



Stage 2

Exposed bone associated with pain, soft tissue and/or bone infection



Stage 3

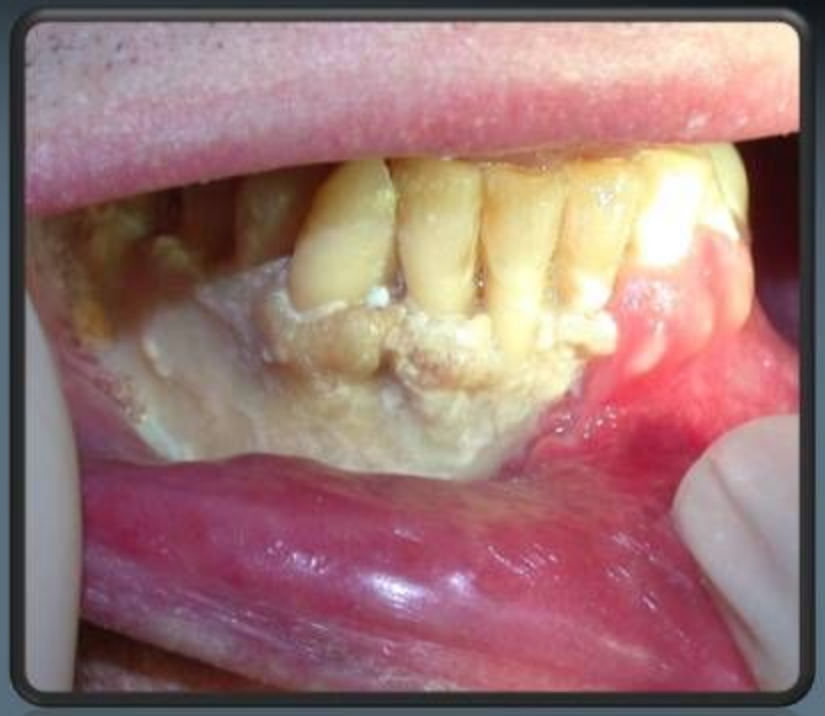
Pathologic fracture

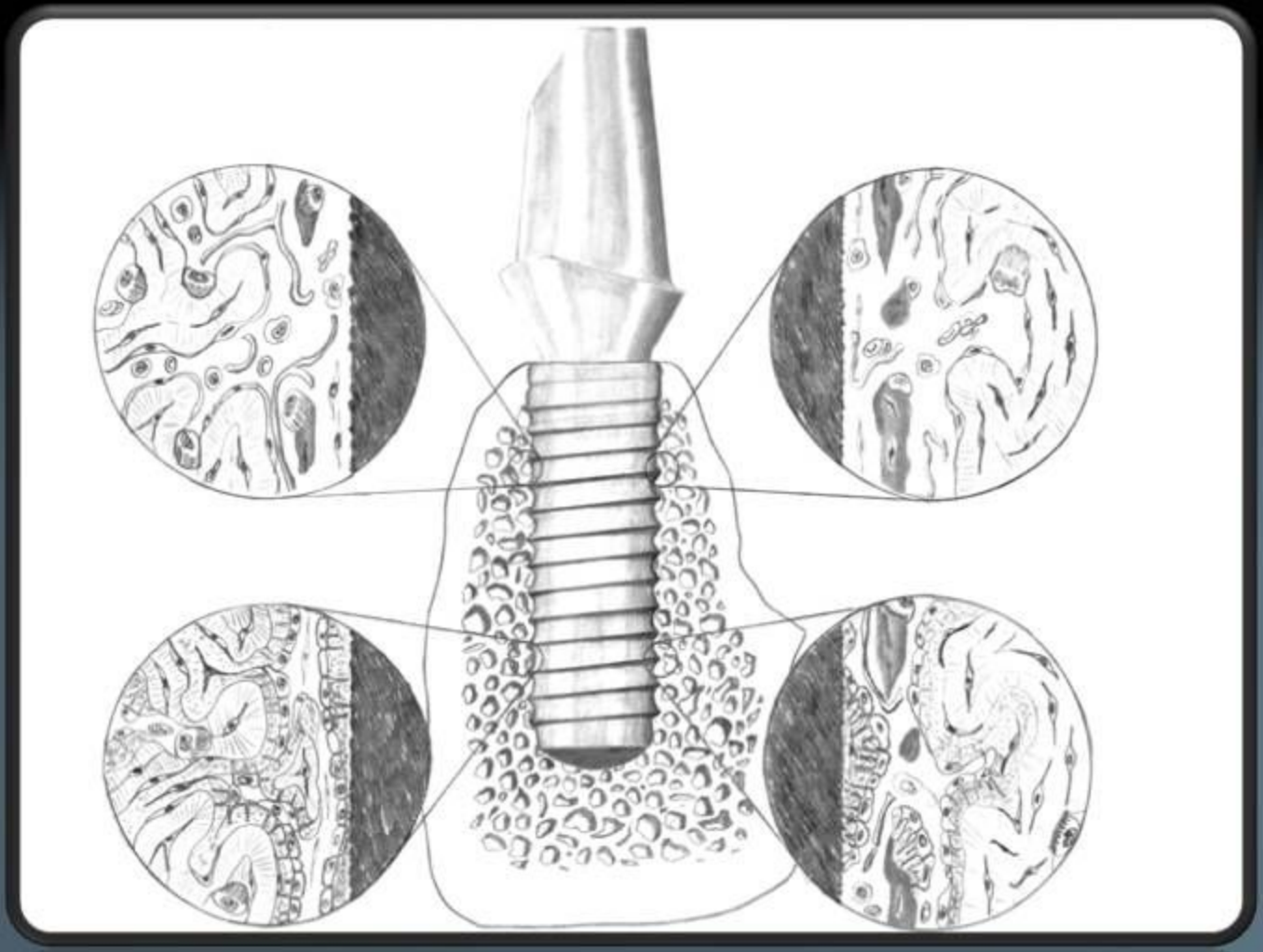
Exposed bone

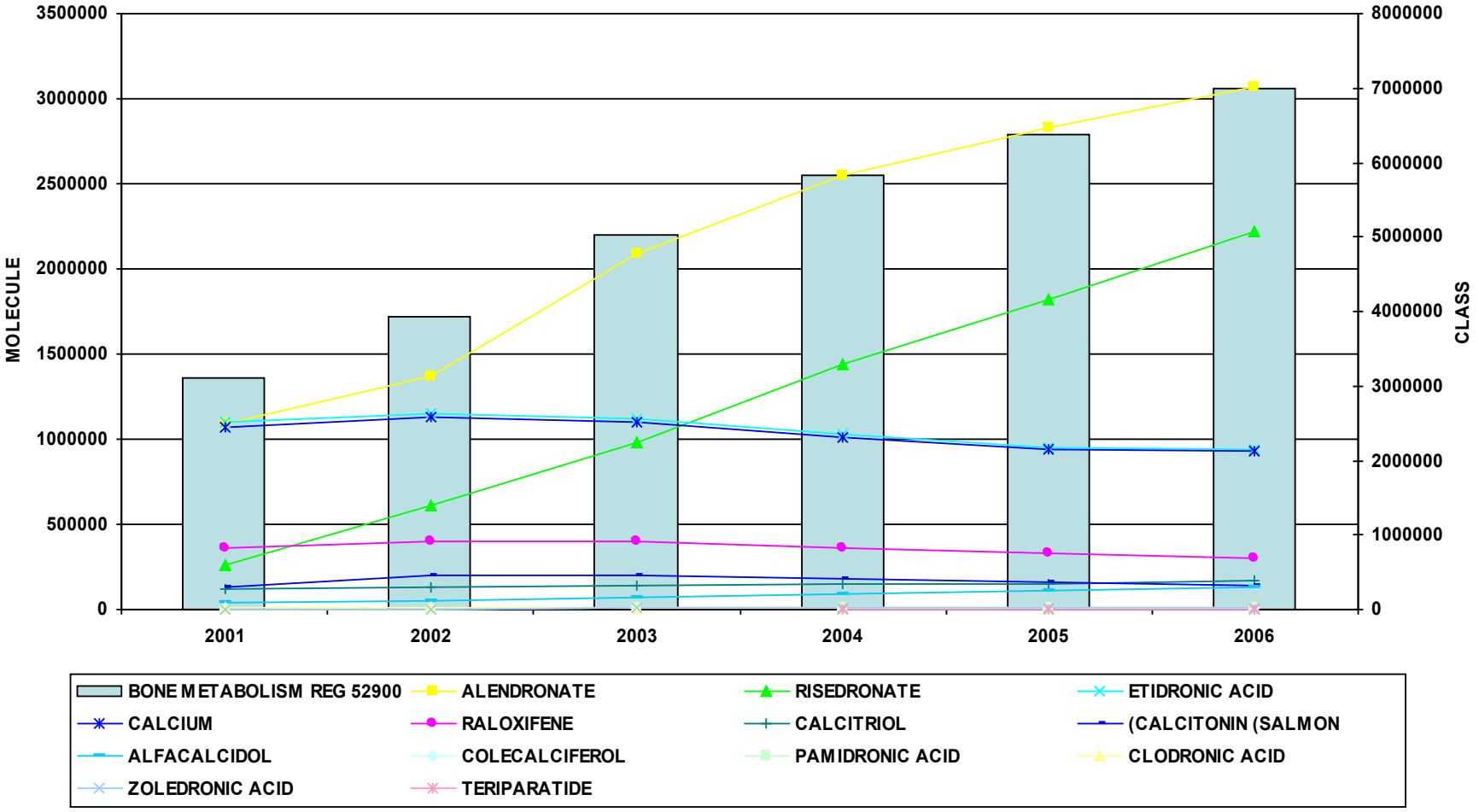
- associated with soft tissue infection or pain

Not manageable

- with antibiotics due to necrotic bone



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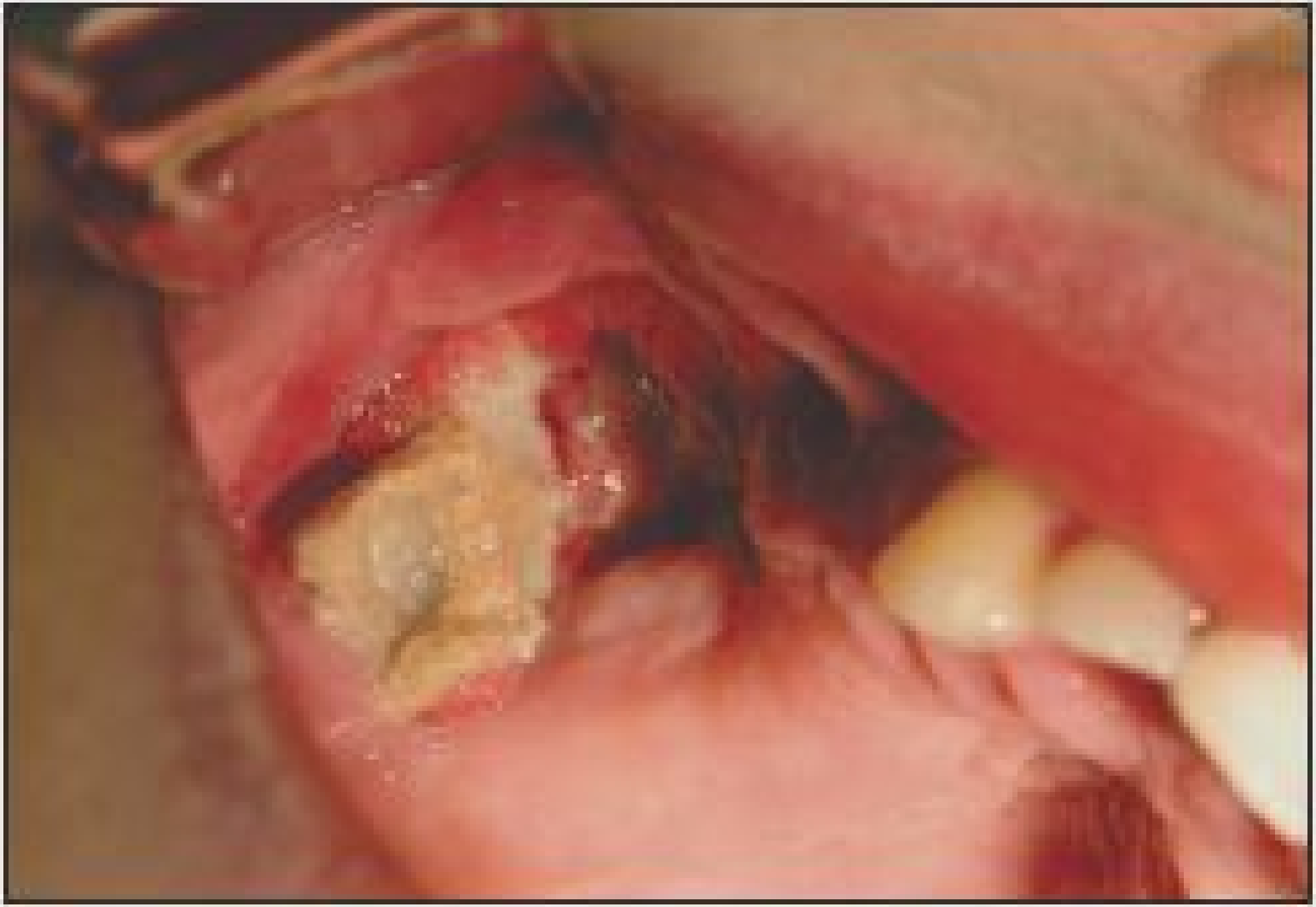
RISEDRONATE
ETIDRONIC ACID
CALCIUM
RALOXIFENE
CALCITRIOL
(CALCITONIN (SALMON
ALFACALCIDOL
COLECALCIFEROL
PAMIDRONIC ACID
CLODRONIC ACID
ZOLEDRONIC ACID
TERIPARATIDE



Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ)

- Background
- Pathophysiology
- Risk Factors
- Clinical signs and symptoms
- Management Strategies

Patients may be considered to have BRONJ if all of the following 3 characteristics are present (AAOMS Position Paper 2006):

1. Current or previous treatment with a bisphosphonate
2. Exposed bone in the maxillofacial region that has persisted for more than 8 weeks
3. No history of radiation therapy to the jaws

History

- Use of IV bisphosphonates was 1st introduced in 1995
- Full knowledge of pharmacokinetics/dynamics is still unclear
- BRONJ is the first described long-term complication
- First reported in 2003 by Marx
- Recently, several investigators have reported BRONJ in the medical/dental literature
  - Majority of cases involve IV bisphosphonates to control metastatic bone disease
  - A few cases in patients taking PO doses to treat osteoporosis or osteopenia
- True incidence unknown

- **Today, bisphosphonates (e.g. Fosamax) are commonly prescribed to stabilize bone loss caused by osteoporosis in millions of postmenopausal women**
  - **22.4 million prescriptions of Fosamax in 2005**
- **In 2004, Novartis acknowledged potential risk of BRONJ:**

NOVARTIS
ONCOLOGY

September 24, 2004

Dear Doctor:

Post-Marketing Experience

Cases of osteonecrosis (primarily involving the jaws) have been reported in patients treated with bisphosphonates. The majority of the reported cases are in cancer patients attendant to a dental procedure. Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g., anemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged. (See PRECAUTIONS)

Incidence

IV Bisphosphonates

- Limited retrospective studies report the incidence of BRONJ from 0.8-12%
- Incidence likely to rise with increased recognition, duration of exposure and follow-up

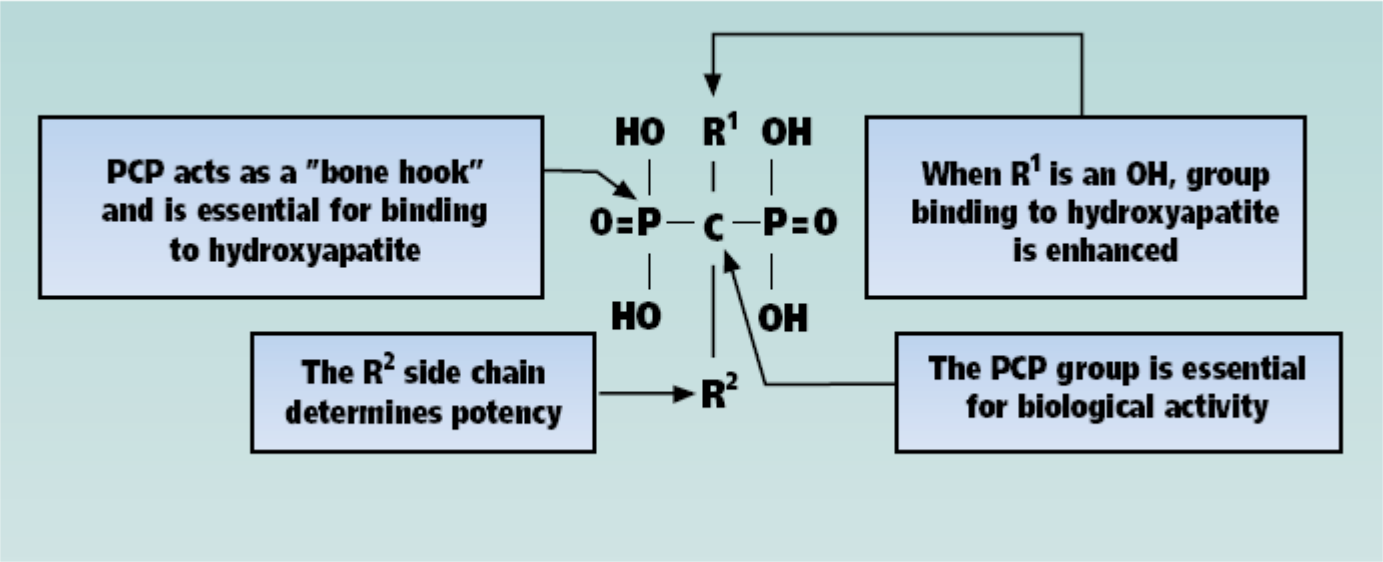
Oral Bisphosphonates

- Considerably lower risk
- Manufacturer of alendronate (Merck) reports a calculated incidence of 0.7/100,000 person years of exposure
- Australia data reports the incidence of alendronate associated BRONJ to be 0.01-0.04% (rate increases to 0.09-0.34% following extractions)

Bisphosphonates

- Synthetic analogs of the naturally occurring pyrophosphate
- Before 2001, pamidronate (Aredia) was the only drug approved in the USA. Zoledronic acid was approved in 2002
- Potent inhibitors of osteoclastic activity
- Bind to bone mineral (Ca^{2+}) around resorbing osteoclasts → accumulate over time in mineralized bone matrix
- Leads to severe compromise in physiologic bone deposition and remodeling

Chemical Structure



Potency determined by variations of the R chains – cyclic nitrogen chain most potent

ANTIRESORPTIVE POTENCY OF BISPHOSPHONATES OBSERVED IN HUMAN CLINICAL TRIALS.*

COMPOUND	PRECLINIC ANTIRESORPTIVE RELATIVE POTENCY	ROUTE OF ADMINISTRATION
Short Alkyl or Halide Side Chain		
Etidronate (Didronel†)	1	Oral (O)/ Intravenous (IV)
Cyclic Chloro Side Chain		
Tiludronate (Skelide‡)	10	O
Aminterminal Group		
Pamidronate (Aredia§)	100	IV
Alendronate (Fosamax¶)	100-1,000	O
Cyclic Nitrogen–Containing Side Chain		
Risedronate (Actonel#)	1,000-10,000	O
Ibandronate (Boniva**)	1000-10,000	O
Zoledronic acid (Zometa††)	≥ 10,000	IV

* Adapted from Watts.[16]
† Didronel is manufactured by Procter & Gamble Pharmaceuticals, Cincinnati.
‡ Skelide is manufactured by Sanofi-Aventis Bridgewater, N.J.
§ Aredia is manufactured by Novartis Pharmaceutical Co., East Hanover, N.J.
¶ Fosamax is manufactured by Merck,Whitehouse Station, N.J.
# Actonel is manufactured by Procter & Gamble Pharmaceuticals.
** Boniva is manufactured by Roche Pharmaceuticals, Nutley, N.J.
†† Zometa is manufactured by Novartis Pharmaceutical Co.

Clinical Uses

- Osteporosis / osteopenia
- Paget's Disease
- Osteogenesis imperfecta of childhood
- Hypercalcemia associated with malignancy
- Osteolytic lesions arising from any solid tumor (such as breast, lung and prostate cancer) and multiple myeloma

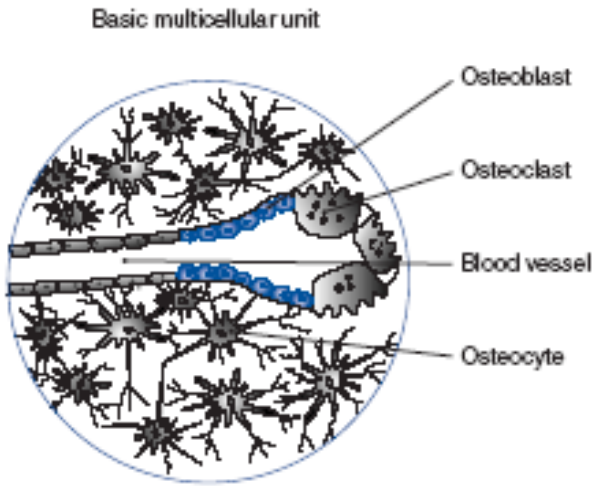
Therapeutic Goal

arrest bone loss, ↑ bone density and

↓ risk of pathologic fractures

Pathophysiology

- Bone remodeling is a physiologic ongoing function in normal bone
- Removes micro-damage and replaces damaged bone w/ new elastic osseous tissues
- Maintains optimum concentrations of Ca^{2+} in blood
- Remodeling occurs w/in compartments called "bone multicellular units" (BMUs):
  - Osteoblasts
  - Osteoclasts
  - Blood vessels

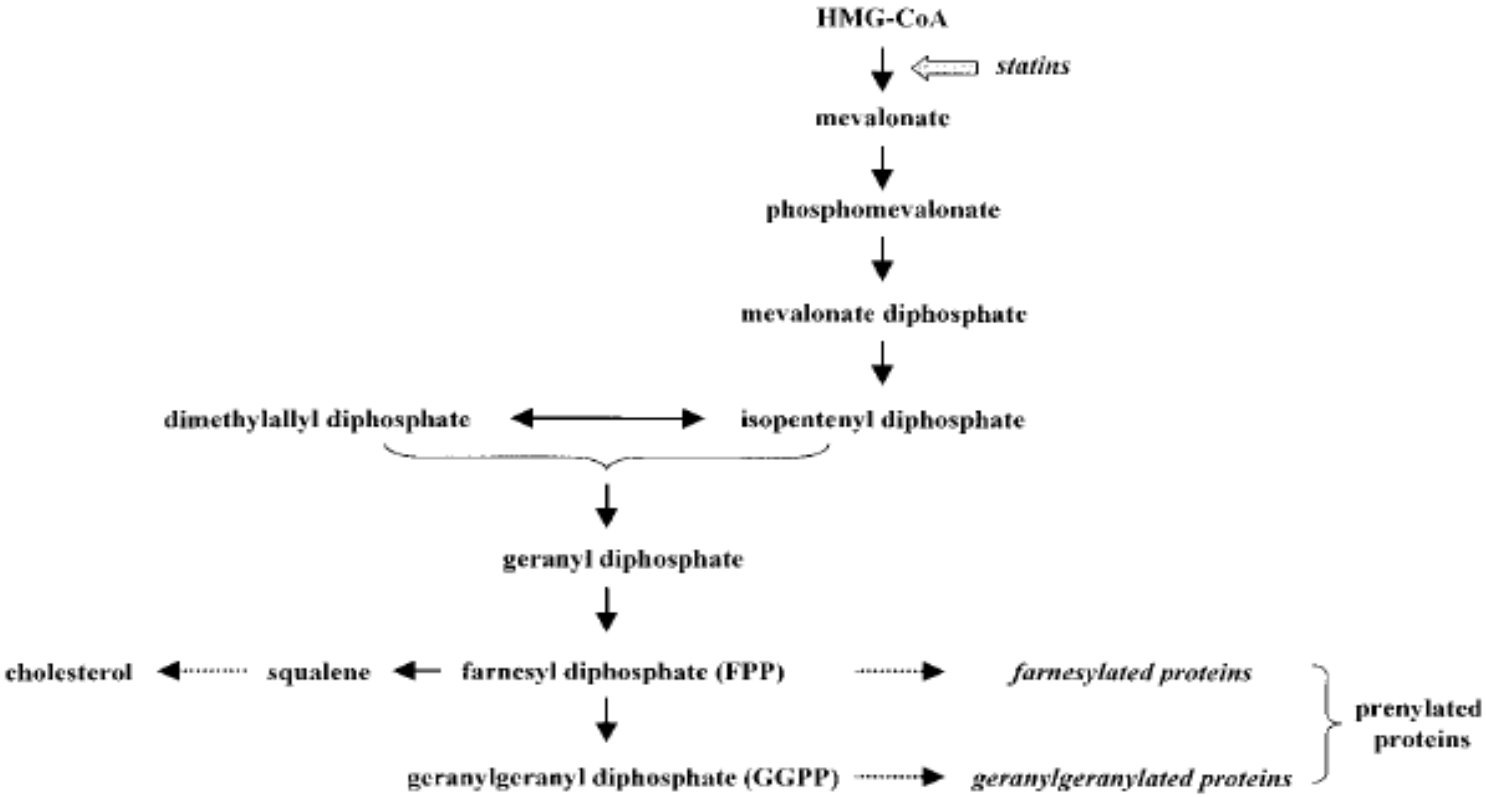


Pathophysiology

- Bone turnover profoundly suppressed → little physiologic remodeling
- Demand for remodeling in oral cavity due to:
  - Physiologic microdamage and microfractures occur daily from masticatory forces
  - Infections (e.g. periodontal disease)
  - Local trauma (e.g. denture irritation / extraction)
- Bone becomes brittle and unable to repair physiologic microfracture and damage

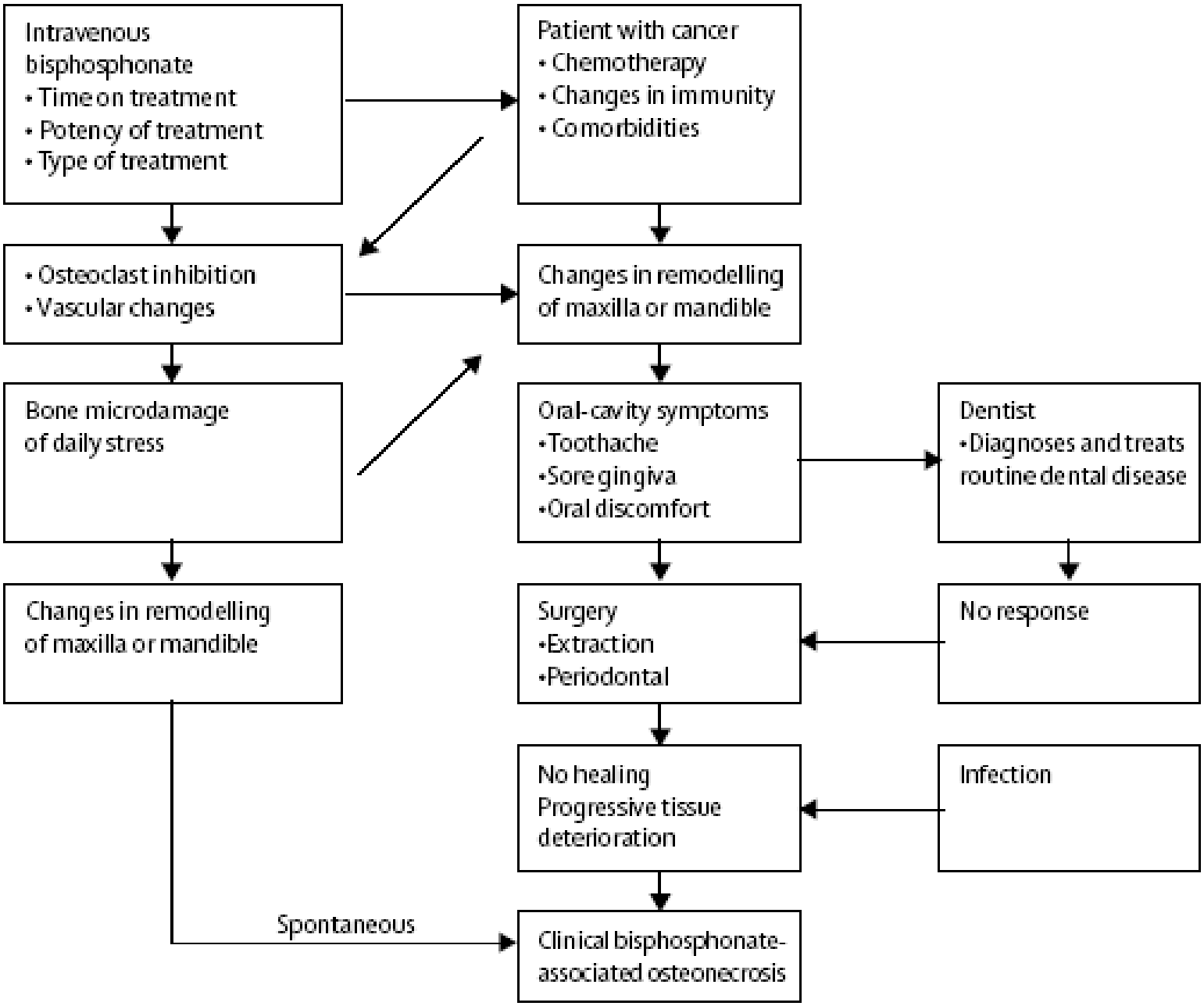
BACKGROUND

- Mechanism of Action of Bisphosphonates
  - Inhibit intracellular mevalonate pathway



BRONJ results from a complex interplay of

- Bone metabolism
- Local trauma
- Increased demand for bone repair
- Infection
- Hypovascularity


Intravenous bisphosphonate
• Time on treatment
• Potency of treatment
• Type of treatment
Patient with cancer
• Chemotherapy
• Changes in immunity
• Comorbidities
• Osteoclast inhibition
• Vascular changes
Changes in remodelling of maxilla or mandible
Bone microdamage of daily stress
Oral-cavity symptoms
•Toothache
•Sore gingiva
•Oral discomfort
Dentist
•Diagnoses and treats routine dental disease
Changes in remodelling of maxilla or mandible
Surgery
•Extraction
•Periodontal
No response
No healing
Progressive tissue deterioration
Infection
Spontaneous
Clinical bisphosphonate-associated osteonecrosis

Why is BRONJ exclusive to jaws?

- ✓ **Bisphosphonates are highly concentrated in the jaws due to:**
  - **Greater blood supply compared to other bones**
  - **Faster bone turnover rate (mastication / PDL)**
- ✓ **Chronic invasive dental disease and treatment**
- ✓ **Thin overlying mucosa**

Risk Factors

1. Drug-related factors
   - Potency of particular drug
   - Duration of therapy
2. Local risk factors
   - Dentoalveolar surgery
   - Local anatomy
   - Concomitant oral disease
3. Demographic and systemic factors

Strong association of incidence of BRONJ to number of infusions and time of exposure (Bamias et al):

- No patient with < 13 treatments developed BRONJ
- Median time of exposure was 39.3 months for patients with BRONJ

Table 1. Patient Characteristics

Characteristic	Osteonecrosis: Yes, No. of Patients	Osteonecrosis: Yes, %	Osteonecrosis: No, No. of Patients	Osteonecrosis: No, %	*P*
Sex					.258
Male	10	8.7	113	91.3	
Female	7	5.1	138	94.9	
Age, years					.247
Median	61		64		
Range	43-72		26-85		
Disease					.289
Breast cancer	2	2.9	68	97.1	
Multiple myeloma	11	9.9	[illegible]	[illegible]	
Prostate cancer	3	6.5			
Other	1	4			
Type of bisphosphonate					.063
Zoledronic acid	7	6.7			
Pamidronate	0	0			
Ibandronic acid	0	0			
Pamidronate + zoledronic acid	9	13			
Zoledronic acid + ibandronic acid	1	6.7			
Thalidomide use					.571
Yes	6	8.8			
No	5	12.2			

All BRONJ cases were treated with zoledronic acid either alone (6.7%) or after pamidronate (13%) or preceding ibandronic acid (6.7%)

Pamidronate and ibandronic acid alone were NOT associated with BRONJ

Bamias et al found a significant difference in the respective hazards of developing BRONJ based on type of bisphosphonate (P=.003)

- **BRONJ was significantly higher in the zoledronic acid group (P<.001)**
- **Zoledronic acid = 1% within 1st yr → 21% at 3 years**
- **Other groups = 0% with 2 years → 7% after 4 years**

Table 3. Cumulative Hazard of Developing Osteonecrosis of the Jaw *v* Duration of Treatment

	Cumulative Hazard							
	12 Months		24 Months		36 Months		48 Months	
Treatment	%	95% CI	%	95% CI	%	95% CI	%	95% CI
All (N = 252)	0		3	1 to 5	7	1 to 13	11	3 to 19
Zoledronic acid (n = 105)	1	0 to 3	7	1 to 13	21	3 to 39	21	3 to 39
Pamidronate/pamidronate and zoledronic acid (n = 127)	0		0		2	0 to 6	7	0 to 15

- **Marx et al (JOMS 2005) evaluation of 119 cases of BRONJ also support development w/ type of bisphosphonate:**
  - Pamidronate (26%) – 14.3 mo
  - Zoledronate (40.3%) – 9.4 mo
  - Pamidronate → Zoledronate (2.5%) – 12.1 mo
  - Alendronate (2.5%) – 3 yrs

- **Suggest potency related to faster onset of BRONJ**

- **IV compounds containing an aminoterminal group (e.g. pamidronate) or a nitrogen-containing side chain (e.g. zoledronic acid) seem to present the highest risk (Lancet Oncol 2006)**

Is there a risk with oral bisphosphonates?

- Rugierro reported a total of 12 or 13 cases of BRONJ in patients treated with an oral bisphosphonate
- Marx states he's aware of at least 40 or 50 cases of BRONJ nationwide in patients who had taken Fosamax
- Small fraction of the approximately 3 million women in the USA who are taking the drug
- Unknown co-existing variables?

Risk of BRONJ with IV Therapy

- IV drug carries the highest risk - 7 cases of spontaneous BONJ in 3000 treated patients (0.4%).
- Current thinking with Breast Cancer is prophylaxis against bony metastastasis.
- IV Zoledronic acid, oral Ibandronate or oral Clodronate

Local Risk Factors

- AAOMS position paper implicates the following dentoalveolar procedures:
  - Extractions
  - Dental implant placement
  - Periapical surgery
  - Periodontal surgery involving osseous injury

- Patients receiving IV therapy and undergoing dentoalveolar surgery are at least 7-times more likely to develop BRONJ than those not having surgery

Marx et al (2005) reported the following precipitating events:

- Tooth removal (37.8%)
- Advanced periodontitis (28.6%)
- Spontaneous (25.2%)
- Periodontal surgery (11.2%)
- Dental implants (3.4%)
- Root canal surgery (0.8%)

BRONJ more common in the Md than Mx:

- Md (68.1%) > Mx (27.7%) > both (4.2%)

Common in areas with thin mucosa overlying bony prominences:

- Mandible
  - Lingual tori / Mylohyoid ridge
- Maxilla
  - Palatal tori

Demographic & Systemic Factors

- Age:
  - With each passing decade, there is a 9% increased risk for BRONJ in MM pts treated with IV bisphosphonates
- Race:
  - High prevalence in Caucasian population
- Cancer Diagnosis:
  - Risk ↑ with MM < Breast Ca < other Ca
- Osteopenia/osteoporosis diagnosis concurrent with cancer diagnosis

The following factors are thought to be risk factors for BRONJ (AAOMS position paper):

- **Corticosteriod therapy**
- **Diabetes**
- **Smoking**
- **Alcohol use**
- **Poor oral hygiene**
- **Chemotherapeutic drugs**

Further studies are required to determine association

Clinical Presentation

Early Findings:

- Area of exposed non-vital bone
- Spontaneous or trauma induced
- Often secondarily infected
- Mucosal tissue margins are erythematous and edematous
- Sensitive to palpation
- Refractory to debridement
- Tooth mobility

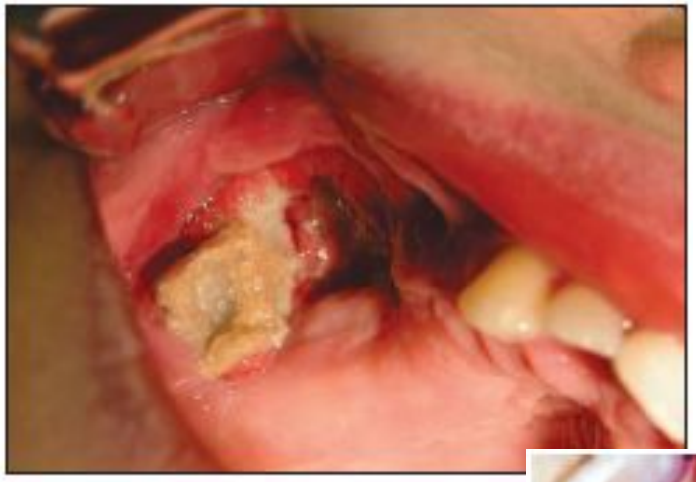
Late Findings:

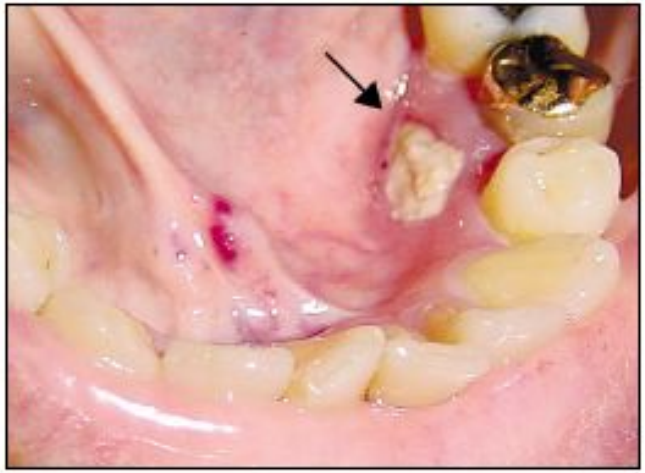
- Paraesthesia (nerve compression)
- Cutaneous fistula / mucosal fistula
- Pathological fracture of Mx/Md
- +/- acute osteomyelitis
- Recently, avascular necrosis of the hip has been reported in patients w/ MM
  - Possible systemic effects w/ oral complications manifesting first?

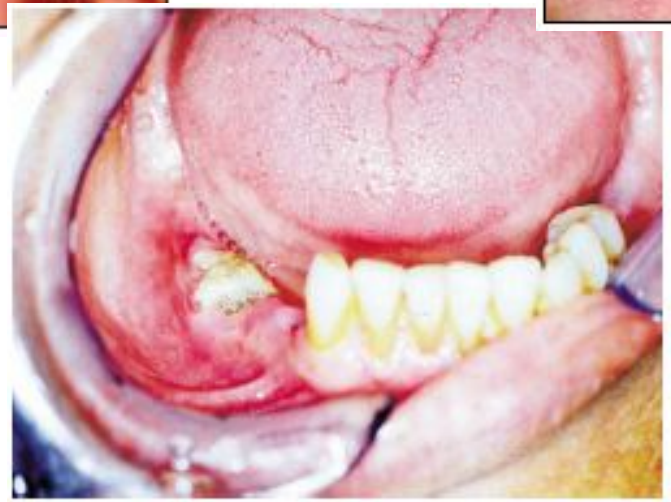
Marx et al described 119 patients w/ BRONJ:

- Area of exposed bone and pain (68.9%)
- Asymptomatic exposed bone (31.1%)
- Mobile teeth (23.5%)
- Cutaneous / mucosal fistula (17.6%)
- Periodontitis (84%)
- Radiographic findings (73.1%)

Clinical Presentation





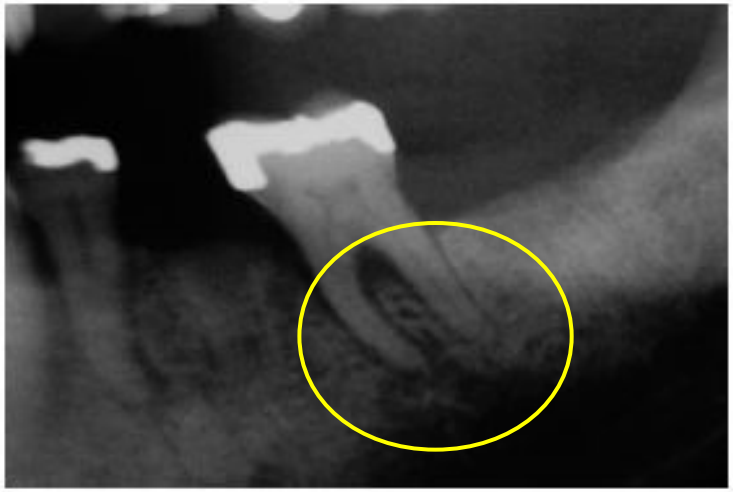


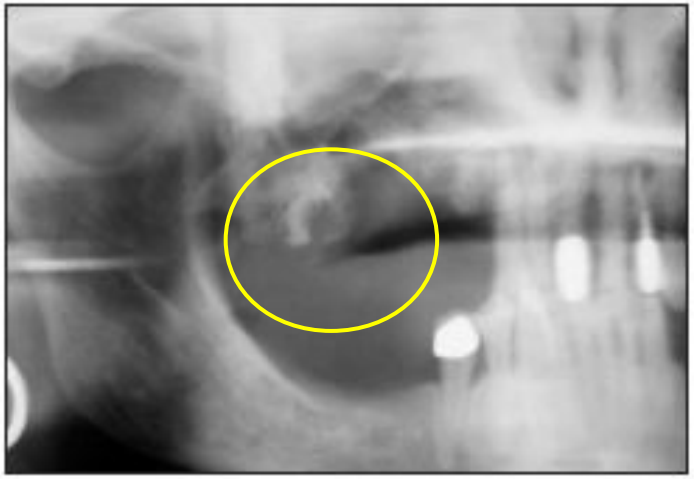
Radiographic findings

- Mixed radiolucent/radiopaque bone lesions
- Borders
  - ill-defined
  - sclerotic
  - non-corticated
- Internal structure
  - Multi-loculated
  - Mixed internal radiolucent/radiopaque consistency
- Non-healing extraction sockets
- Widened periodontal membrane space (especially @ furcation of molar teeth)
- +/- pathological fractures

Radiographic Findings

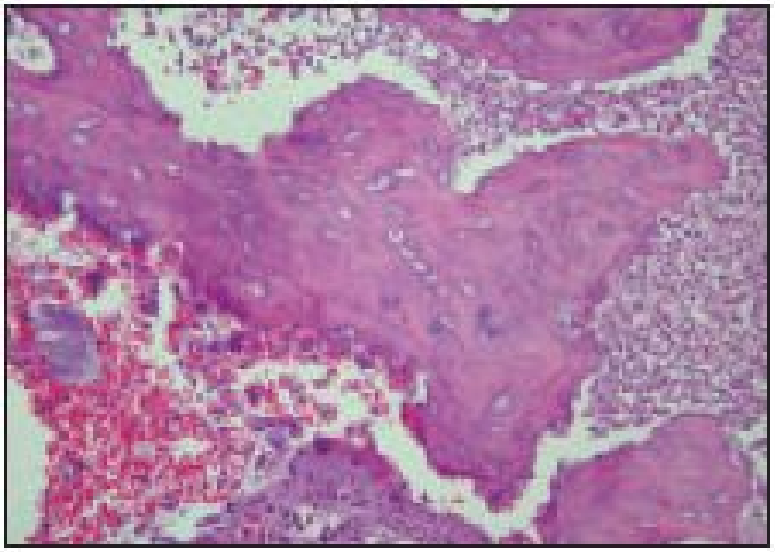
Abnormal trabecular pattern in furcation region





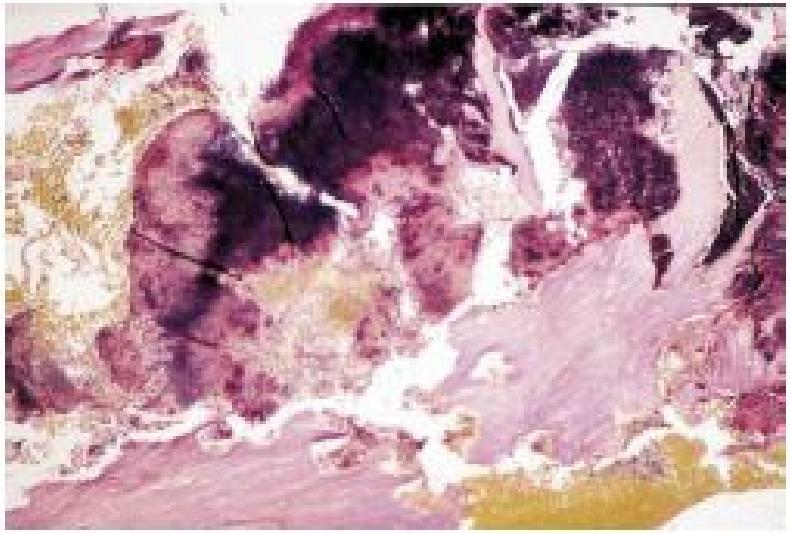
Ill defined mixed radiolucent / radiopaque bony lesion

Histology



Necrotic bone w/ numerous inflammatory cells & clusters of bacteria

Colonies of actinomyces are frequently noted on the surface of necrotic bone



Management Strategies

Treatment Goals:

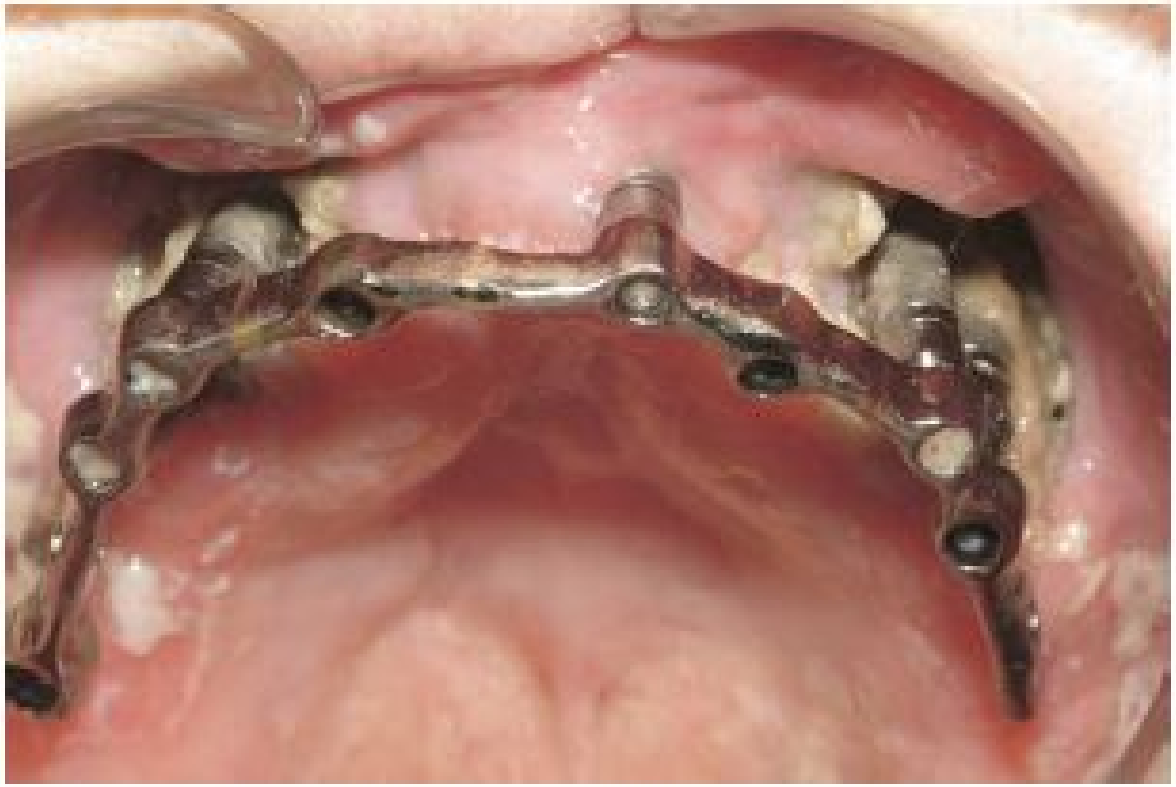
- Prioritization and support of continued oncologic treatment
- Preservation of quality of life through:
  - Patient education and reassurance
  - Control of pain
  - Control of secondary infection
  - Prevention of extension of lesion and development of new areas of necrosis

For patients about to initiate IV therapy:

- ✓ Delay IV therapy (if systemic conditions permit) until dental health is optimized
- ✓ Extract non-restorable teeth and those with a poor prognosis
- ✓ Complete necessary elective dentoalveolar surgery
- ✓ Delay therapy (if conditions permit) until extraction site has mucosalized (14-21 days) or until adequate osseous healing
- ✓ Educating patients about good oral hygiene, symptom reporting, and regularly scheduled dental assessments
- ✓ Baseline and routine dental exams including radiographs
- ✓ Dentures should be examined for areas of mucosal trauma

Marx suggests:

- Impacted teeth that are completely covered by bone or soft tissue should be left undisturbed
- Dental implants are contraindicated



Asymptomatic Patients Receiving IV Therapy:

- Importance in preventing dental disease
- Dentoalveolar surgery should be avoided
- Root canal treatment is recommended for non-restorable teeth
- Placement of dental implants should be avoided (especially those exposed to more potent bisphosphonates & frequent dosing schedules)

<u>Note:</u> IV use for osteoporosis (↓ frequency/dosage) is believed to pose an equivalent risk of developing BRONJ as oral therapy

Asymptomatic Patients Receiving Oral Therapy:

- Lower risk for developing BRONJ than IV
- Less severe manifestations of necrosis
- Respond more readily to stage specific treatment regimens
- Elective dentoalveolar surgery does not appear to be contraindicated
- Risk may be associated with increased duration
  - Clinical experience from AAOMS task force members believe the risk is elevated w/ **> 3 yrs** of use

Asymptomatic Patients Receiving Oral Therapy:

- **Oral therapy < 3 yrs and no risk factors:**
  - No alteration or delay in planned surgery
  - Inform patient of possible osteonecrosis if placing dental implants (regular recalls)
- **Oral therapy < 3 yrs and steroids**
  - Consider discontinuation of bisphosphonate for 3 months prior to oral surgery
  - Restart after completion of osseous healing
- **Oral therapy >3 yrs +/- steroids**
  - Consider discontinuation of bisphosphonate for 3 months prior to oral surgery
  - Restart after completion of osseous healing

Patients with a Diagnosis of BRONJ:

- Respond less predictably to established surgical treatment algorithms for osteomyelitis or ORN
- Surgical treatment should be delayed if possible
- Necrotic bone that is a source of soft tissue irritation should be removed or recontoured w/out exposure of additional bone
- Extract symptomatic teeth w/in necrotic bone (unlikely will exacerbate necrotic process)
- Avoid dentoalveolar surgical procedures

Staging Categories (AAOMS):

1. **Patients at risk**
   - No apparent exposed/necrotic bone in patients who were treated w/ either IV or PO bisphosphonates
2. **Patients with BRONJ**
   - **Stage 1:** Exposed/necrotic bone in asymptomatic patients and no evidence of infection
   - **Stage 2:** Exposed/necrotic bone in symptomatic patients and clinical evidence of infection
   - **Stage 3:** Exposed/necrotic bone with pain, infection and one or more of the following: pathologic fracture, extra-oral fistula or osteolysis extending to the inferior border

Treatment Strategies

Stage 1 :

- No surgical treatment is indicated
- Antibacterial oral rinse (chlorhexidine 0.12% rinse)

Stage 2 :

- Broad-spectrum oral antibiotics
- Only superficial debridement

Stage 3 :

- Antibacterial mouth rinse
- Antibiotic therapy and pain control
- Surgical debridement/resection for longer term palliation of infection and pain

Antibiotic Therapy

- Most isolated microbes are penicillin sensitive
- Actinomyces may be present (adjust accordingly)
- If penicillin allergy → success with fluroquinolones, metronidazole, clindamycin, doxycycline and erythromycin
- Refractory cases may require a course of IV therapy, combination or long-term antibiotic maintenance

American Academy of Oral Medicine suggest:

- Amoxicillin and/or clindamycin (empiric therapy)
  - Better bone penetration / Wider spectrum of coverage
  - Coverage against actinomyces

Suggestion by Marx (2005) for refractory cases:

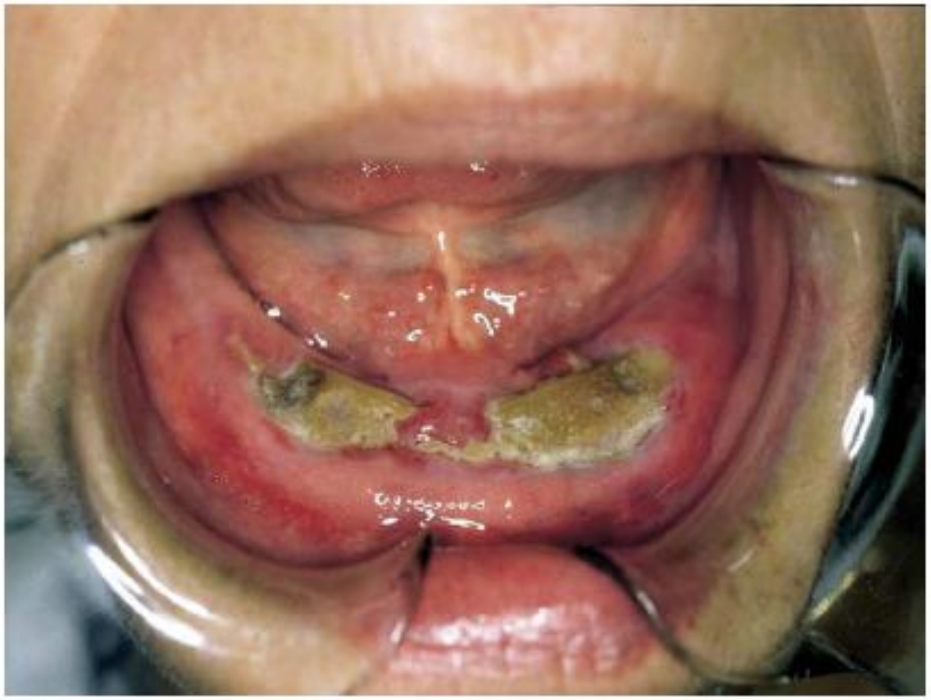
- Ampicillin 1g w/ clavulonate 500 mg IV q6h + Flagyl 500 mg q8h
- Reported a 90.1% effectiveness with ABX + CHX

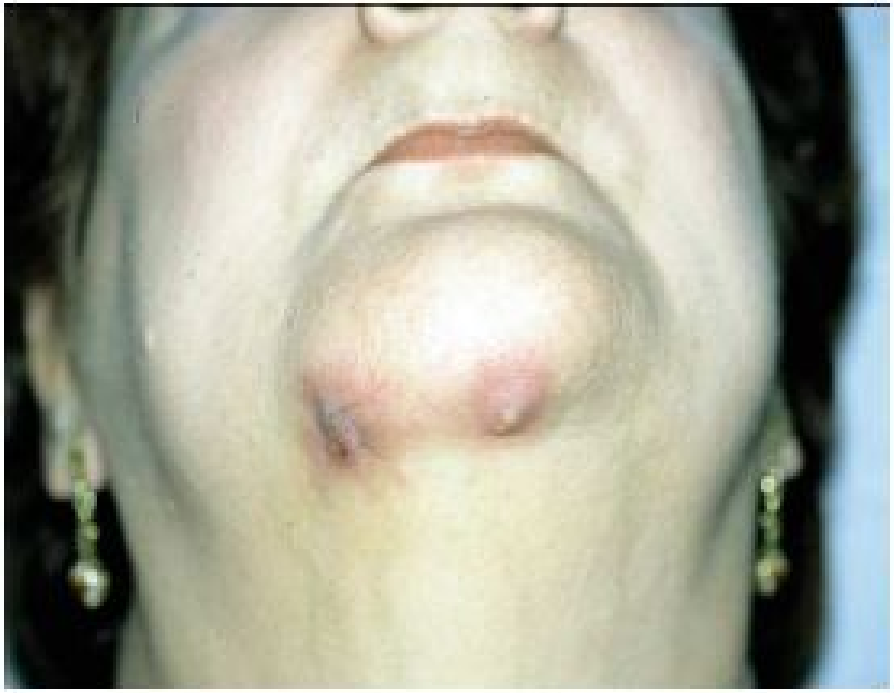
Surgical Intervention

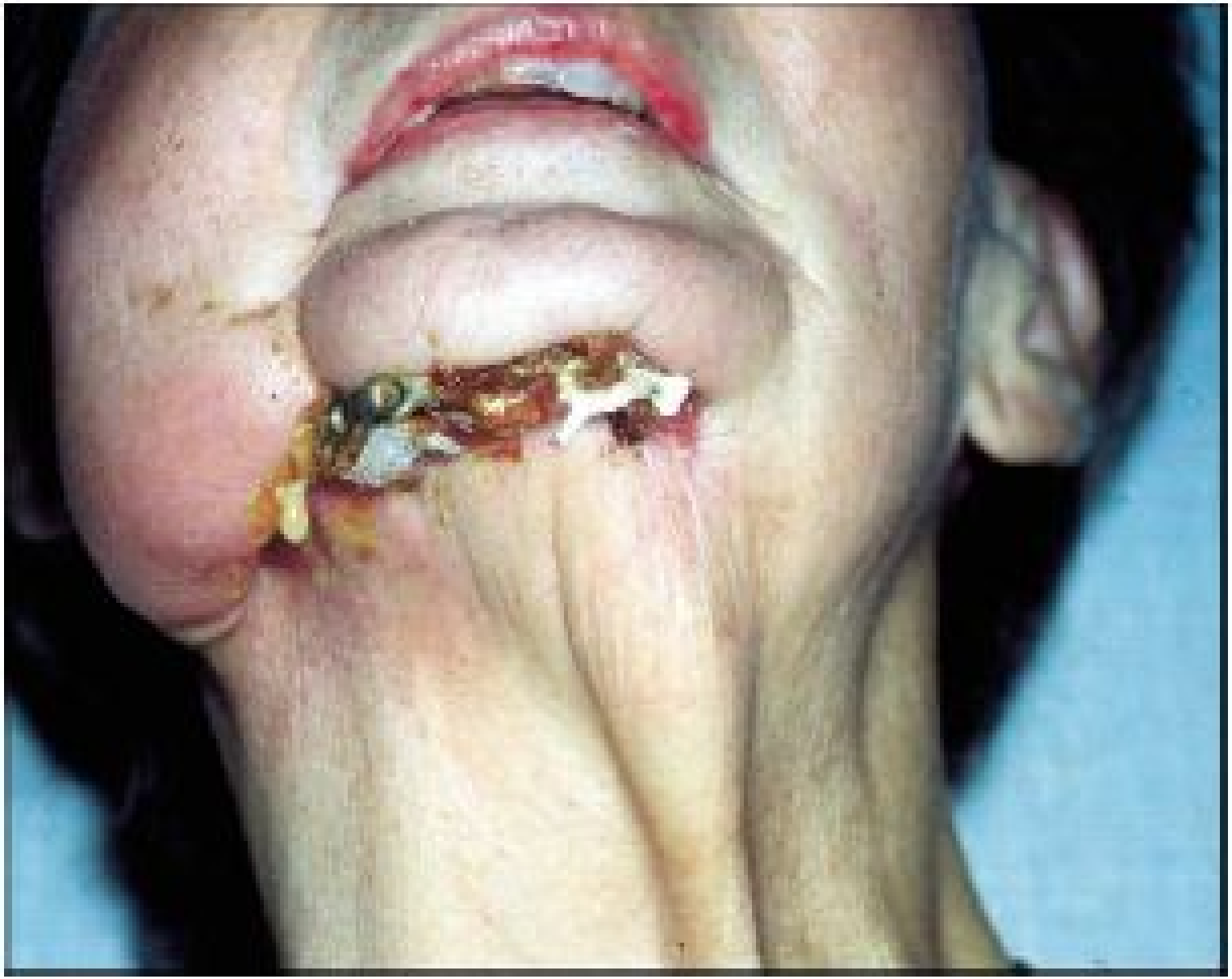
:

- Delay surgical treatment if possible
- Remove bony sequestrum
- Do not expose uninvolved bone
- Pathologic Md fractures may require segmental resection + immediate reconstruction with a reconstruction plate
  - Surgical margin w/ viable bleeding bone may be problematic as drug influences entire jaw
  - Potential of plate failure due to bisphosphonate effect
- Immediate reconstruction w/ non-vascularized or vascularized bone may be problematic as necrotic bone may develop at recipient site

We must treat conservatively







Discontinuation of Therapy?

IV Bisphosphonates:

- Discontinuation offers no short term benefit
- Long term discontinuation may be beneficial in:
  - Stabilizing established sites of BRONJ
  - Reducing the risk of new site development
  - Reducing clinical symptoms
- Discontinuation may reduce anti-angiogenic activity and promote mucosal healing?

Discontinuation of Therapy?

Oral Bisphosphonates:

- Definitive recommendations are difficult in the absence of evidence-based information
- Discontinuation of oral bisphosphonates for 6-12 months may result in either spontaneous sequestration or resolution following debridement surgery (AAOMS Task Force)
- Bisphosphonates have a long residence time in bone:
  - Terminal half-life of alendronate is approximately 10 years
  - Unclear whether stopping therapy will increase skeletal related events

Review of BRONJ

- Risk Factors
- Dental Co-morbidities
- Prevention
- Drug Holidays and Alternatives
- Marx's Protocol and CTx Testing

Risk Factors

History of Intravenous Bisphosphonate Therapy with:

- Multiple Myeloma.
- Metastatic Bone Disease with Breast or Prostate Cancer.
- Osteoporosis.
- Osteogenesis Imperfecta.
- Steroid treatment.

Dental Co-morbidities

- Active Periodontitis.
- Dental Caries.
- Dental Abscesses.
- Failing Root Canal Treatment.
- Any Elective Dento-alveolar Surgery in the Oral Cavity.

Prevention

- All patients which are going to embark on a course of bisphosphonate care must be seen by a dentist to idealize their dentition pre-treatment.

- Especially for iv bisphosphonates but this applies to oral bisphosphonates until the risk is clarified.

Drug Holidays and Alternatives

- Dental practitioner to contact prescribing physicians.
- Discuss temporary discontinuence of the drug versus alternatives.

- Calcium supplements.
- Calcitonin.

Marx's Suggested Protocol

Patient Taking Oral Bisphosphonates in Need of Oral Surgical Procedure:

Bisphosphonate use >3 years

- Contact MD to Discontinue Bisphosphonate 3 months pre-op and for at least 3 months post-op but preferably for 1 year.
- Serum CTx at time of consultation and repeated immediately pre-op.
- CTx must be $\geq$ 150 pg/ml in order to proceed with surgery.
- Detailed informed consent regarding risk of BON
- Use an alternative to Bisphosphonate long-term if possible.

Bisphosphonate use <3 years

with *no clinical or radiographic risk factors* (steroid use, widened lamina dura and sclerotic bone)

- CTx values >150 pg/ml.
- Proceed with planned surgery but with informed consent regarding the increased risk of possible future BON with surgical treatment.
- Regular recall schedule, contact MD to discuss alternate treatment and intermittent drug holidays.

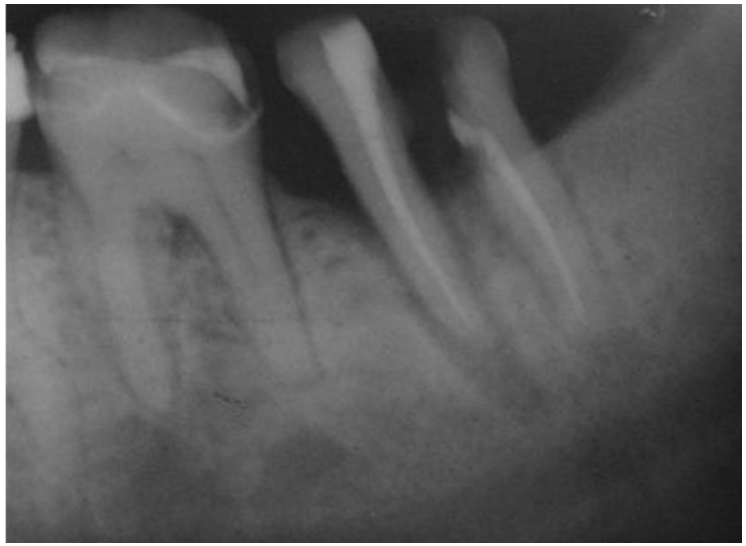
Bisphosphonate use <3 years

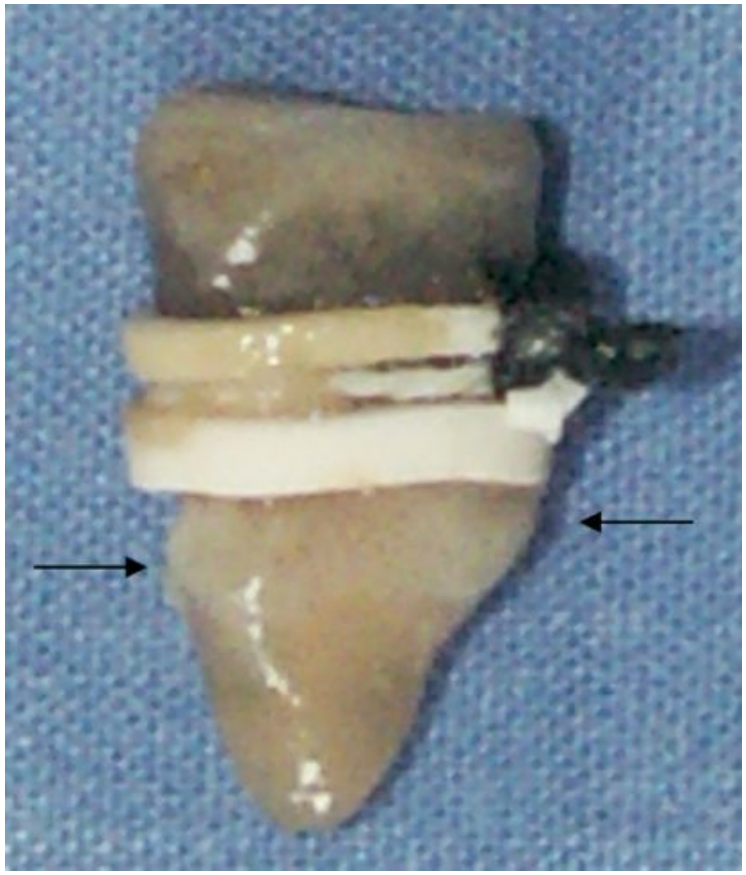
with *one or more clinical or radiographic risk factors* (steroid use, widened lamina dura and sclerotic bone)

- Stop bisphosphonate for 3 month drug holiday
- If CTx values <150 pg/ml:
  - Delay surgery and stop bisphosphonate for at least 3 more months
  - Recheck CTx levels 3 months later
- If CTx >150 pg/ml then proceed to surgery.
- If CTx remains below 150 pg/ml then no surgery and repeat CTx again in 3 months.
- If CTx >150 pg/ml then 3 month drug holiday post-surgery.

Atraumatic Teeth Extraction in Bisphosphonate-Treated Patients

Eran Regev, DMD, MD, Joshua Lustmann, DMD,†*
and Rizan Nashef, DMD‡





Rapidly Developing Area

- Bisphosphonate Related Osteonecrosis of the Jaws Consensus Conference:

Intercontinental Hotel

Toronto, Ontario

Saturday June 2, 2007

Consensus Conference

Canadian Consensus Practice Guidelines for Bisphosphonate Associated Osteonecrosis of the Jaw

ALIYA A. KHAN, GEORGE K.B. SÁNDOR, EDWARD DORE, ARCHIBALD D. MORRISON, MAZEN ALSAHLI, FAIZAN AMIN, EDMUND PETERS, DAVID A. HANLEY, SULTAN R. CHAUDRY, DAVID W. DEMPSTER, FRANCIS H. GLORIEUX, ALAN J. NEVILLE, REENA M. TALWAR, CAMERON M. CLOKIE, MAJD AL MARDINI, TERRI PAUL, SUNDEEP KHOSLA, ROBERT G. JOSSE, SUSAN SUTHERLAND, DAVID K. LAM, ROBERT P. CARMICHAEL, NICK BLANAS, DAVID KENDLER, STEVEN PETAK, LOUIS GEORGES ST-MARIE, JACQUES BROWN, A. WAYNE EVANS, LORENA RIOS, and JULIET E. COMPSTON

ABSTRACT. ***Objective***. Following publication of the first reports of osteonecrosis of the jaw (ONJ) in patients receiving bisphosphonates in 2003, a call for national multidisciplinary guidelines based upon a systematic review of the current evidence was made by the Canadian Association of Oral and Maxillofacial Surgeons (CAOMS) in association with national and international societies concerned with ONJ. The purpose of the guidelines is to provide recommendations regarding diagnosis, identification of at-risk patients, and prevention and management strategies, based on current evidence and consensus. These guidelines were developed for medical and dental practitioners as well as for oral pathologists and related specialists.

J Rheumatol 2008; 35 (7): 1-7.

Recommendations

For the osteoporosis patient prescribed oral or IV bisphosphonate therapy:

(a) For the osteoporosis patient expecting to receive oral or IV bisphosphonate therapy who has practiced appropriate preventive dental care and reports no acute dental problems, routine followup dental examinations are appropriate. If appropriate dental care has not taken place, or if there is an acute dental problem, this should be addressed prior to initiating a bisphosphonate. As is recommended for all individuals, patients taking bisphosphonates should maintain good oral hygiene practices and attend semiannual dental examinations[27]. In osteoporosis patients receiving an oral or IV bisphosphonate who present with a true dental emergency, invasive surgery should not be delayed. Consideration should be given to interrupting the bisphosphonate during the healing period.

Recommendations

(b) For the osteoporosis patient requiring non-emergent invasive dental surgery, interruption of bisphosphonate therapy for several months prior to the procedure and throughout the healing period may be considered. However, there are no clinical trial data to guide the duration of cessation of therapy; and it should be emphasized that, at present, only anecdotal data exist to suggest discontinuing a bisphosphonate reduces risk.

Clearly, implementation of the above guidelines is dependent upon the type and extent of dental coverage a given patient may have. As the relationship between bisphosphonate use and ONJ in the patient with osteoporosis remains unproven, it is not recommended that bisphosphonate therapy be withheld for osteoporosis if a patient is unable to be in full compliance with these guidelines in the absence of other major risk factors for ONJ. Delaying the initiation of bisphosphonate therapy pending a dental evaluation rarely would seem necessary in the osteoporosis patient.

As bisphosphonates have longterm skeletal retention, it is not known if stopping treatment will alter the course of any ONJ lesions. No prospective data exist to address this question, but there are anecdotal reports of patients in whom ONJ seemed to resolve with appropriate dental care and cessation of the bisphosphonate[29], suggesting that cessation of the drug is reasonable. Certainly the cessation of bisphosphonate therapy for several months does not seem to have a detrimental effect on osteoporosis management[30].


°F
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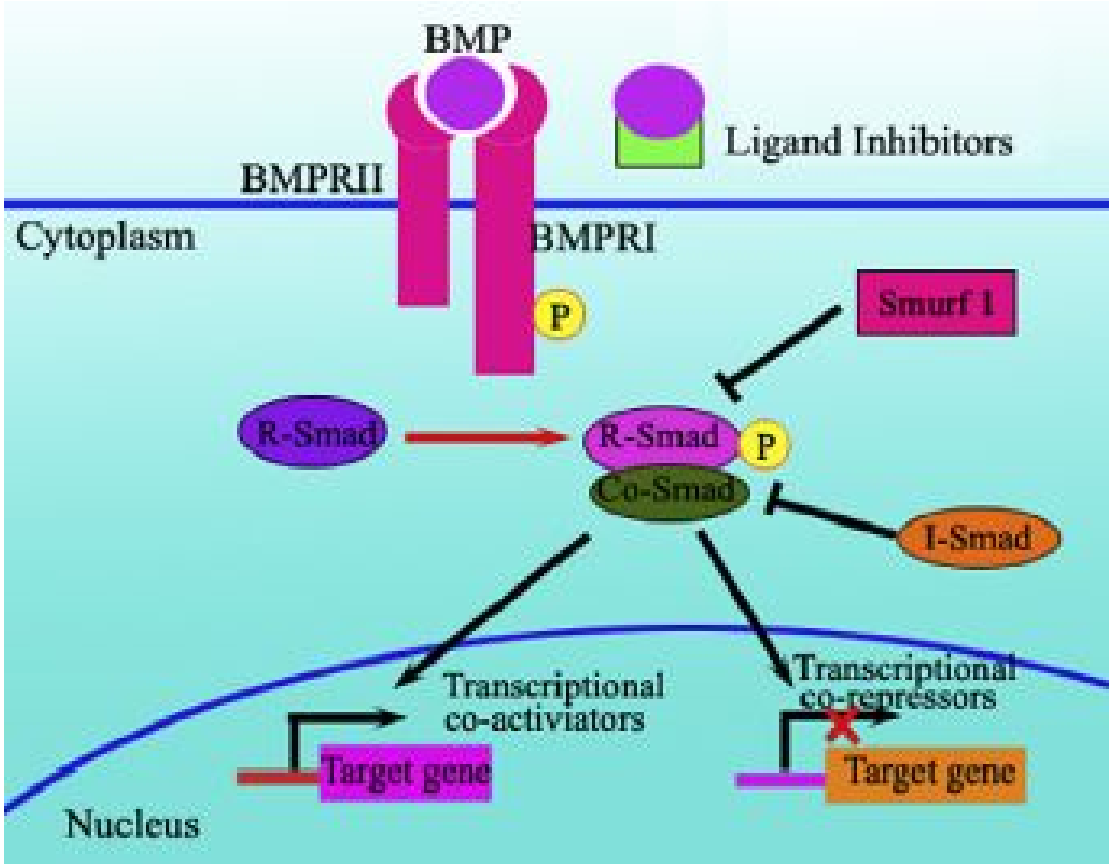
FOSAMAX
HUMIDITY
VERY HUMID
VERY DRY
NORMAL
%

FUTURE RESEARCH

- Bone Morphogenetic Proteins (BMPs) at the molecular level



Concluding thoughts….

- The increasing # of cases should be viewed as an ominous predictor that long-term complications exist
- Long-term prospective studies are required
- Improved understanding of the pharmacokinetics/dynamics is clearly needed
- Evidence based treatment recommendations are needed

Thank You

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