Inland Empire Perio Study Club

Member Presentation

March 11, 2011

Dr. Rob Hardwick

Bisphosphonates: The Good the Bad and the Ugly

Implant considerations with Bisphosphonates

What are bisphosphonates (also called diphosphonates)?

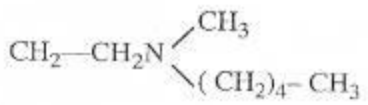
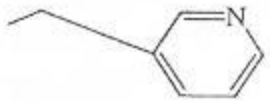
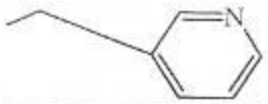
- They are organic compounds with 2 phosphonate (PO_3) groups.
- They are related to pyro-phosphates, the endogenous regulator of bone turnover.
- -They were developed in 1800's.
- -They have been used (etidronic acid) in detergents, water treatment and cosmetics.

Nitrogen vs. non-Nitrogen containing Bisphosphonate

- Nitrogen containing Bisphosphonates are the newer generation created for medical use.
- Nitrogen containing Bisphosphonates are more powerful and specific (e.g., osteoclastic inhibition) than non-Nitrogen containing Bisphosphonates.
- Nitrogen containing Bisphosphonates can be oral (Ibandronate, Alendronate) or IV (Pamidronate, Zoledronate).

Bisphosphonate chemical formulas

Table 1. **Chemical structure, potency and route of administration of main prescribed BPs**

Generic name	Brand name	R1 side chain	R2 side chain	Relative potency Comparing with etidronate	Delivery
Etidronate	Didronel® Laboratoire Procter et Gamble Pharmaceuticals France, Neuilly sur Seine, France	OH	$-CH_3$	× 1	Oral
Clodronate	Bonefos® Bayer Schering Pharma Suisse, Zurich, Switzerland, Loron® Roche Pharma, Reinach, Switzerland	CL	–CL	× 10	Oral/IV
Tiludronate	Skelid®	H		× 10	Oral
Pamidronate	Aredia® Novartis, Basel, Switzerland	OH	$CH_2—CH_2-NH_2$	× 100	IV
Alendronate	Fosamax® Merck, Sharp & Dohme-Chibret, Whitehous Station, NJ, USA	OH	$-(CH_2)_3-NH_2$	× 1000	Oral
Ibandronate	Bonviva® Roche Pharma, Reinach, Switzerland	OH		× 5000	Oral/IV
Risedronate	Actonel® Laboratoire Procter et Gamble Pharmaceuticals France, Neuilly sur Seine, France	OH		× 5000	Oral
Zoledronate	Zometa® Novartis, Basel, Switzerland, Aclasta® Novartis, Basel, Switzerland	OH		× 10,000	IV

BP, bisphosphonate; IV, intravenous.

History in Medical Use

- They were first investigated in 1960's for use in disorders of bone metabolism.
- 1977 Etidronate (Didronel) (oral non-nitrogen containing bisphosphonate): approval for prescription by FDA to reduce turnover rate of bone. It controls heterotopic ossification (HO) where bone tissue forms outside of the skeleton often after orthopedic surgery or bone injury and to treat Paget's bone disease (Paget disease is a chronic disorder that can result in enlarged and misshapen bones).

History in Medical Use

- 1995 Merck launched Fosamax (Alendronate)-(oral nitrogen containing bisphosphonate) and it made its debut for treatment of osteoporosis primarily in post-menopausal women and Paget's disease.

History in Medical Use

- 2001 Pamidronate (Aredia) was approved in US.
- 2002 Zoledronic acid or zoledronate (Zometa) was approved in US.
- Both of these IV drugs are powerful, nitrogen containing bisphosphonates. They are approved for treatment of metastatic bone disease, such as multiple myelomas, malignant hypercalcemia (high levels of calcium in the blood caused by tumors) and other tumors with bone metastasis, such as prostate and breast cancers.

Mechanism of Action of Non-Nitrogen Containing Bisphosphonates

- Primarily reduces osteoclastic activity and eventually creates atypical osteoclasts.
- Creates apoptosis of osteoclasts.
- Inhibits osteoblasts preventing bone calcification.
- Is metabolized and has very short half-life.
- In the long run they can cause osteomalacia (soft bones).

Mechanism of Nitrogen Containing Bisphosphonates

- They inhibit activity of enzymes that utilize pyrophosphates.
- These drugs preferentially stick to calcium and bind to it, i.e. mostly on hydroxyapatite in bones.
- Inhibit osteoclastic mediated bone resorption and eventually creates atypical osteoclasts.
- Creates apoptosis of osteoclasts.
- Not metabolized by the body.
- Half-life over ten years (the effect may not be as great if unaffected new bone covers the old).

Patients taking nitrogen containing bisphosphonates run the risk of developing BRONJ.

Approved by the Board of Trustees of AAMOS

September 25, 2006

Bisphosphonate-Related Osteonecrosis of the Jaw

BRONJ Case Definition

To distinguish BRONJ from other delayed healing conditions, the following working definition of BRONJ has been adopted by the AAOMS:

Patients may be considered to have BRONJ if all of the following three characteristics are present:

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

Note that diagnosis of BRONJ is driven by clinical observation.

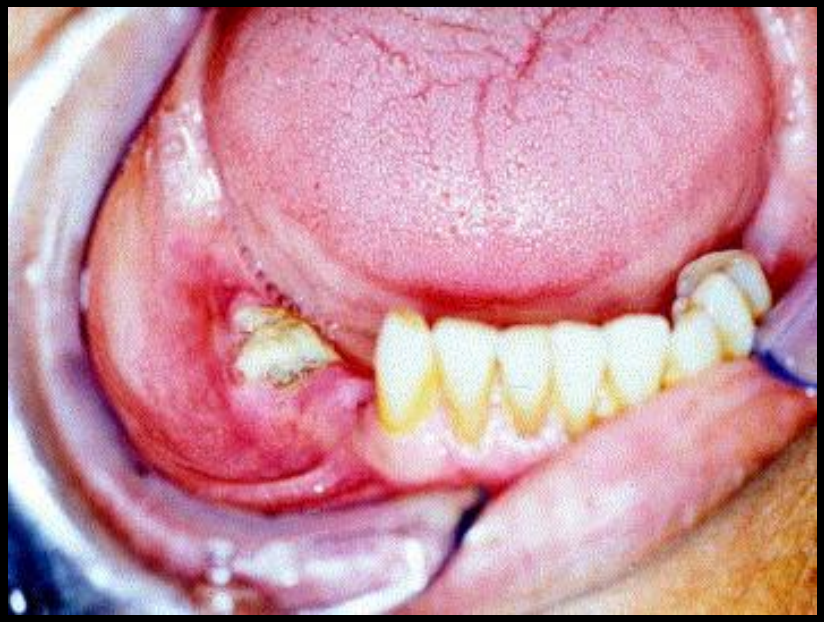
Possible additional risk factors for BRONJ

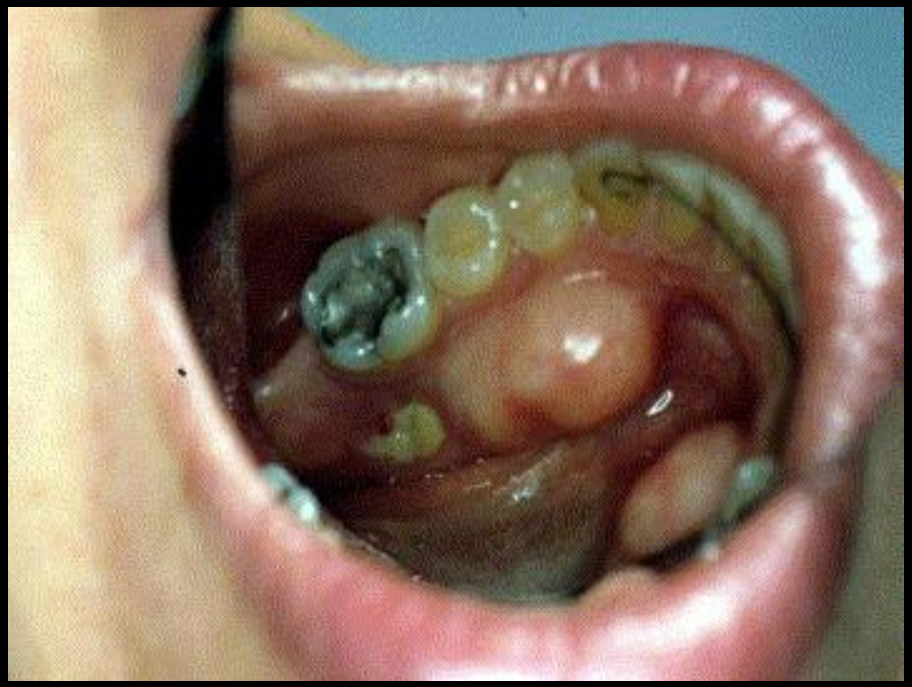
Approved by the Board of Trustees of AAMOS September 25, 2006

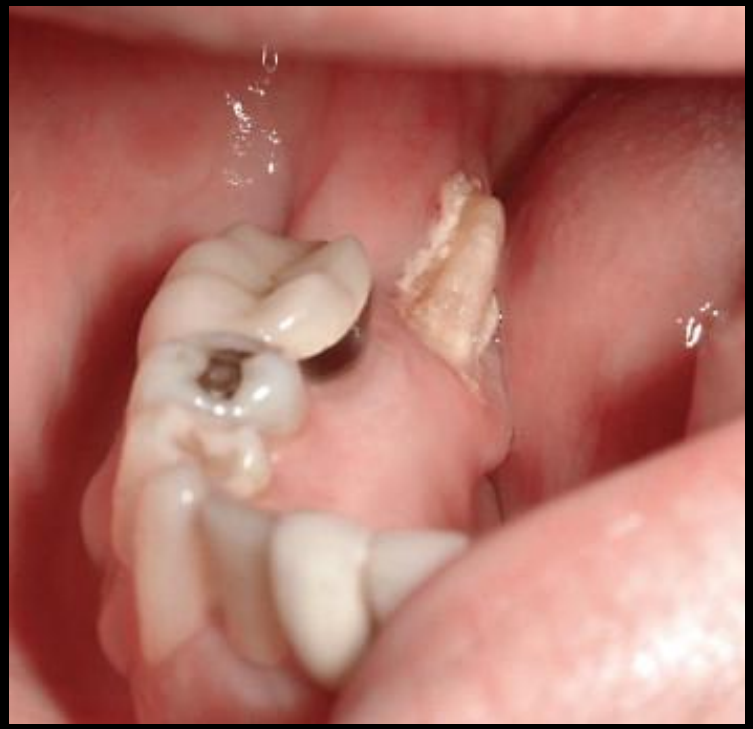
- Corticosteroid therapy
- Diabetes
- Smoking
- Alcohol use
- Poor oral hygiene
- Chemotherapeutic drugs

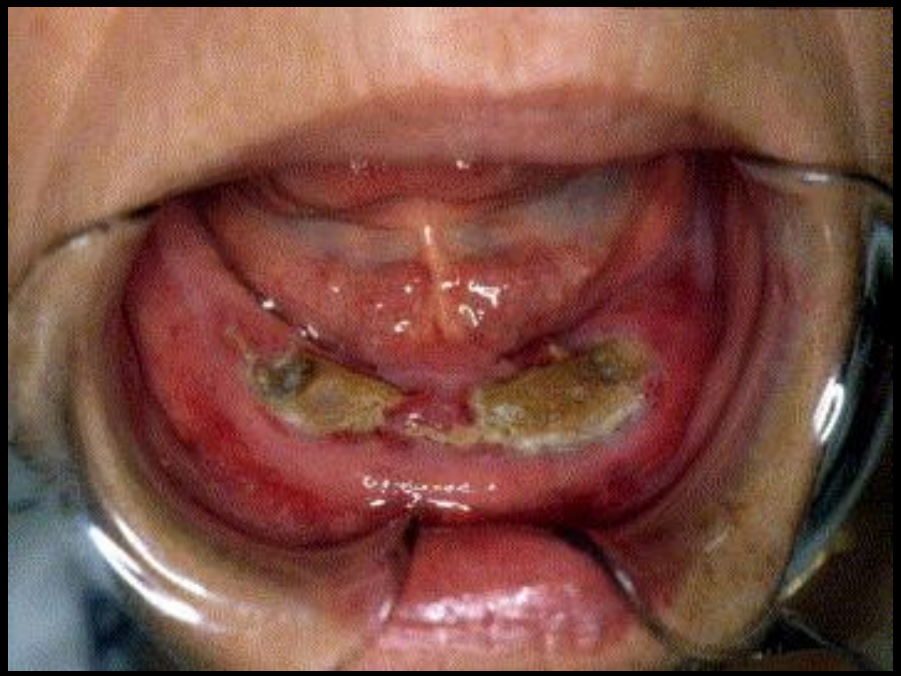
Early signs of BRONJ

- PA
  - Sclerosis of lamina dura
  - Widening of PDL
  - Also see in hyper-occlusion
  - Bone becomes hyper-mineralized
    - Short term Good
    - Long term Brittle
- Mobile teeth
- Pain

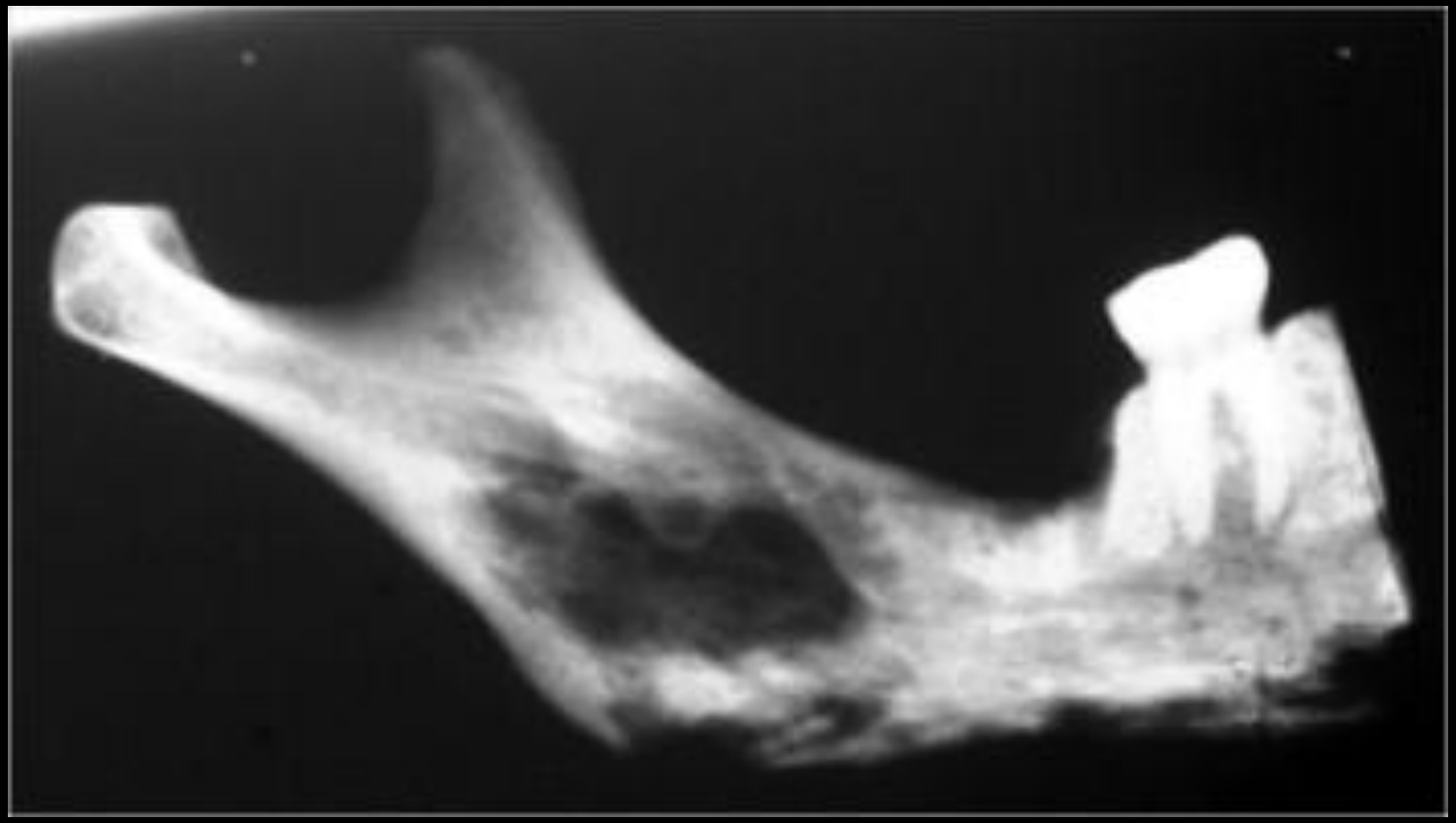


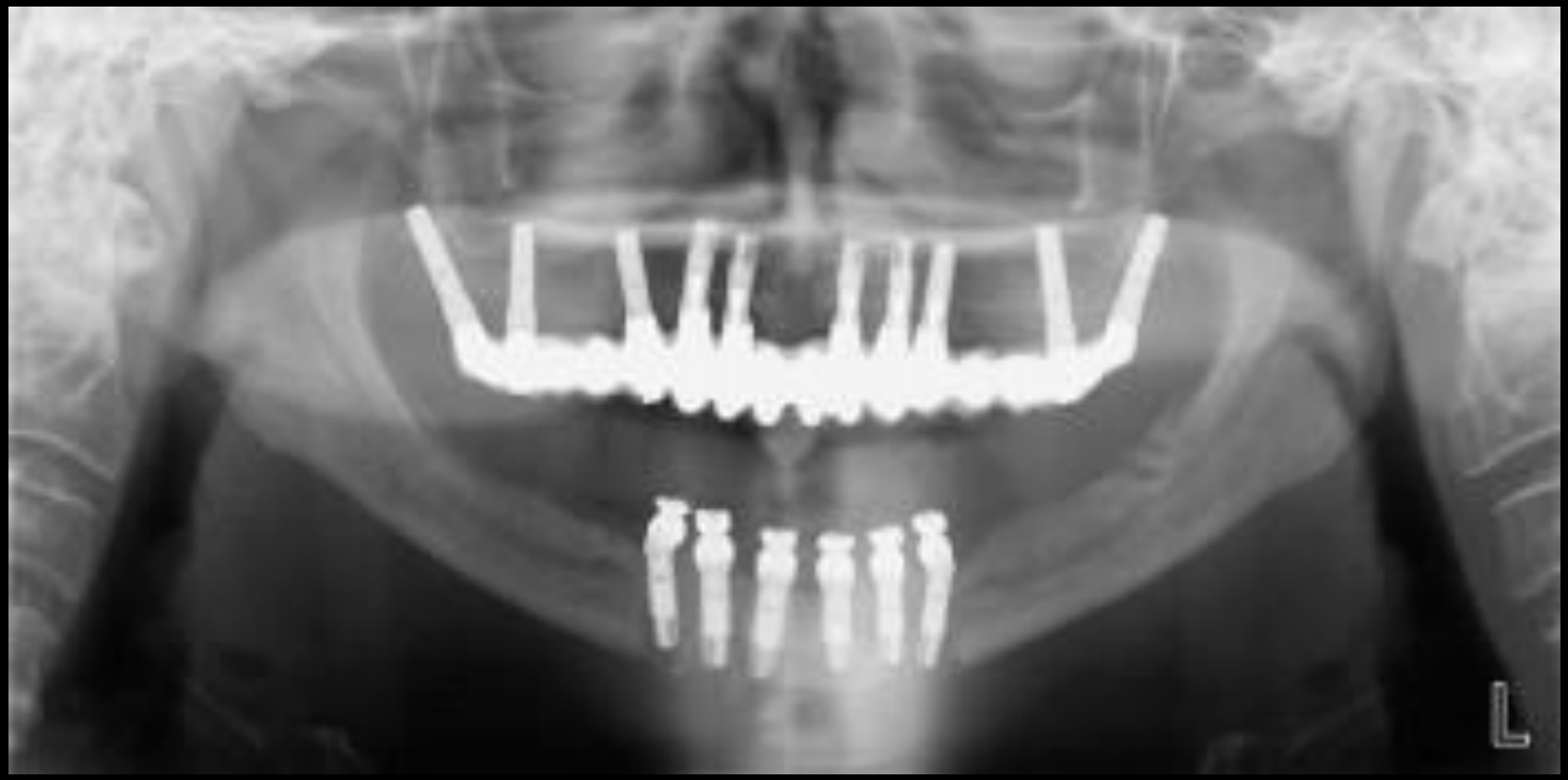






Bone Lesion





- Mx implants 10 years ago
- On Fosamax for last 5.5 years
- 6 implants placed in Md
- Necrosis of lower implants
- Implants placed into bone that had already absorbed bisphosphonates is the problem bone.

Table 2. CRITERIA FOR IMPLANT SUCCESS

An individual, unattached implant is immobile when tested clinically.

A radiograph does not show any evidence of peri-implant radiolucency.

Vertical bone loss is less than 0.2 mm annually after the implant's first year of service.

Individual implant performance is characterized by an absence of persistent and/or irreversible signs and symptoms such as pain, infection, neuropathies, paresthesia, or violation of the mandibular canal.

To be considered successful, the dental implant should provide functional service for 5 years in 75% of the cases.

Adapted with permission from Albrektsson et al.[19]

Patients taking nitrogen containing bisphosphonates run the risk of developing BRONJ.

Approved by the Board of Trustees of AAMOS
September 25, 2006

Table 1 Staging and Treatment Strategies

BRONJ† Staging	Treatment Strategies‡
At risk category No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates	• No treatment indicated • Patient education
Stage 1 Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	• Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2 Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	• Symptomatic treatment with broad-spectrum oral antibiotics, e.g. penicillin, cephalexin, clindamycin, or 1st generation fluoroquinolone • Oral antibacterial mouth rinse • Pain control • Only superficial debridements to relieve soft tissue irritation
Stage 3 Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border	• Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer term palliation of infection and pain

Risk of IV Bisphosphonates

- Rapid osteo-accumulation, i.e., within days, weeks or months.
- The cumulative risks of IV BP's therapy for the incidence of BRONJ are the range of .8 to 12 %.
- Placement of dental implants should be avoided in the oncology patient exposed to IV BP's.
- Oncology patients taking IV BP's are advised to avoid dental implants, and existing implants need to be monitored closely. The patient needs to be advised to do excellent home care and receive regular prophylaxis.

Risk of Oral Bisphosphonates

- The cumulative risks of oral bisphosphonate for the incidence of BRONJ were calculated by Merck (Fosamax) to be 0.7/100/000 person/years of exposure.
- This was calculated from the number of reported cases likely to have been BRONJ, divided by the number of alendronate pills prescribed since the drug's approval.
- This implies an unspecific cumulative effect.

Risk of Oral Bisphosphonates

- Another comparison of oral bisphosphonates vs. IV bisphosphonates is .01% to .04% versus .07% to 12% (Bedogni, MD 2010).

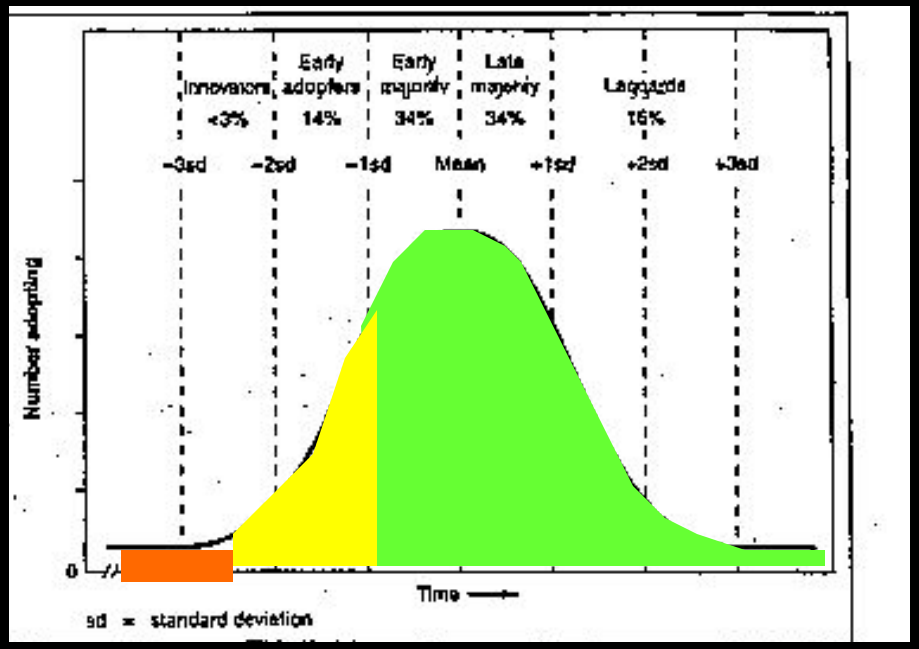
- In other words the prevalence of BRONJ in *oral* bisphosphonates use is much lower.

Are oral BPs worth the risk?
For Treatment of Osteoporosis

- The medical consensus is definitely yes.
- It is estimated that the number of hip fractures in the United States will triple by 2020 and that 1 of every 2 women will sustain an osteoporosis fracture in her lifetime. In people who sustain hip fractures, less than 25% regain full function and twenty-four percent of the women who fracture a hip will die within a year.

  (US Dept. of Health 2004, and ADA Council Scientific Affairs 2006)
- Fosamax claims 50% reductions in fractures of the spine and hip with three year use.
- Concerns: Atypical bone fractures are reported and bone quality is questioned.

- Osteoporosis & Bone Mineral Density (BMD) WHO definition
  - Normal T > -1
  - Osteopenia T -1 to -2.5
  - Osteoporosis < -2.5



Recommendations concerning IV and oral BPs

Table 3. Guidelines on implant therapy in cancer and osteoporotic patients taking IV or oral BPs

Guidelines author	Association or Task Force	Implant placement in cancer patient	Implant placement in oral-BP patient	Antibiotic prophylaxis	Discontinuation of BP before/after placement
Migliorati et al. (2005)	American Academy of Oral Medicine	No position	No position	Not addressed	No position
No author listed (2007)	French Agency for Safety of Health Products	Contraindicated	No contraindicated	Not addressed	No position
No author listed (2007)	American Dental Association Council on Scientific Affairs	Not addressed	Should be considered carefully Extensive implant placement or GBR at risk	Not recommended To be considered: in risky patients for risky procedures	Not addressed
No author listed (2007)	American Association of Oral and Maxillofacial surgeons	Should be avoided	BP intake <3 year: no contraindication BP intake >3 year or <3 year + corticosteroids: drug holiday recommended	Not addressed	Oral-BPs: 3 months before 3 months after
Khosla et al. (2007)	American Society of Bone and Mineral Research	Not recommended	Not contraindicated	Not addressed	No data to suggest improvement of outcomes Discontinuation of oral-BP unlikely to have adverse effect
Edwards et al. (2008a, 2008b)	American Dental Association Council on Scientific Affairs	Not addressed	Dentists should consider treatment options Extensive implant placement or GBR at risk Non-surgical therapy of peri-implantitis	No evidence that antibiotics prevent BRONJ	Not recommended
Khan et al. (2008)	Canadian Consensus Practice for BPs associated osteonecrosis of the jaw	Not recommended	Currently not contraindicated	Not addressed	To be considered in case of non-emergent invasive dental procedure: 3–6 months before the procedure and until healing is achieved

Updated ADA Recommendations for Managing the Care of Patients Receiving oral BP Therapy 2008

Implant placement and Maintenance

- Patients need to be informed of risk. Considered to be small.
- Because implant placement requires an osteotomy the dentist and patient should consider other treatment options.
- Discontinuing BP therapy may or may not eliminate or reduce the risk of developing BRONJ.
- Sound oral hygiene and regular dental care are vital.
- Use bone grafts judiciously with primary closure if feasible.
- CTX testing is unreliable and therefore no recommendation.
- Carefully stage treatment and watch healing results (i.e. one quadrant at a time.)

- Test Slide to see if Sal’s awake.

Suggested Treatment Guidelines

Proposed by Marks 2007

- CTX Test
  - CTX ≤ 100 pg/ml High risk
  - CTX 101-150 pg/ml Moderate risk
  - CTX ≥ 151 pg/ml Little-no risk
- CTX Rx

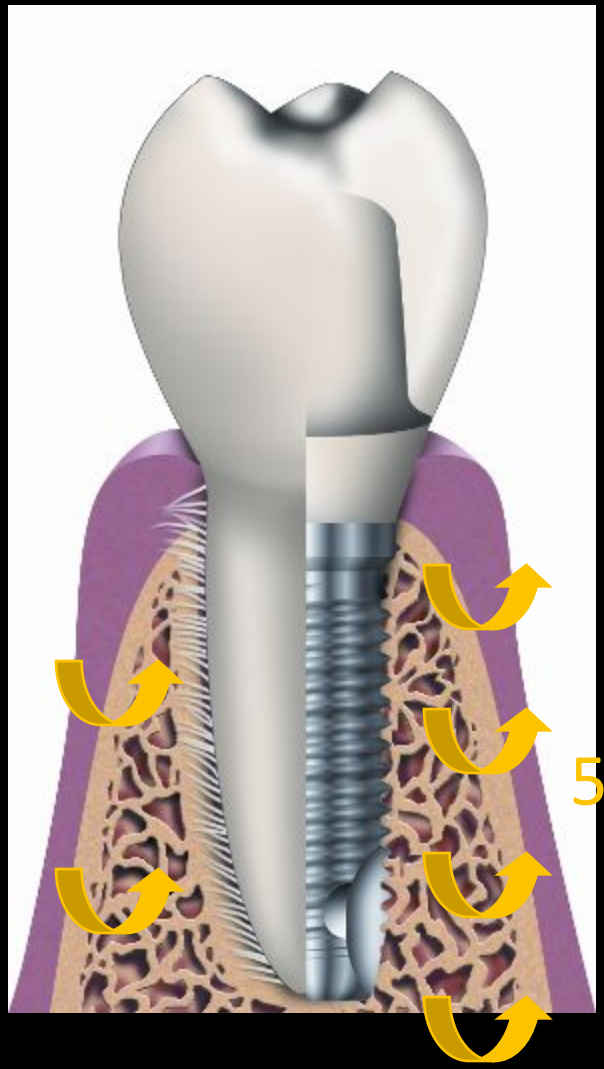
  Morning fasting serum C-Terminal Telopeptide (CTX) bone turnover marker

  Dx = Osteonecrosis 733.40

Why the jaws?

- BRONJ starts in the alveolar bone.
- Recall high remodeling rate in jaws (300%).
- Remodeling rate in alveolus 10x than that of long bone.
- All cases have occurred in the jaws, except for a single case occurring after ear surgery.

- Bone is a *living* tissue
  - Constant turnover
  - Body 30% per year
  - Jaws 300% per year
  - Implants 500% per year



Iran Retrospective Study

Shabestari DDS, MS, 2009

- Purpose: To evaluate implant survival in patients with a history of oral bisphosphonate therapy.
- Data:
  - There were 46 ITI implants placed in 21 osteoporotic females, average age 53, who were evaluated with regards to probing depth, mobility, thread exposure and bleeding.
  - Mean duration of oral BP therapy was 20.5 months(<2yrs).

Iran Study (The Good)

- Summary:
  - None of the implants showed mobility and all patients could be considered free from peri-implantitis.
  - Many other studies report similar findings, especially with short-term oral bisphosphonate use.

Swiss Systemic Review

Dr. Madrid, Dept of Oral Surgery, 2009

- Purpose: Evaluating the risk of developing BRONJ with implant patients receiving IV and oral BP therapy.
- Data:
  - Literature review found: there is a consensus on contraindicating implants under IV BP therapy, and not contraindicating dental implants in oral BP patients.

Swiss Study (The Good)

- Summary:
  - The placement implants may be considered a safe procedure in patients taking oral BPs less than 5 years related to BRONJ.
  - Also, BPs do not influence short-term (1-4 years) implant survival rate.

Swiss Study

- Points of Interest: The Good
  - Animal studies using monkeys and beagle dogs showed retarded bone loss around affected teeth with alendronate.
  - Orthopedic surgery has studied alendronate with experimental arthroplasty on animals. Results suggest increased bone density and pull-out force necessary to remove implant. There has also been an attempt to coat implants with BPs, which promotes osteogenesis at the bone implant interface.

Kaiser Retrospective Study
Martin DDS, 2010

- Purpose of the Study: Examine the pattern of implant failures reported in a large cohort of patients (8,572) who received oral bisphosphonate therapy.

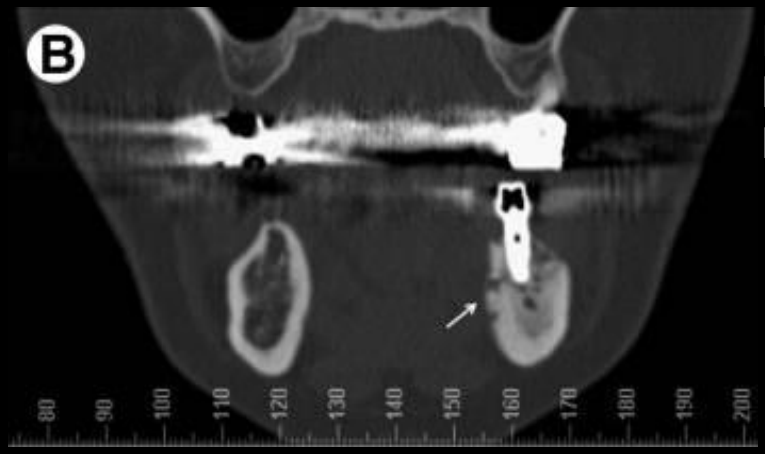
- Data/Results: 16 patients (all women, average aged 70 years) had 26 implant failures.

Kaiser Study (The Bad)

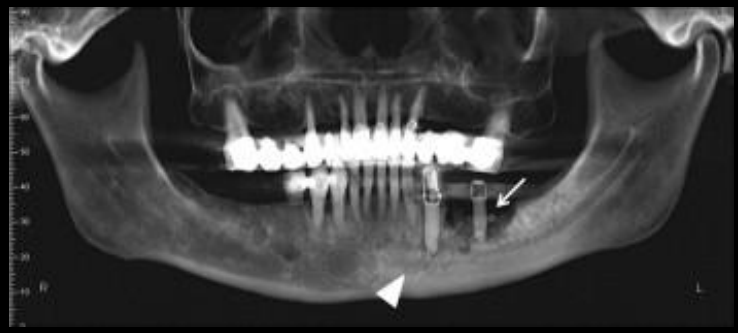
- Summary:
  - There were more late than early failures (over one year).
  - Among the 10 patients with 18 late implant failures, 4 were patients whose 10 implants were placed and osseointegrated before starting bisphosphonates.
  - None of the 16 patients with failed implants met AAOMS criteria for BRONJ.

Italian Case Report (The Ugly)
Bedogni MD, 2010

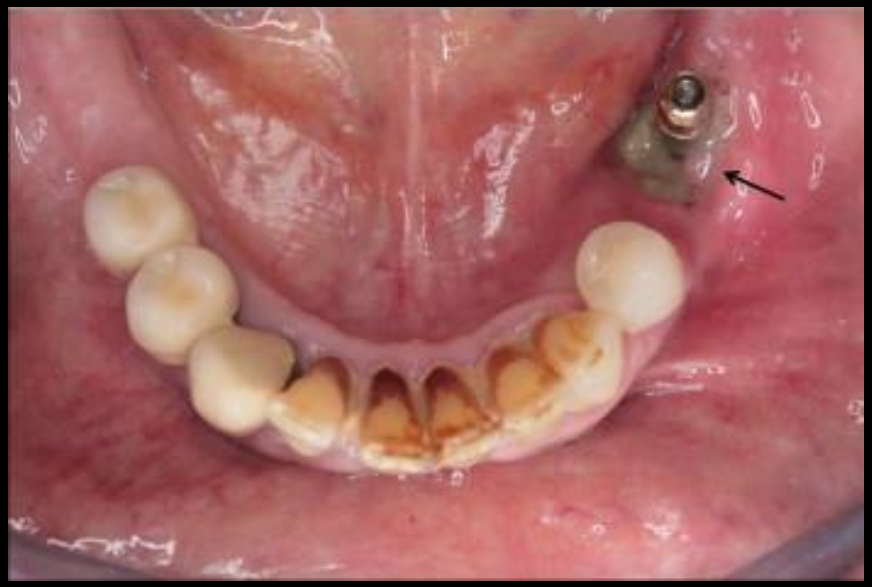
- Purpose: Documents case of BRONJ as a result of oral BP therapy.
- Data:
  - 63 year old patient who developed BRONJ 6 years after oral BP therapy, and two years after implant placement.



Notice increased bone density of left mandible.

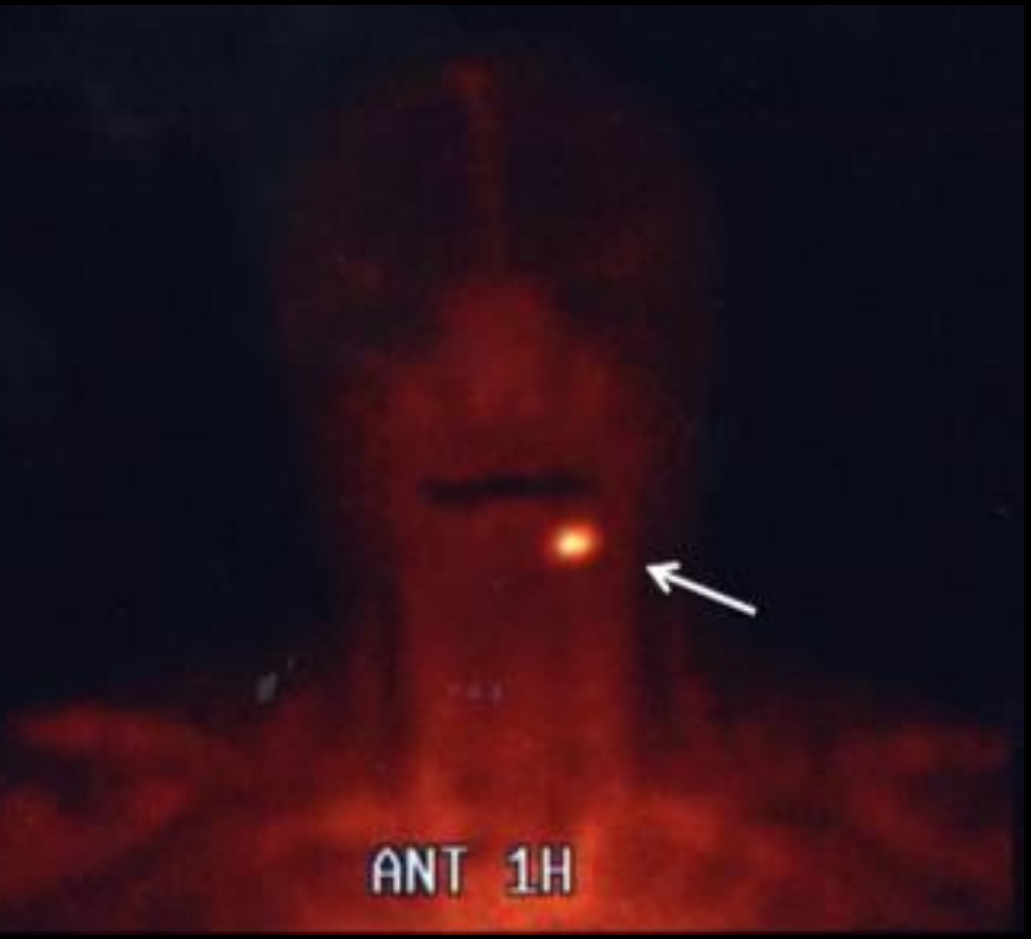


Italian Case Report



- Peri-implant necrotic bone exposed in first molar region (arrow) associated with purulent discharge. This is BRONJ with late onset (>1 yr), i.e. not related to osteotomy. The patients poor oral hygiene should be noted.

Italian Case Report



- Anterior View of technetium 99-labeled lukocyte scintigraph. The persistent contrast uptake at 24 hours at the site of mandibular involvement provides evidence of active bone infection.

Italian Case Report

Literature Review

- Summary: The literature review found 9 BRONJ cases of implants which began with infection. These were oral BP cases with mean duration of 5.5 years of treatment. Mean time from implant placement to jaw infection and BRONJ development was 5.7 months.

Israeli Study

Lazarovici, DMD, 2010

- An Israeli study in Sheba Medical Center from 2003 to 2009 reviewed patients who had developed BRONJ associated with dental implants subsequent to bisphosphonate treatment.
- 145 patients were diagnosed with BRONJ, of which 27 were associated with dental implants.
- 11 of the 27 were associated with oral bisphosphonate (Fosamax). The rest were IV.
- All patients stopped receiving the BPs soon after the diagnosis of BRONJ was established.

Israeli Study
Oral bisphosphonate average length of time for development of BRONJ was 5.33 years.

Table 2. INTAKE DURATION OF BP RELATED TO DI PLACEMENT AND DEVELOPMENT OF BRONJ

Case	BP Intake	Duration of BP Intake Before DI Placement (mos)	Duration Between DI Placement and BRONJ Development (mos)	Overall Duration of BP Intake Before BRONJ Development (mos)
1	A	42	0	42
2	A	50	10	60
3	A	0	46	46
4	A	42	7	49
5	A	18	0	18
6	A	108	3	111
7	A	59	1	60
8	A	36	15	51
9	A	78	0	78
10	A	66	6	72
11	Z	15	13	28
12	Z	3	7	10
13	Z	0	17	17
14	Z	36	7	43
15	Z	10	3	13
16	P	24	11	35
17	P	18	7	25
18	P	20	8	28
19	P	18	30	48
20	P	96	19	115
21	Con	24	20	44
22	Con	15	53	68
23	Con	54	13	67

Abbreviations: A, alendronate; BP, bisphosphonate; Con, concomitant use of pamidronate and zoledronic acid; DI, dental implant; P, pamidronate; Z, zoledronic acid.

3 years = 36 month window

5 years = 60 month window

Discuss case #5, #3

Israeli Study

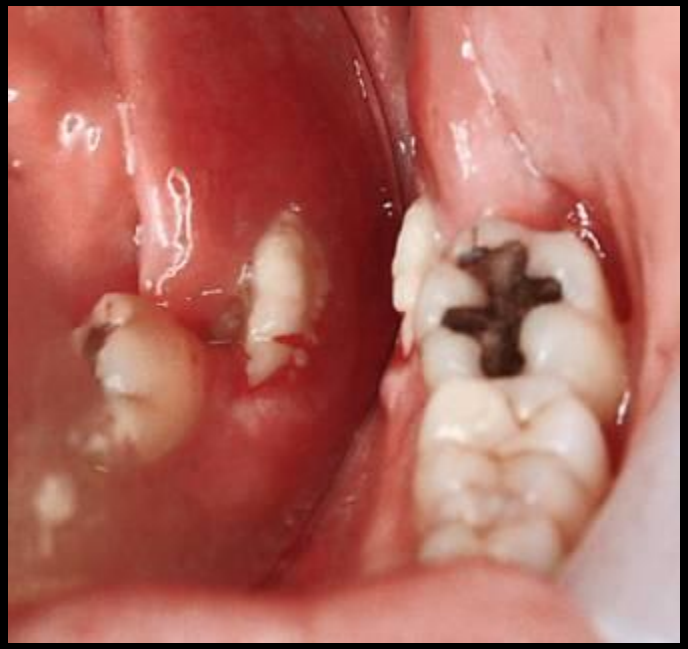
Table 4. TREATMENT AND RESPONSE

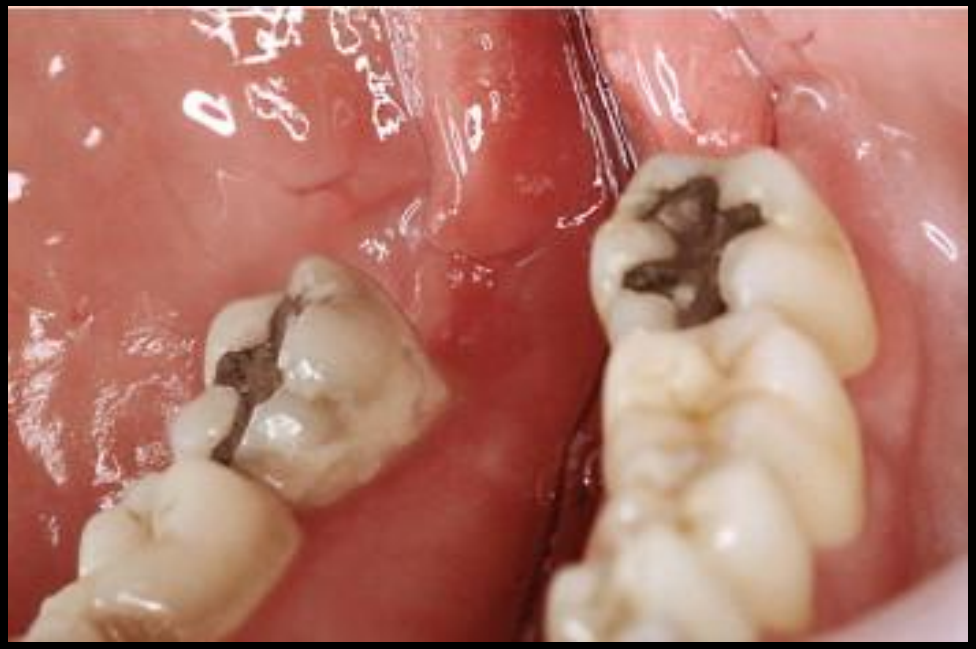
Type of BP	Patients Treated With Amoxicillin (1.5-3 g/d)	Patients Treated With Doxycycline (100-200 mg/d)	Response
Alendronate	3	4	CR
	1	3	PR
	0	0	NR
IV	0	5	CR
	2	7	PR
	1	1	NR

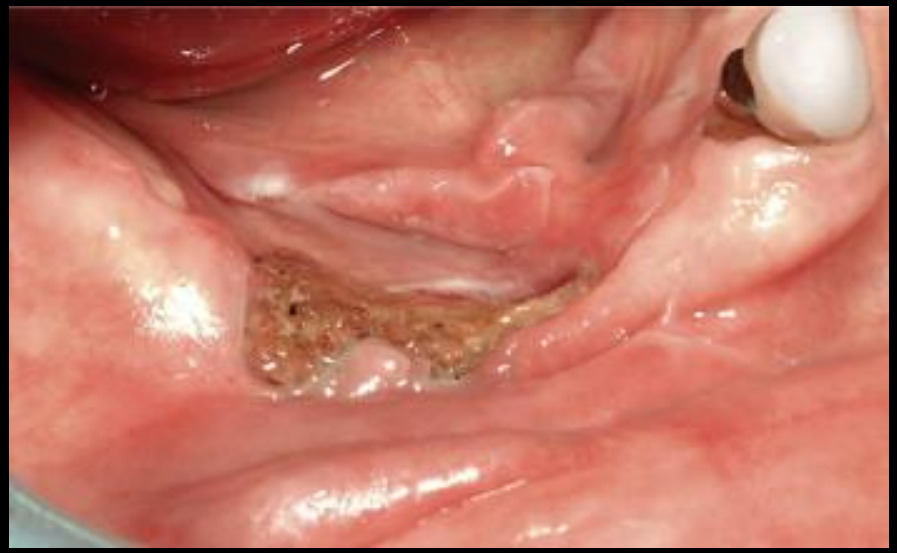
Abbreviations: BP, bisphosphonate; CR, complete response; IV, intravenous BPs (zoledronic acid, pamidronate, or concomitant use of both); NR, negligible or no response; PR, partial response.

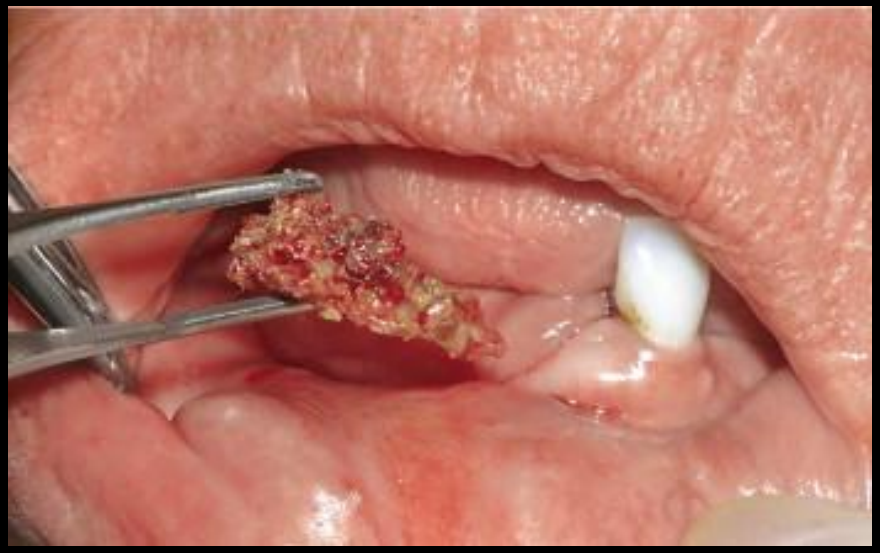
The response to the treatment among patients taking oral BPs was better than that for the patients receiving IV BPs i.e., 63% of the oral BP patients had a complete response compared with only 31% of the IV.

Before and After

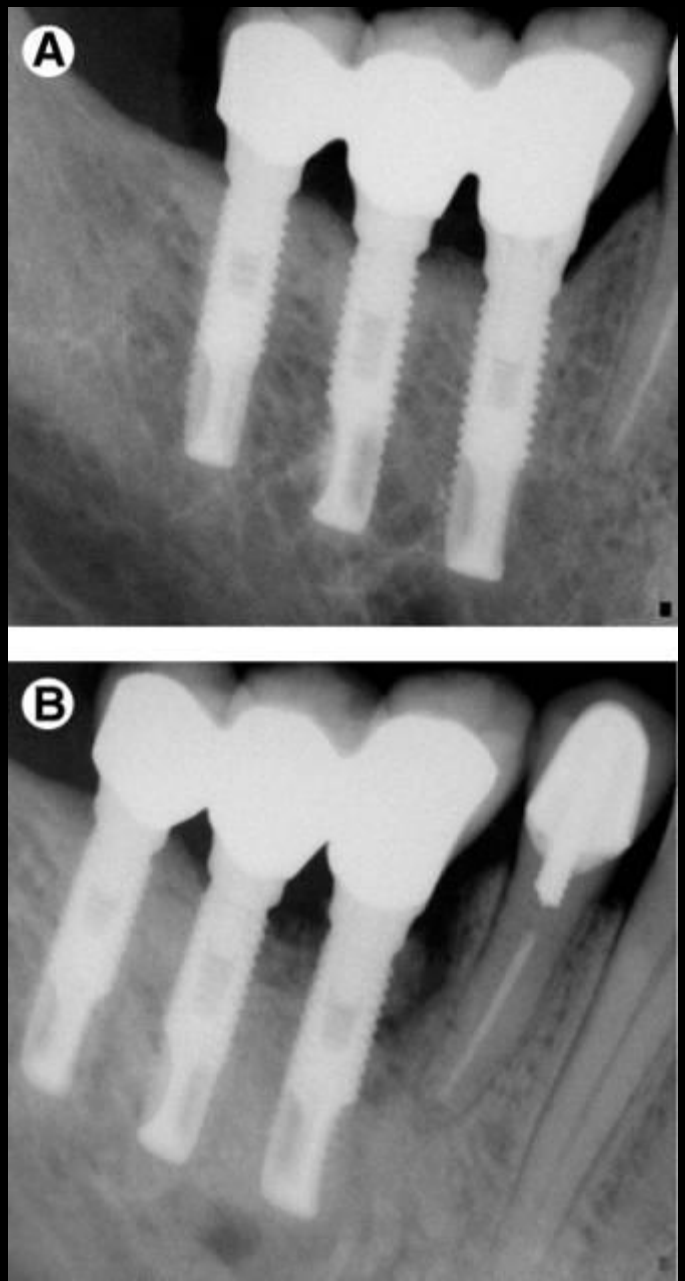








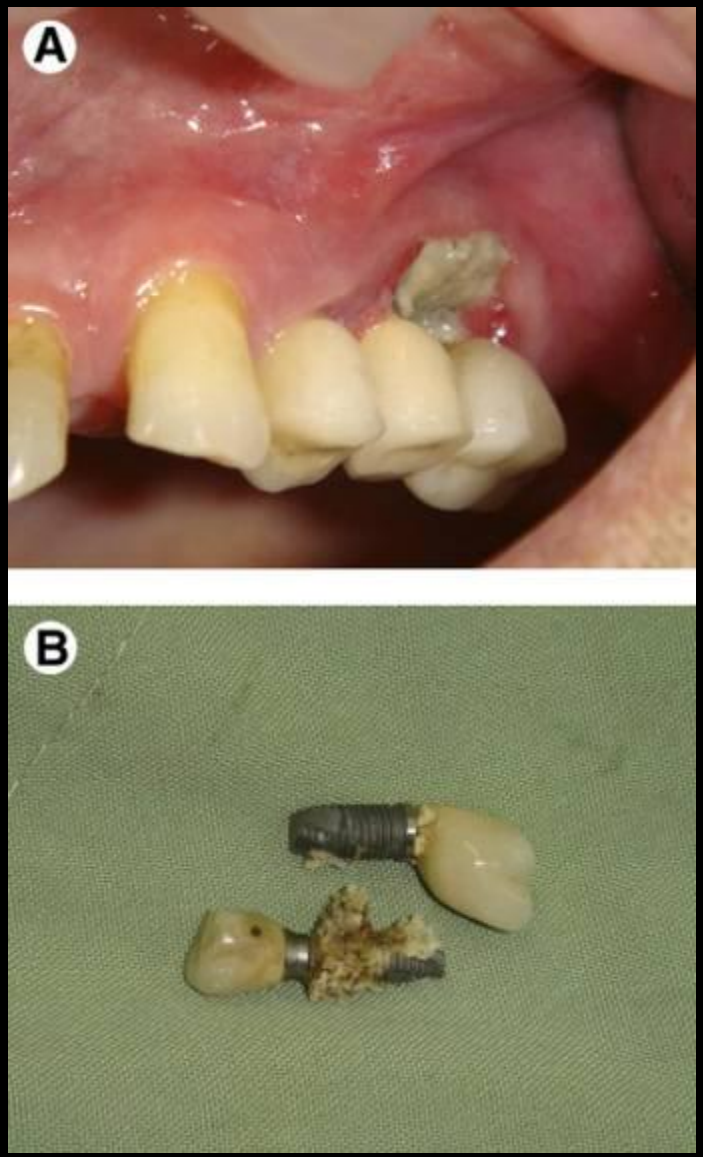
Israeli Study (The Bad)



Spontaneous Implant BRONJ in 65-year-old man with multiple myloma.

- #A Implants were placed 58 months before comencing IV BP therapy.
- # B is the same area 33months after commencing IV BP therapy. Raiograph demonstrates a sequestrum attached to the mesial of the anterior implant

Israeli Study (The Ugly)



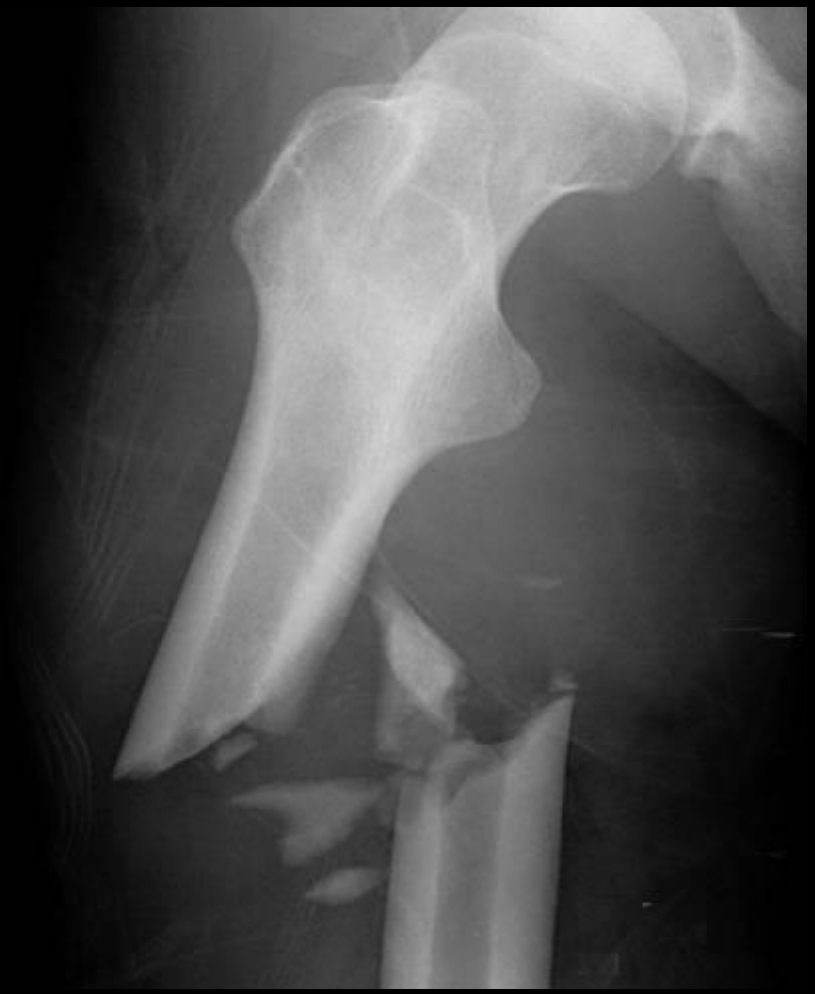
Because the IV BP 60 year old multiple myeloma patient did not respond to nonsurgical treatment, the implants were removed. Note the necrotic bone integrated with the implants.

Israeli Study

Conclusions:

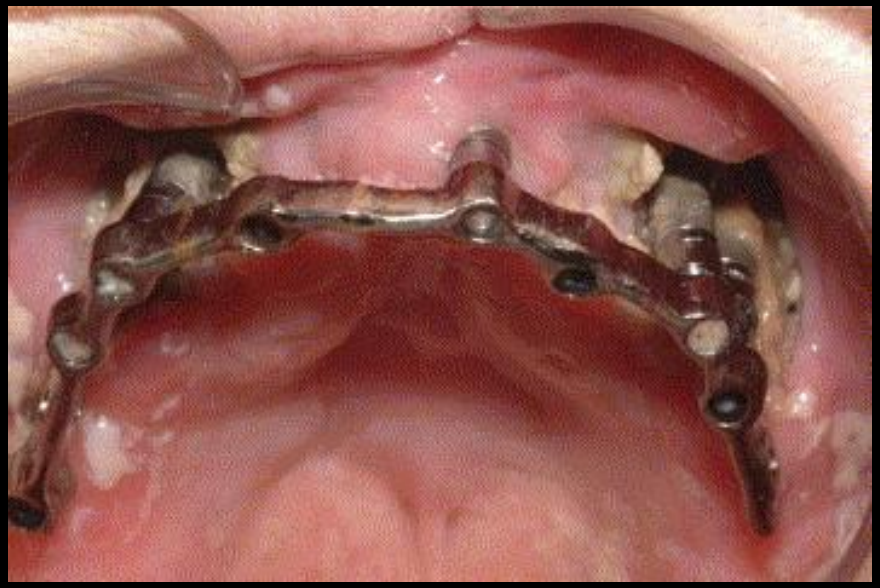
- The study revealed that the development of BRONJ associated with implants is a late complication and that it is usually not related to the oral surgery.
- Some cases of BRONJ can be cured with discontinuation of BP and antibiotics, especially oral BP.
- Patients treated with BPs who receive implants should be followed for long periods of time.

The Ugly



In large studies, women taking bisphosphonates for osteoporosis have had atypical fractures in the femur in the shaft, rather than at the head of the bone, which is the most common site of fracture. These unusual fractures, however, are extremely rare.

The Ugly



- IV Induced
- Multiple myeloma
- Implants still solid
- Manage with antibiotics and peridex
- Best bet is to manage non-surgically
  - Surgery is last resort
- Minor debridement is counter-productive

Conclusions

1. Do not place implants in IV bisphosphonate cancer patients.
2. Furthermore, if your current implant patient ends up with IV bisphosphonate, do a regimented recall schedule with heavy emphasis on home care and regular prophylaxis. Also counsel to limit other possible risk factors, such as smoking, etc.
3. If your patient is on oral bisphosphonates less than 3 years and no corticosteroids, proceed as normal with well-documented counseling and informed consent.
4. If your patient is on oral bisphosphonates in the 3-5 year range, consider CTX test along with counseling and informed consent. Consider a 3-6 months drug-holiday before placement and at least 3 months past placement (must be approved and coordinated with MD). Do one quadrant at a time and observe healing. OHI and regular prophylaxis.
5. If your patient is on oral bisphosphonates over 5 years, consider alternative treatment to implants. If you and the patient choose implants, be sure to have well-documented counseling and informed consent. I would definitely have a CTX test in the file for supportive evidence. Plan a 3-6 months drug-holiday before placement and at least 3 months past placement or until healing has occurred (must be approved and coordinated with MD). Do one quadrant at a time and observe healing. OHI and regular prophylaxis.

The End

Bibliography

- American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws. September 25, 2006
- Bisphosphonate-Related Osteonecrosis of the Jaw Associated With Dental Implants. T. Lazarovici, DMD, R. Yabalom, DMD, S. Taicher, DMD, D. Schwartz-Arad, DMD, PhD, O. Peleg, DMD, and N. Yarom, DMD. American Association Oral and Maxillofacial Surgeons. 2010.

Bibliography

- Characteristics of Implant Failures in Patients With a History of Oral Bisphosphonate Therapy. D. Martin, DDS, F. O'Ryan< DDS, A. Indresano, DMD, P. Bogdanon, B. Wang, R. Hui, PharmD, MS, J Lo, MD. American Association of Oral and Maxillofacial Surgeons. 2010.
- Correaltion Between Serum C-Terminal Cross-Linking Telopeptide of Type I Collagen and Staging of Oral Bisphosphonate-Related Osteonecrosis of the Jaws., Y Kwon, DMD, MSD, PhD, D. Kim, MD, PhD, J Ohe, DMD, J. Yoo, DMD, C Walter, MD, DDS.
- Implant Placement in Patients with Oral Bisphosphonate Therapy: A Case Series. G Shabestari, DDSM MS, Y Shayesteh, DDS, MS, A Hhojasteh, DMD< MS, M Alikhasi, DDS, MS, N Moslemi, DDS, MS, A Aminian, DDS, R, Masaeli, DDS, B. Eslami, DDS, MS, N. Treister, DMS, SMSc. Clinical Implant Dentistry and Related Research. Vol 12, No .3, Sept 2010.

Bibliography

- Oral Bisphosphonates and Dental Implants: A Retrospective Study. B. Bell, R Bell DDS. Ouranl Oral Maxillofacial Surgery 66:12022-1024, #5, May, 2008.
- Oral Bisphosphonate-Associated Osteonecrosis of the Jaw After Implant Surgery:
- A Case Report and Literature Review. Italy. Albert Bedagni, MD, Georgia Sia, MD, Andrea Totola, DMD, Pier Francesco Nocini, MD, DDS. 2010.
- Oral Bisphosphonates: Risk, Prevention & Management. Presentation by David Engen. DDS, MSD & R. Hahn, DMD, MS.
- Osseointegration of Dental Implants in Patients Undergoing Bisphosphonate Treatment: A Literature Review. F. Javed, K Almas. J. Periodontal, April 2010.

Bibliography

- Outcomes of Placing Dental Implants in Patients Taking Oral Visphosphonates: A Review of 115 cases. B Grant, DDS, C Amenenedo, DDS, K Freeman, DrPh, R Kraut, DDS. American Association of Oral and Maxillofacial Surgeons. Received from Albert Einstein College. 2008.
- Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy. An advisory statement from the American Dental Association Council on Scientific Affairs. B. Edwards, MD, FACP, J Hellstein, DDS< MS, P Jacobsen, PhD, DDS, S Kaitmean, DMD, MD, A Mariotti, DDS, PhD, C Migliorati, DDS, MS, PhD. Jada 2008.
- What impact do systemically administrated bisphosphonates have on oral implant therapy? A systematic review. C. Madrid, M. Sanz, Switzerland. Clinical Oral Implant Res. 20, 2009.

The bad