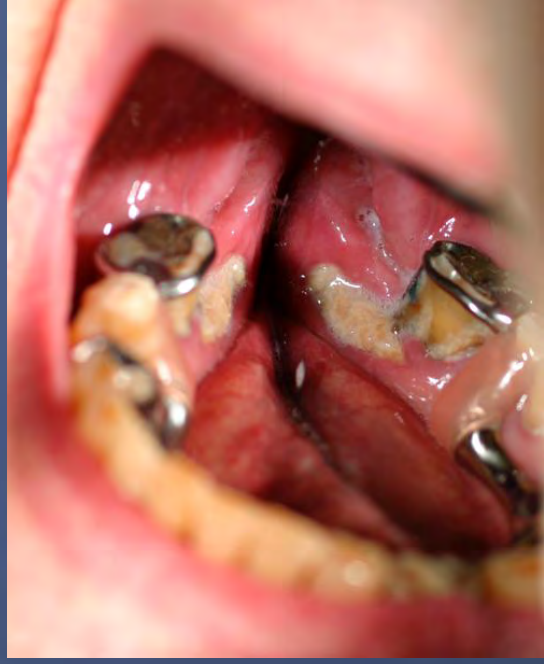


# BISPHOSPHONATES: Importance in oral surgery

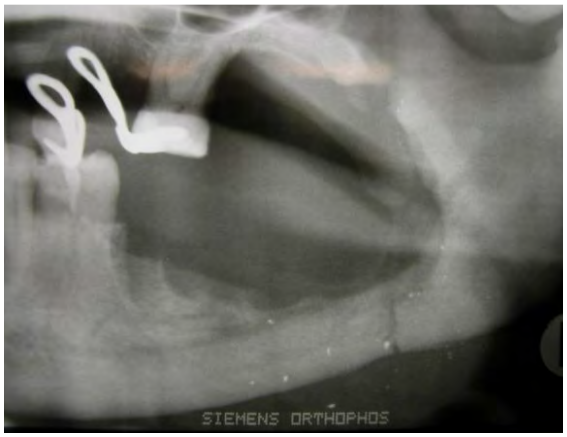

Carlos Madrid

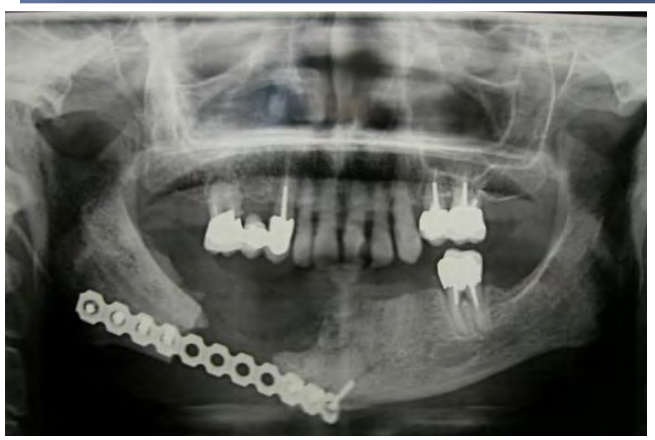
Service de Stomatologie et de médecine dentaire
Policlinique Médicale Universitaire
Département Universitaire de Médecine et Santé Communautaire
**Université de Lausanne**

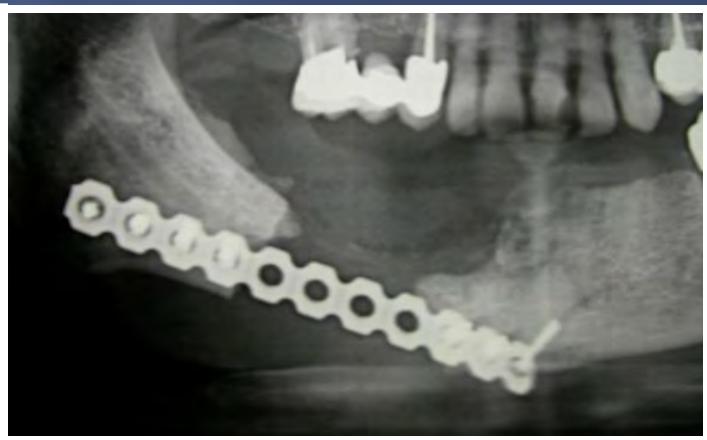
# Update 2009 – Aims

- Bisphosphonate without osteonecrosis
- Bisphosphonates with ON
- Incidence
- Pathogenesis & risk factors
- Dosing effect

- Oral BPs & Osteoporosis main problem today in terms of
  - Level of prevention
  - Surgical approach of patients.
  - Introduction of once-yearly IV 5mg zoledronic acid to prevent SRE in severe osteopenia/osteoporosis
- Investigations
- Treatment
- Future





# Bisphosphonates without ON

- potent osteoclast inhibitors
- first choice therapy in diseases affecting bone metabolism
  - osteoporosis
  - Paget's disease,
  - malignant tumors
- a highly selective deposition in bone due to a high affinity interaction between the BPs molecular structure and the hydroxyapatite crystals (Rogers et al. 2000).
- Once deposited in bone, very small amounts are released into the circulation during bone turnover.
- the half-life of BPs in bone is estimated in years (Lin 1996).

# Bisphosphonate without ON

- BPs. : oral administration, few weeks of intake, adequate levels of bone resorption inhibition observed.
- These dosages insufficient to counterbalance the resorptive activities of bone metastastatic tumors
- in these situations : intravenous BPs
- the high resorptive process can be halted in 24 - 48 hours. Table 1 shows the main BPs with their chemical structure, relative potency and used route of administration.

# Bisphosphonate and perio

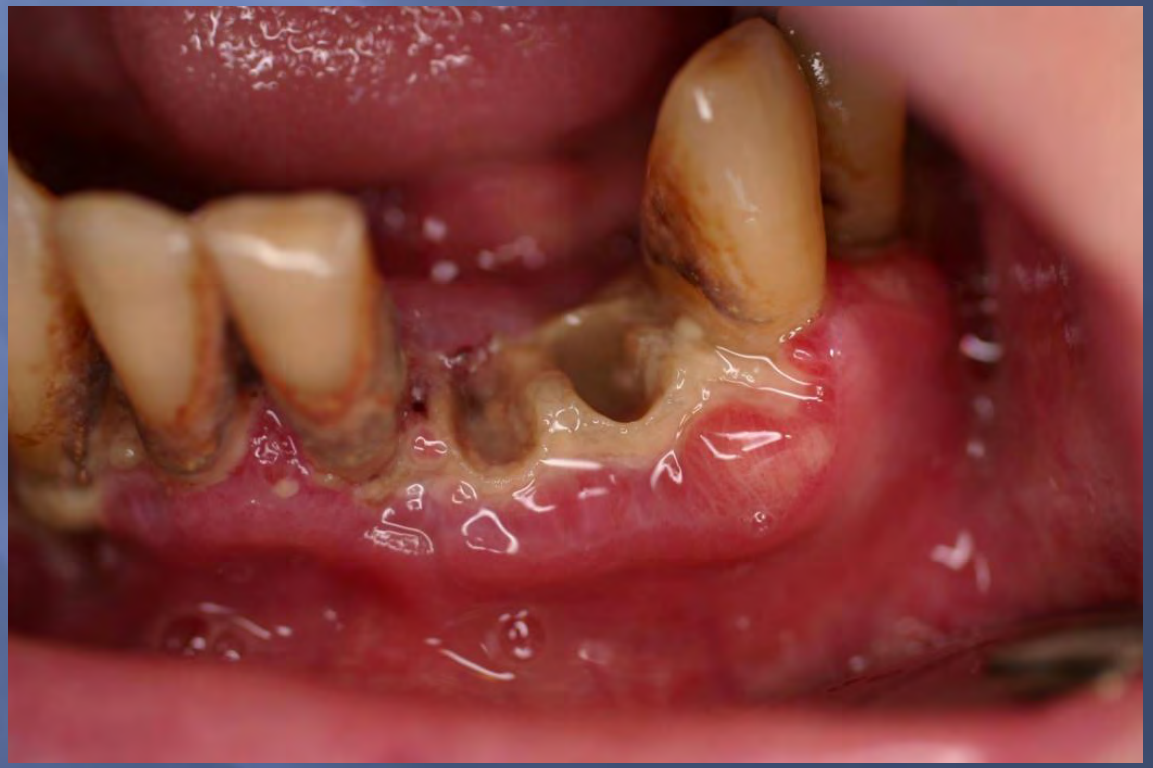
- an adjunctive host-modulating therapy in the treatment of periodontal diseases.
- biweekly IV-alendronate at a concentration of 0.05mg/kg could retard bone loss around affected teeth in comparison to controls (Brunsvold et al. 1992).
- a course of 3mg/kg of alendronate showed a significant reduction in bone loss (Reddy et al. 1995).
- in humans using clinical and radiographic outcome variables demonstrated a significant decrease in the proportion of teeth with alveolar bone loss at 9 months after use of alendronate (Reddy et al. 2003, Rocha et al. 2001).
- A 2 years clinical trial using 70 mg alendronate once-weekly in patients with moderate or severe periodontal disease (Jeffcoat 2006).
- a significant gain in alveolar bone height was demonstrated in the alendronate group in comparison to the placebo. No side effect

# Bisphosphonate and implants

- In order to avoid the systemic administration of BPs and the use of such high doses,
- topical application of BPs has been investigated in experimental models (Peter et al. 2005, Peter et al. 2006).
- BPs specifically bind to hydroxyapatite (HA), implants coated with HA or other calcium coating have been used in this investigations (Kajiwara et al. 2005, Peter et al. 2005).
- These BP-coated implants have demonstrated a high concentration of BPs in the first 20 μm of bone around the implant promoting osteogenesis at the bone tissue/implant interface by inhibiting osteoclastic activity (Yaffe et al. 1995, 1997, 1999)
- a positive correlation between increased bone density and higher implant mechanical properties (Peter et al. 2005).

# BUT

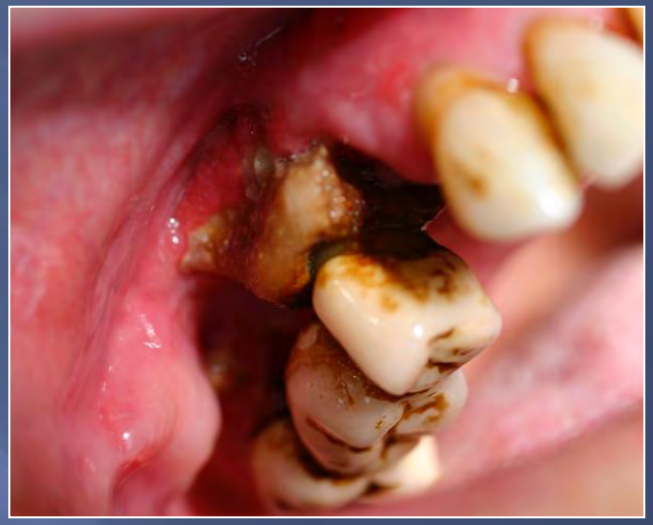
# BRONJ

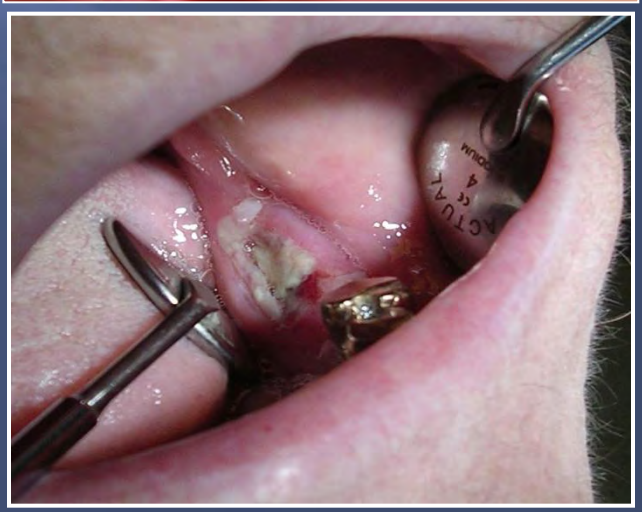


# BRONJ Definition

- Exposed bone
- Maxillofacial region
- > 8 weeks
- BP exposure
- No history of radiation therapy to craniofacial region

*Khosla S et al 2007*
*Khan et al 2008*
*Rizzoli 2008*
*AAOM 2009*





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# BRONJ – Presenting features

- Exposed bone
- Pain
- Infection +/-extraoral/intraoral fistula
- Traumatic ulceration $2^0$ to sharp exposed bone
- Halitosis
- Paraesthesia
- Fractured mandible

# Staging & management of BRONJ

*Adapted from AAOMFS position paper 2007; Migliorati 2005; Ruggiero 2006*

| Stage | Clinical presentation |
|---|---|
| ↑Risk | No exposed bone |
| 1 | Asymptomatic exposed bone |
| 2 | Exposed bone + pain +/- infection |
| 3 | Exposed bone + pain +infection +/- fracture +/- E/O fistula |

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# Classification of BRONJ

*Adapted from Madrid et al 2007*

| **Disabling ONJ** | **Non-disabling ONJ** |
|---|---|
| Moderate – Severe pain (VAS 3-10) | Absent or controlled pain (VAS ≤ 3) |
| Diffuse infection | Infection absent or controlled |
| Mastication impossible | Mastication satisfactory |
| Social life severely impaired | Acceptable social life |

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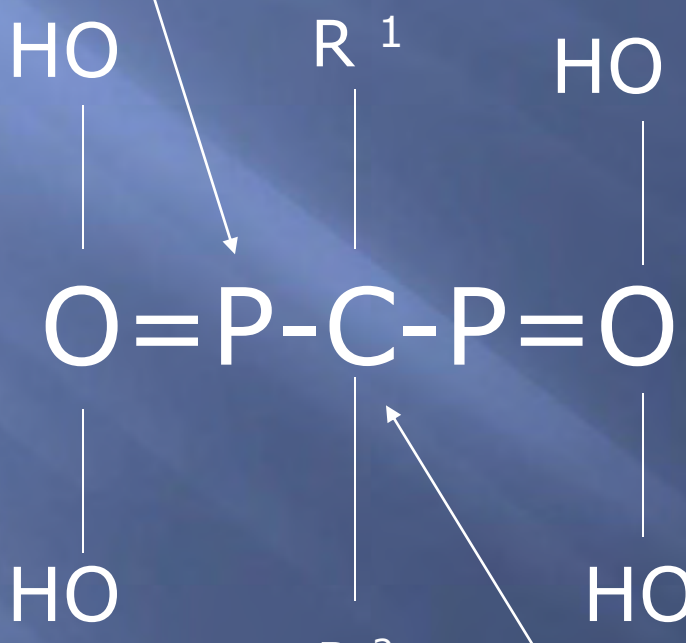
**PCP acts as bone hook**
**Essential for binding to HA**




**If R1 is an OH, group binding to HA is enhanced**

**R 2 chain determines potency**

**PCP group essential for biological activity**

*Ann Pharmacother 2005, 39:668-677*

# Pharmacology of BPs

Presence or absence of NH2 → Osteoclastic effect

**Non-NH2 BPs**

clodronate & etidronate

antagonise cell ATP →

- cell apoptosis
- ↓ bone resorption

**NH2 BPs**

PA, AA, RA, ZA

Inhibit mevalonate pathway →

- Osteoclast apoptosis
- Loss of adherence of osteoclasts to bone surface

Zoledronic acid inhibits human endothelial cell proliferation & modulates endothelial cell adhesion & migration

*Devogelaer 2000*
*Fleisch 2002*
*Woo 2006*
*Dass 2007*
*McLeod 2007*

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| Drug | Brand name | Nitrogen-containing | Route of admin | Potency | FDA approval | Cases of BRONJ |
|---|---|---|---|---|---|---|
| Etidronate | Didronel | N | Oral | 1 | 1977 | None |
| Clodronate | Bonefos | N | Oral | 10 | | 2 |
| Tiludronate | Skelid | N | Oral | 10 | 1997 | None |
| Pamidronate | Aredia | Y | IV | 100 | 1991 | 211 |
| Alendronate | Fosamax | Y | Oral | 100-1000 | 1995 | 63 |
| Alendronate plus vitamin D | Fosamax plus D | Y | Oral | 100-1000 | 2005 | |
| Risedronate | Actonel | Y | Oral | 1000-10000 | 1998 | 12 |
| Risedronate plus calcium carbonate | Actonel with calcium | Y | Oral | | 2005 | |
| Ibandronate | Boniva | Y 3rd gen | Oral/IV | 1000-10000 | 2003 | 2 |
| Zoledronate | Zometa<br>Aclasta | Y<br>Y | IV<br>IV | 10000+<br>10 000+ | 2001<br>2008 | 219<br>??? |

*Adapted from Zahrowski 2007; Hess 2008; Sarin 2008 Black 2008*

# Pharmacology – drug elimination

| Elimination phase | Where | Drug | Total elimination time |
|---|---|---|---|
| I (hours) | 50% through kidneys | Ibandronate | 37-157 hrs |
| II (weeks) | Drug leaves high bone turnover areas | Zoledronate | 146 hrs |
| III (years) | Sequestered drug leaving from slow bone turnover areas | Risedronate<br>**Pamidronate**<br>**Alendronate** | 224-480 hrs<br>**300 days**<br>**10 years** |

*Zahrowski 2007*

# Epidemiology

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# BRONJ Incidence – 2008 studies

| Reference | Patients | Oral/IV | Incidence | Study type |
|---|---|---|---|---|
| Boonyapakorn 2008 | 80 | IV | 28% : MM+ breast CA +other CA | Prospective |
| Hoff 2008 | 4019 | IV | 1.2% breast cancer<br>2.4% MM | Retrospective |
| La Verde 2008 | 186 | IV | 8.6% | Retrospective |
| Rizzoli 2008 | 443 | Oral | 54 cases<br>1 per 100,000 person-years exposure | Review of literature |
| Walter 2008 | 43 | IV | 18.6% Prostate CA cohort | Prospective<br>X-sect |
| Estilo 2008 | 310 | IV | 95 | Retrospective |
| King 2008 | 481 | Oral/IV | 94.2% cases IV 5.8% cases oral | Review of literature |

# BRONJ Incidence

Higher numbers reported by:

- Council on Scientific Affairs of the ADA
  - 170 cases $2^0$ to alendronate
- Medical claims databases

**No RCTs or well-designed clinical trials testing efficacy or safety of BPs in osteoporosis/Pagets report ONJ cases**

*Black 2007; Pazianas 2007; Gueiros 2008; Reid 2008; Edwards 2008*

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- Risk factors :
  - Drug-related
  - Local
  - Demographic

| Drug-related | Local | Systemic & demographic |
|---|---|---|
| **Dose/Potency**<br>ZA > PM<br>PM > oral BPs | Surgical procedures<br>- **exts** in up to 80% | **Age** 78% >60yrs<br>**Gender** F>M for oral |
| **Route of administration**<br>IV > oral | Anatomy<br>- **Mandible** > maxilla<br>- Areas of thin mucosa | Race<br>- Caucasians |
| **Exposure**<br>ZA from 1% - 21% at 3yrs<br>**Oral BPs** > 3 yrs | Concomitant **oral disease**<br>Trauma<br>Dentures | **Cancer diagnosis**<br>**Osteoporosis**<br>DM/RA |
| **Cumulative risk**<br>>1% at 1yr<br>11% at 4yrs | | Smoking/alcohol<br>**Corticosteroid use**<br>Immunosuppressant use |

*Migliorati 2005; Bamias et al 2005; Durie 2005; Mavrokokki et al 2006; Ruggiero 2006; Body et al 2006; Badros 2006; Zervas 2006; McLeod 2007; Jadu 2007; Diel 2007; Vieillard 2008; Cavanna 2007; Khosla 2007; Pazianas 2007; Boonyapakorn 2008; Coleman 2008; Wessel 2008; Hess 2008*

# Pathogenesis

| Theories | Pathogenic basis | Refs |
|---|---|---|
| **'Inside-out'** | BP-induced low bone turnover<br>↓ Osteoblast cell viability as BP conc ↑ ↓ Blood flow<br>Bone cell necrosis & apoptosis Infection<br>Exposed non-healing bone areas | *Ruggiero 2004; Bauss 2008; Yarom 2007; Naidu 2008* |
| **'Outside-in'** | Mucosal damage then infection & subsequent bone necrosis | *Hoff 2005; Landesberg 2008 Reid 2008* |
| **Angiogenesis inhibition** | Mediated through inhibition of VEGF<br>(↓ levels shown in vitro & in vivo)<br>& other angiogenic factors.<br>BPs cause ↓IL-17 a proangiogenic cytokine<br>↓endothelial cell proliferation, adhesion & migration in rats<br>Obliteration of vessels in <30% | *Wood 2002; Croucher 2003; Vincenti 2005; Oteri 2008; Hansen 2007* |
| **Direct mucosal effect** | High local BP concentration<br>Toxic to oral epithelium at pharmacological concentrations | *Reid 2007; Diel 2007; Marx 2008* |
| **Multifactorial** | Immunosuppressed/medications/smoking/age/wound healing | *Rizzoli 2008* |
| **Infection Interleukins** | Microbial biofilms - actinomyces<br>Improvement with antibiotics<br>?Role of effect of bacteria on IL6 production in osteoblasts<br>Direct effect of BPs on cells of immune system | Khosla 2007; Reid 2008; *Sedghizadeh 2008* |

Microtrauma →teeth,
forces of mastication & daily function or local infection/ext →
Microfractures in acellular, avascular bone.
Suppression of bone remodelling →poor repair

Bone turnover 10-100x > in jaws than long bones

High vascularity with high bone turnover → ↑ concentration of BPs

# Why Jaw Bones? Suggested Hypotheses

?Role of bacteria

Mucosal damage can be caused by oral BPs

?Keratinocyte cell cycle inhibition & effect on wound healing

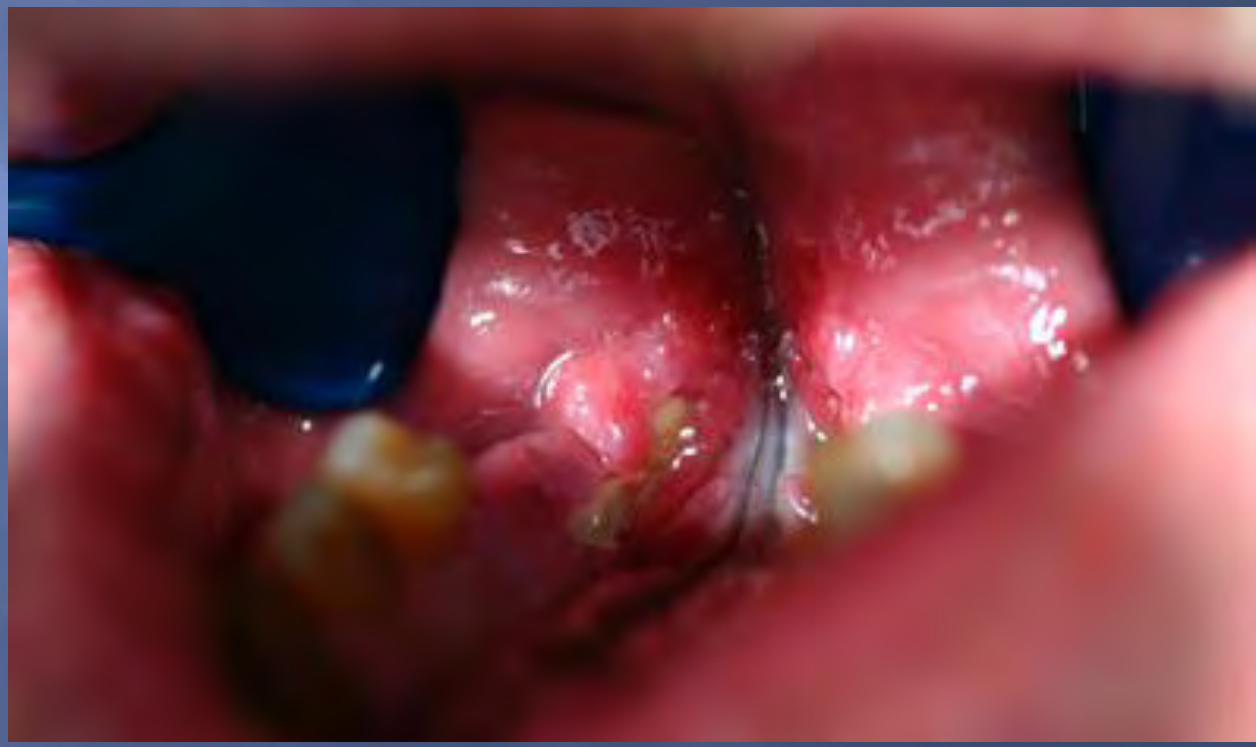
BPs in bone at dose high enough to be directly toxic to oral epithelium – inhibit keratinocyte cell cycle hindering repair mechanisms

Thin mucosa traumatised & contact with causative bacteria actinomyces, eikenella for caries & perio disease

?BP concentration in gingival crevicular fluid similar to bone

*Migliorati 2006; Sarin 2008; Allen 2008; Bauss 2008; Landesberg 2008; Reid 2008*

# Oral BPs



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Dept Ammbulatory Care and Community Medicine
Lausanne University

# Oral Bisphosphonates

- Osteoporosis in 12 million > 50 yrs & osteopenia in 40 million >50 yrs by 2010 in US
- ↓ risk of vertebral fractures by 40-50% & non-vertebral fractures by 20-40%
- >190 million prescriptions for oral BPs worldwide
- Relative prevalence ONJ low
- Oral BPs responsible for < 5% of all cases ONJ
- Majority → alendronate
- Mean time to ONJ 4.1yrs
- Oral & IV formulations of ibandronate for osteoporosis

*Zahrowski 2007;Yarom et al 2007; Macleod 2007; Migliorati 2008; Edwards 2008*

# Investigations

*Adapted from ASBMR*

| Image modality | Advantages | Disadvantages |
|---|---|---|
| **OPT** | Inexpensive<br>Widely available<br>Osteolysis & osteosclerosis<br>Use as 1st line | Less useful if osteolytic<br>Difficult to demarcate margins between necrotic & healthy bone<br>Early lesions often missed |
| **CT** | 3D image<br>Differential diagnosis & extent<br>Cortical involvment | No additional info in asymptomatic patient with ON |
| **Cone beam CT** | Lower radiation dose<br>Higher spatial resolution than CT<br>Better image quality<br>Cortical integrity, marrow & cancellous BMD | Limited in discrimination of soft tissues<br>Low contrast resolution<br>Not yet widely available |
| **MRI** | With contrast gadolinium region of ischaemia recognised<br>Soft tissue extension | Data limited<br>May be associated with ++ false positives |

*Adapted from ASBMR*

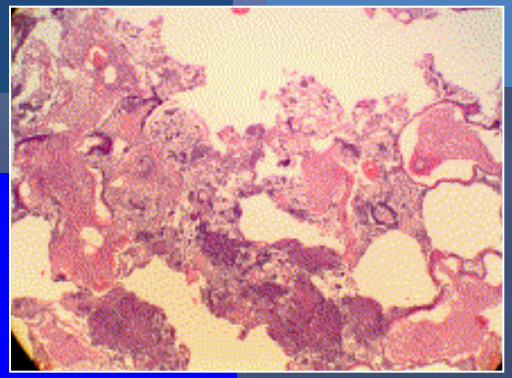
| Image modality | Advantages | Disadvantages |
|---|---|---|
| **Tc-99 radioisotope scintigraphy** | Screening<br>Subclinical lesions | Assumes change in vascularity within necrotic region<br>High radiation exposure<br>Lengthy procedure |
| **PET** | Functional test<br>↑uptake in areas of ONJ | Poor resolution<br>High radiation dose |
| **Optical coherence tomography** | No ionizing radiation<br>Image small pre-lesions in alveolar bone | Depth of penetration image artifacts |
| **Sequential images** | Provide temporal history of developing change | |

# BRONJ – Further Investigations

**Biopsy** → to rule out metastatic disease in high risk patients

**Histopathology**
- Chronic inflammatory infiltrate
- Empty & osteocyte-occupied lacunae
- Necrotic bone usually surrounded by colonies of microbes

**Microbial culture**
- Actinomyces, lactobacillus, candida
- Identification of pathogens → $2^0$ infections



**Suggested:**

**C-terminal telopeptide**

Bone turnover marker (Marx 2007)

*Carter 2005; Dannemann 2006; Kim 2007; Yarom et al 2007; Chiandussi et al 2007; Bedogni 2007; Oda and Bagan 2008; Lobato 2008*

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# CTX – Present thinking

- No scientific data to support use of CTX to predict development of BRONJ
- Validation in clinical trials needed

- Expect low CTX if taking BPs as ↓ bone resorption
- ↓ CTX to <150pg/ml a surrogate index of drug efficacy
- To stop BP based on CTX risks losing BP effect & ↑ risk of fractures

**CTX not a gold standard for BRONJ**

*Khosla ASBMR 2008; Edwards 2008*
*Baim and Miller 2009*

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# Management

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# Consensus Guidelines

AAOMFS 2007;Canadian 2008; AAOM 2009

General Consensus

- INFORM PATIENTS OF RISK
- Consult physician
- Good OH
- Smoking cessation
- ↓Alcohol
- Pre-Tx dental assessment
- Extract unsalvageable teeth
- Complete all invasive dental procedures
- Aim to achieve optimal periodontal health

# BRONJ – Prevention

## Oral

- Routine dental care
- Regular radiographs
- Educate patient
- Informed consent for surgical procedures

*Dannemann 2006*

*Ruggiero 2008*

## IV for CA & OP

- Educate patient
- Evaluate dental/perio status
- Full mouth intraoral & panoramic radiographs
- Plaque control
- Restore carious teeth
- RCT for non-vital teeth
- Extract poor prognostic teeth prior to start of Tx
- Avoid surgery after start of Tx
- Routine dental care regularly

# Preventive measures are effective

- ↓ incidence BRONJ with implementation of dental preventive measures
- ↓ infection rates of any non-infected, already necrotic, exposed bone
- Retrospective & prospective studies
  - MM cases taking ZA
  - Cancer patients with bone metastases

*AAOMFS 2007; Walter 2008*
*Dimopoulos 2008; Ripamonti 2008; La Verde 2008*

# Management guidelines

Since AAOM position paper 2005

- Consensus papers have been published & preservation of QoL through control of pain and infection defined

- American Society Bone Mineral Research 2007
- American Association OMFS 2007
- Canadian Consensus practice Guidelines for BRONJ 2008
- American Association of Oral Medicine 2009

# BRONJ Management

**Goal - to preserve QoL**

- Control pain
- Manage infections
- Maintain function (speech & mastication)
- Prevent new areas of necrosis
- Social life (halitosis)
- Patient education
- Patient reassurance
- Support of continued oncological Tx

*ASBMR 2007;AAOMFS 2007*

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# Management of Bisphosphonate Related Osteonecrosis of the Jaw in Lausanne

# Prevention

| Patients referred before IV BP treatment | Multiple Myeloma M/F | Prostate Cancer M | Breast Cancer F | Severe Osteopenia F | Total M/F |
|---|---|---|---|---|---|
| 2005 | 11/10 | 5 | 4 | - | 16/14 |
| 2006 | 10/4 | 5 | 6 | - | 15/10 |
| 2007 | 9/3 | 7 | 11 | - | 16/14 |
| 2008 | 8/3 | 11 | 13 | 8 | 19/26 |
| total | 58 | 28 | 34 | 8 | 66/62 |
| Total screened patients | 128 patients 66/62 | | | | |

# Prevention

| Patients referred before IV BP treatment | Multiple Myeloma | Prostate Cancer | Breast Cancer | Severe Osteopenia | Total |
|---|---|---|---|---|---|
| Total extraction patients | 4 | 3 | 4 | 2 | 13 |
| Partial extraction patients | 32 | 21 | 12 | 3 | 68 |
| Conservative treatment | 21 | 19 | 11 | 2 | 53 |
| Hospital | 37 | 32 | 18 | 7 | 94 |
| Private Dentist | 20 | 11 | 9 | 0 | 40 |

# Prevention

| Patients referred before IV BP treatment | Multiple Myeloma | Prostate Cancer | Breast Cancer | Severe Osteopenia | Total |
|---|---|---|---|---|---|
| total | 58 | 28 | 34 | 8 | 66/62 |
| **BRONJ occurrence** | 1 | | 1 | | 2/128 **1.56%** |

Mean Follow-up 18.4 months

# TREATMENT BASED ON STAGING

*(adapted from AAOMFS 2009)*

| | |
|---|---|
| **At risk**<br>(No bone exposed) | No treatment<br>Patient education |
| **Stage I**<br>Asymptomatic bone exposure | Remove sharp bone & loose segments of bone<br>Antimicrobial M/W – chlorhexidine 0.12%<br>Regular follow-up<br>Patient education |
| **Stage II**<br>Bone exposed + infection | Broad-spectrum antibiotics<br>- Penicillin<br>-Doxycyclin<br>- Metronidazole<br>- Cephalosporin<br>Superficial debridements<br>Antibiotic M/W |
| **Stage III**<br>Exposed bone + pain, infection, fracture/fistula | Antibiotics<br>Surgical debridement/resection<br>Antibiotic M/W<br>Extract symptomatic teeth in area of ON |

# Management

- Conservative management of non-disabling BRONJ

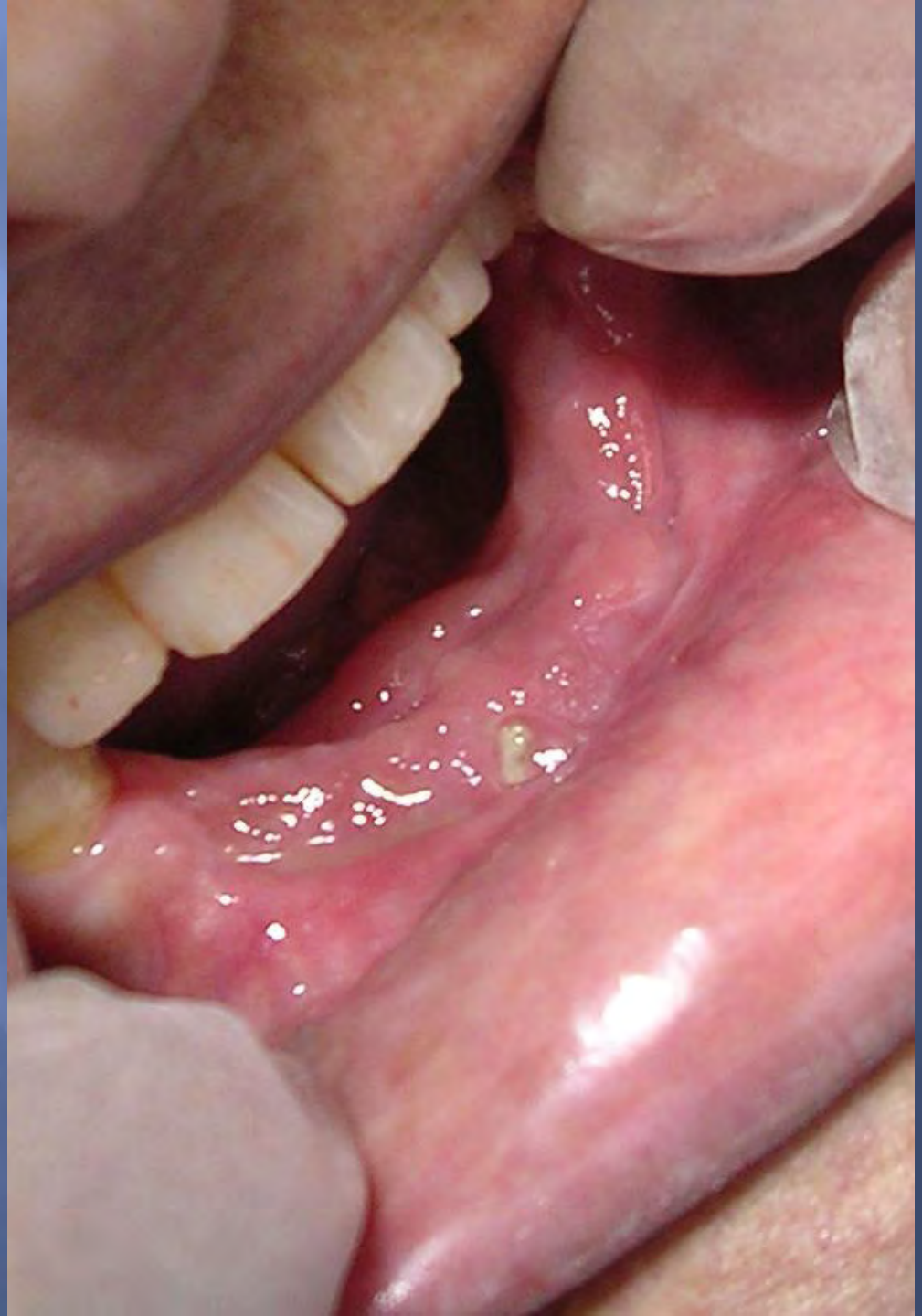
- Daily instillation of chlorhexidine 0.12% without alcool on bone exposition by patient or health professionnal
- Long course anbiotic therapy
  - Amoxicillin 2 to 3 g/d

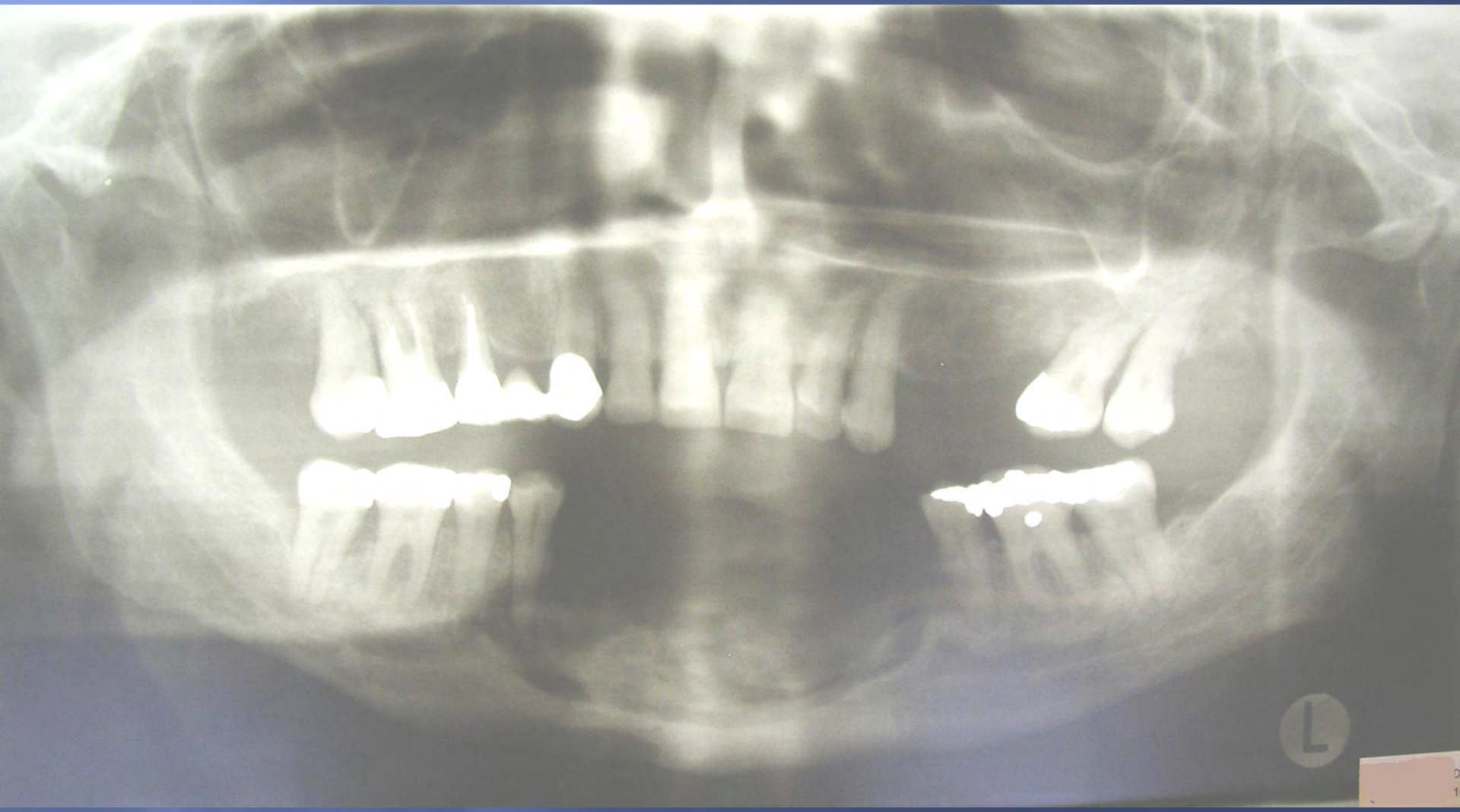
  Or:
  - Levofloxacin (Tavanic): 500mg /d
  - Doxycyclin (Vibramycine): 200mg /d
  - azithromycin (Zythromax): 250mg/d
- Professional dental hygiene every 3 months

# Case report 1

- Female 58 y
- 7 y breast cancer evolution
- Multiple bone metastasis
- Pamidronate: 11 m
- Zoledronate: 10 m
- Dental treatment including extractions after 14 m
- BRONJ discovery after 21 m
- Non disabling
- Conservative management

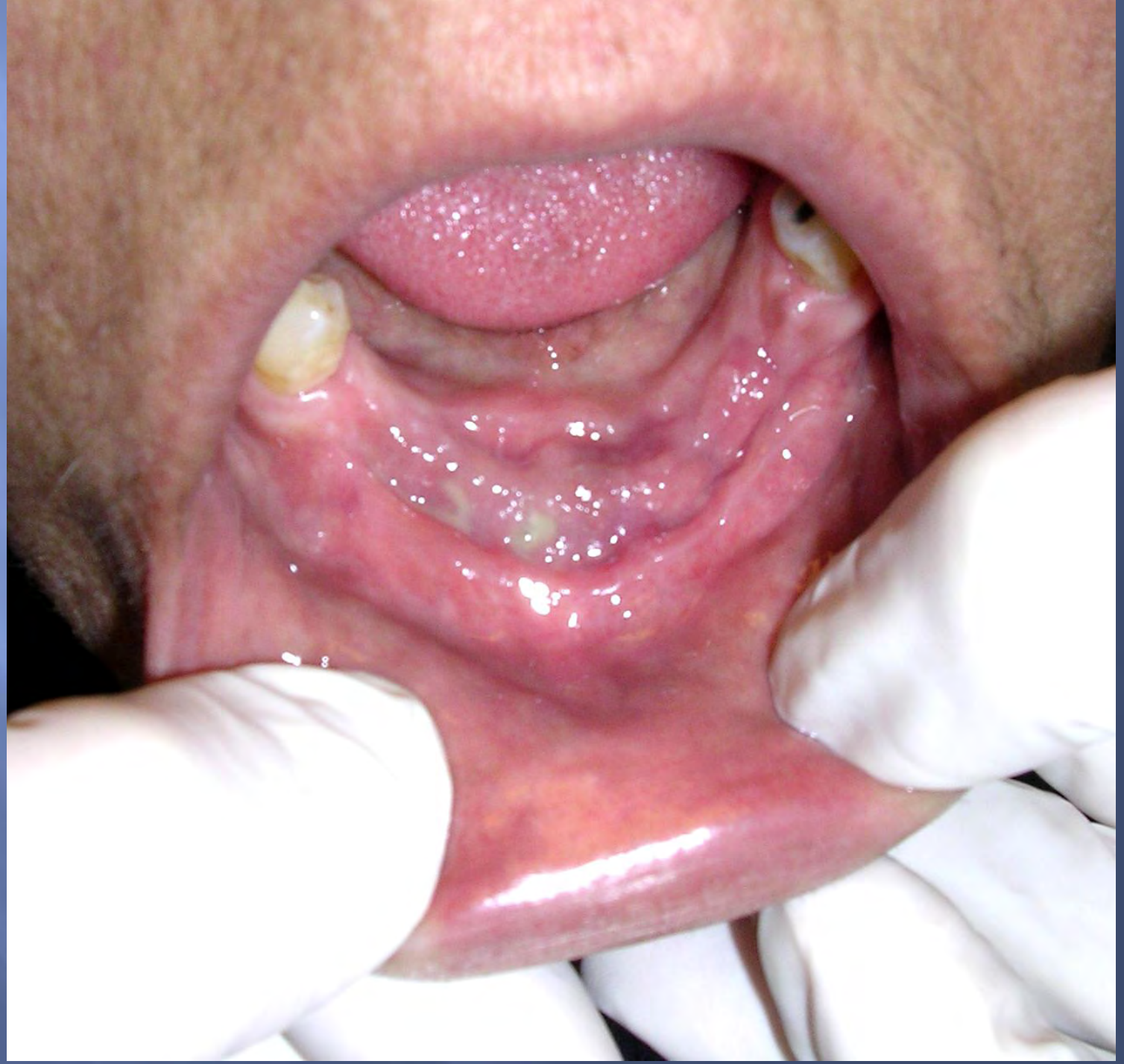
M : 0

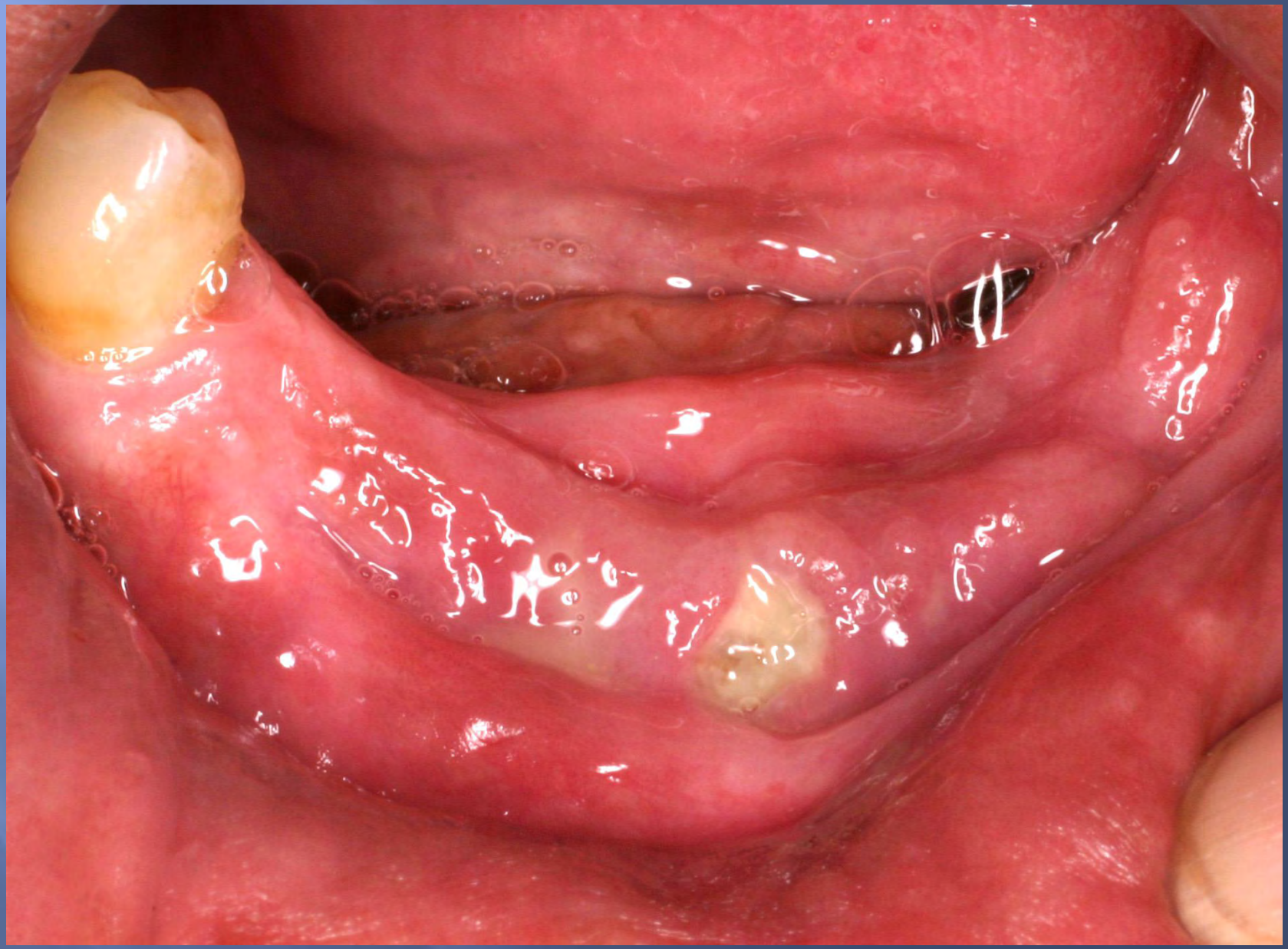




M:0

M: 8





**M: 20**

# Case report 1

- Died of her cancer 28 months after discovery of BRONJ
- Still classified non disabling BRONJ 2 months before death

# Management

- Non-Conservative management of disabling BRONJ

- Long course anbiotic therapy
  - Amoxicillin 3 g/d

  Or:

  - Doxycyclin (Vibramycine): 200mg /d
  - Levofloxacin (Tavanic): 500mg /d
  - azithromycin (Zythromax): 250mg/d
- Professional dental hygiene every 3 months
- Surgery limited to elimination of necrotic bone and infection control
- Exposition coverage by local flaps

# Case report 2

- 64 yr old female 72 kg
- PMH – nil of note
- Developed headache & chest pain Feb 07
- Afebrile
- ESR: 100 mm/h CRP:12 mm/l
- March 2007 - superficial temporal artery biopsy
- - suggestive of diffuse *Giant Cell Arteritis*

- 60 mg Prednisone & Azathioprine 150mg
- May 2007: ESR 35 CRP 10
- Prednisone ↓ 20mg/day

**September 2007**

- Fall in her garden
- Asymptomatic fracture of L1 vertebra
- GMP → osteopenia $2^0$ to Prednisone
- Oral Ibandronate 150 mg/month for 6mths

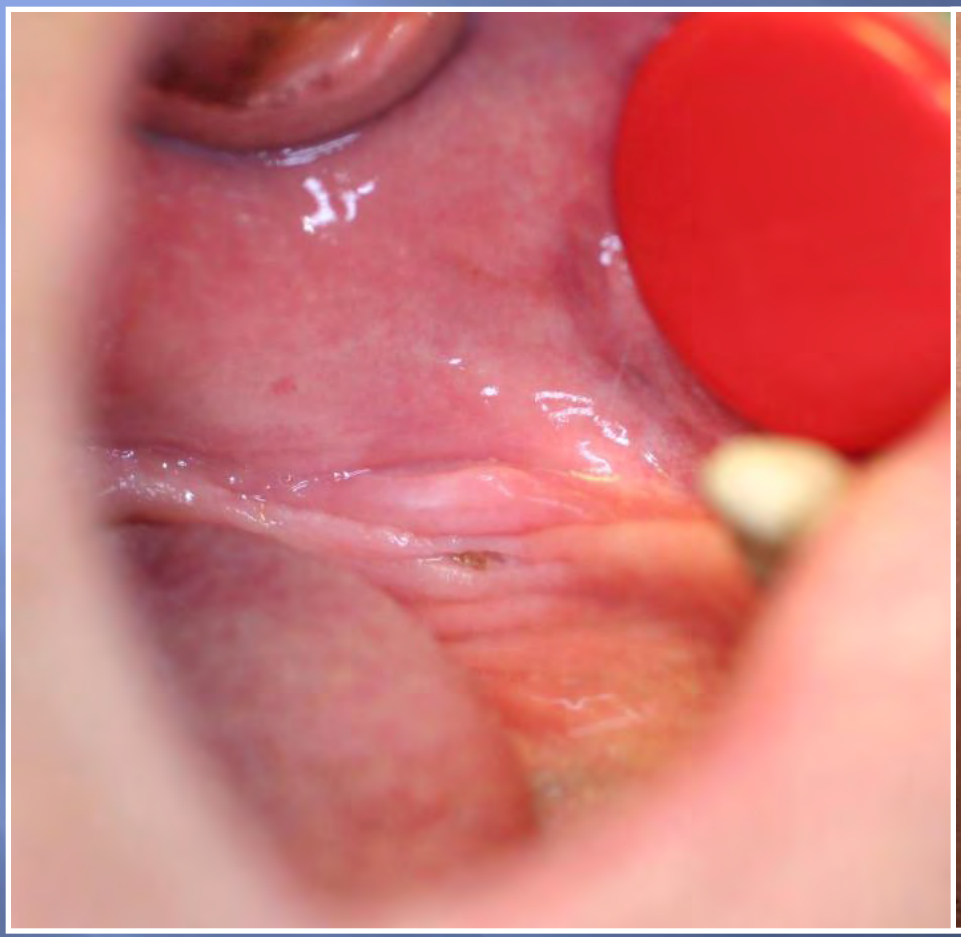
# October – December 2007

Oct/Nov 07 – 2 doses Ibandronate 150mg

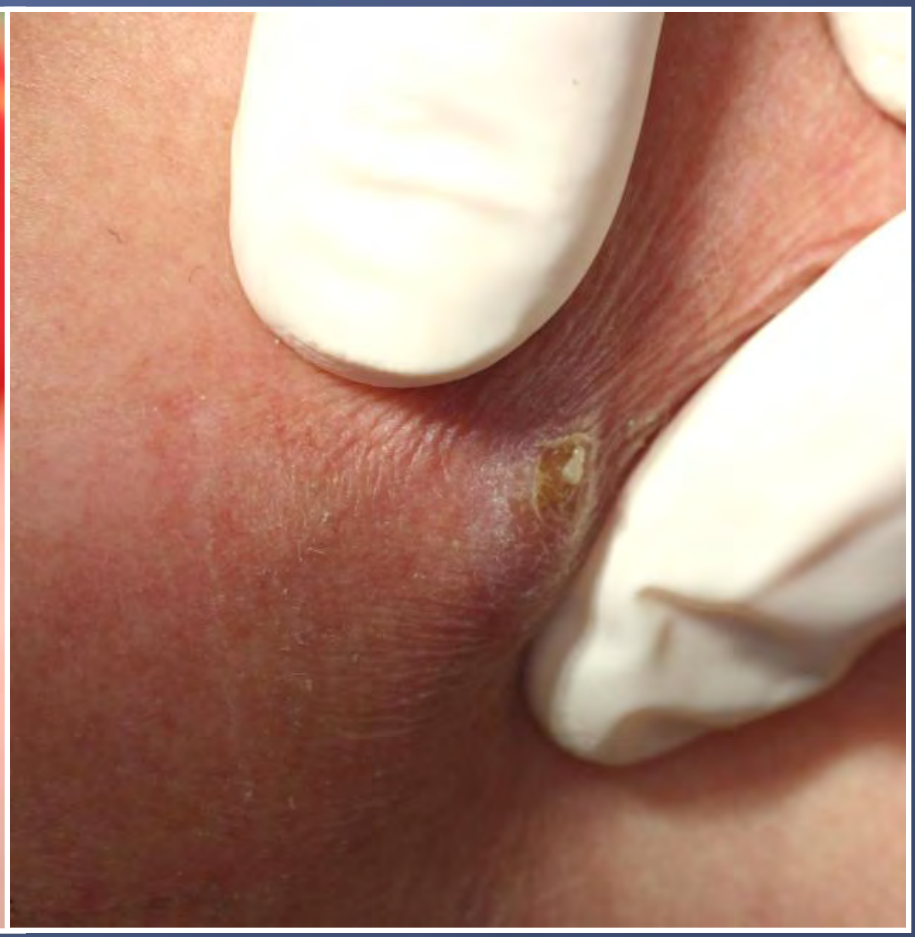
- 14.12.07: pain left lower jaw
- GDP - mouth ulcer & abcess LL6 ridge
- LL6 extracted 6 yrs previously
- Wearing -/P for the last 15 yrs
- 24th Dec 07 – skin fistula L suprahyoid
- Her GMP
  - Stopped Ibandronate after 2 doses
  - Systemic antibiotics Dec 07 – Feb 08
- Symptoms improve

- No resolution
- Patient referred to Oral Medicine
- ? osteonecrosis of the jaw
- 19/03/08 - 1st examination Oral Med
- Levofloxacin 500 mg/day
- Oral Metronidazole 1.5 g/ day

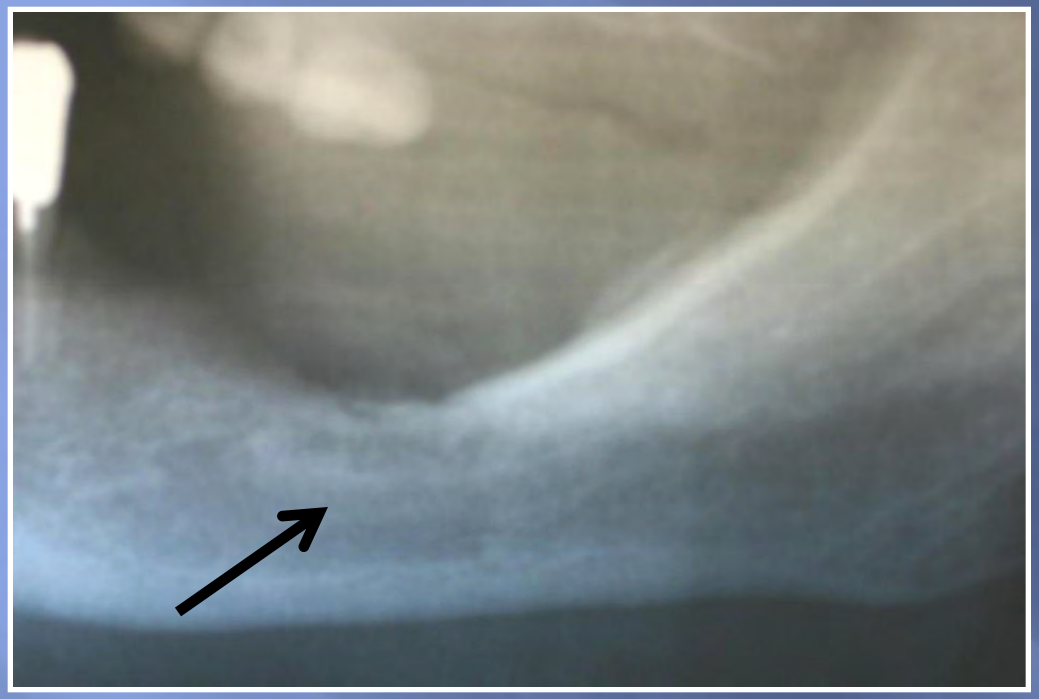
# Clinical Examination



Bone exposure LL6 ridge

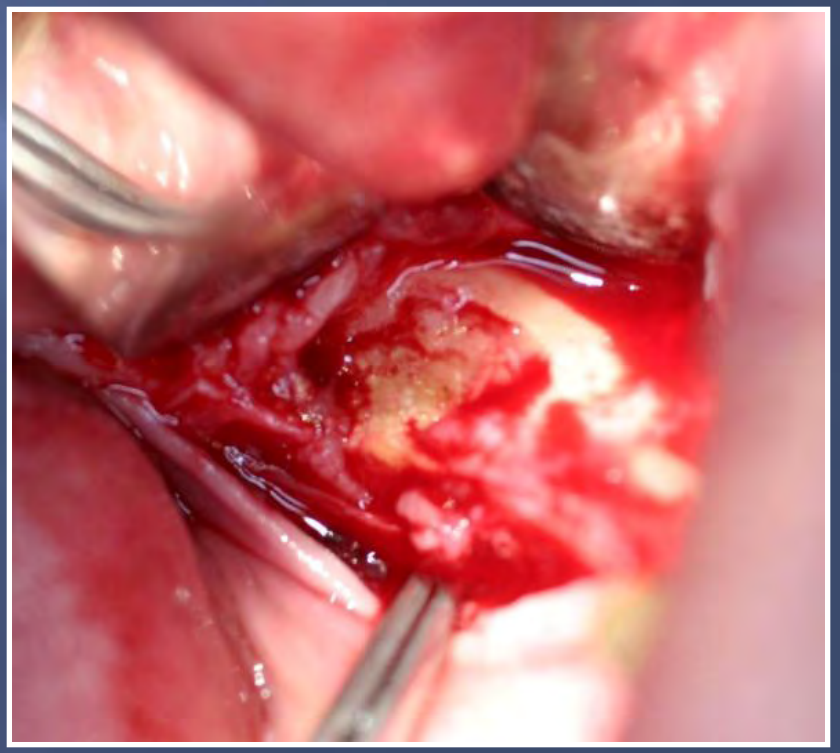


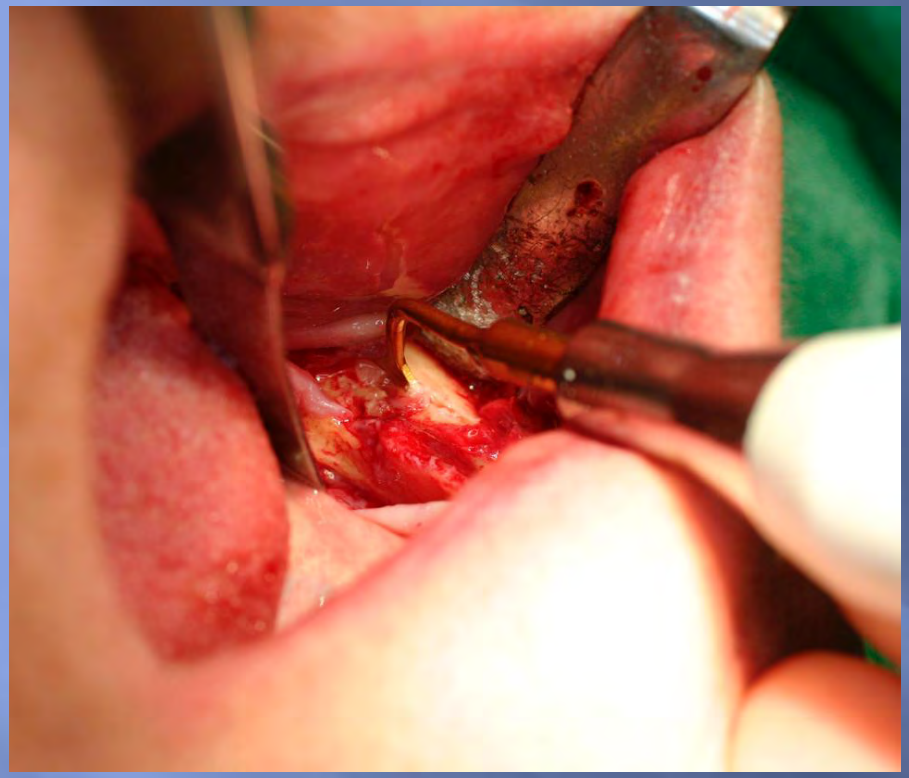
Pus from cutaneous fistula



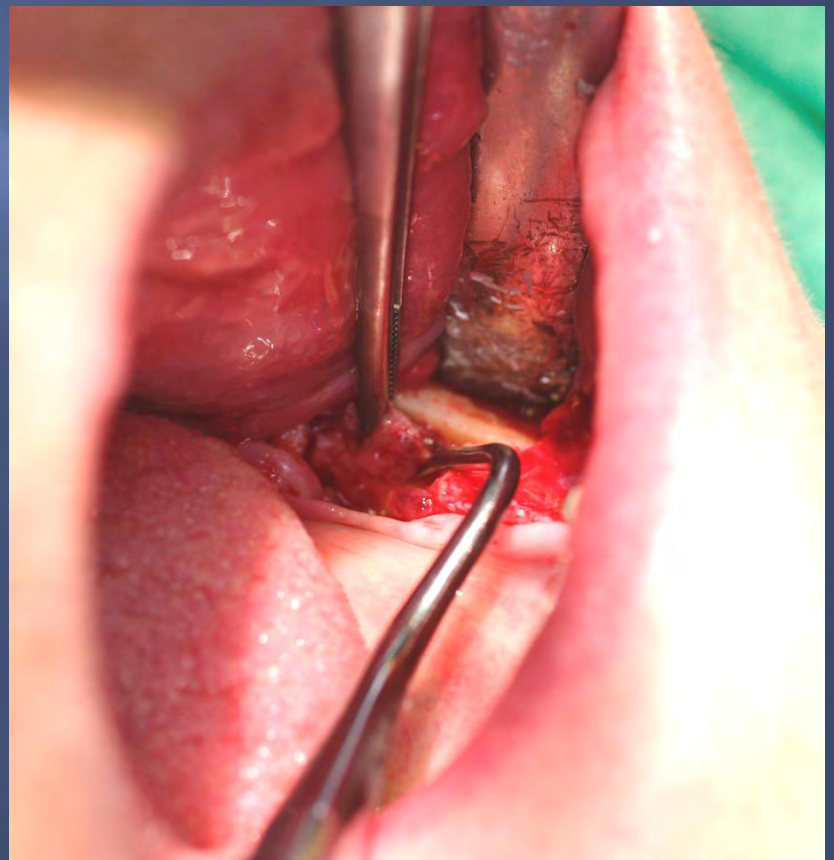
Panoral radiograph depicts proximity to ID canal

27.03.2008
Curettage of bony sequester

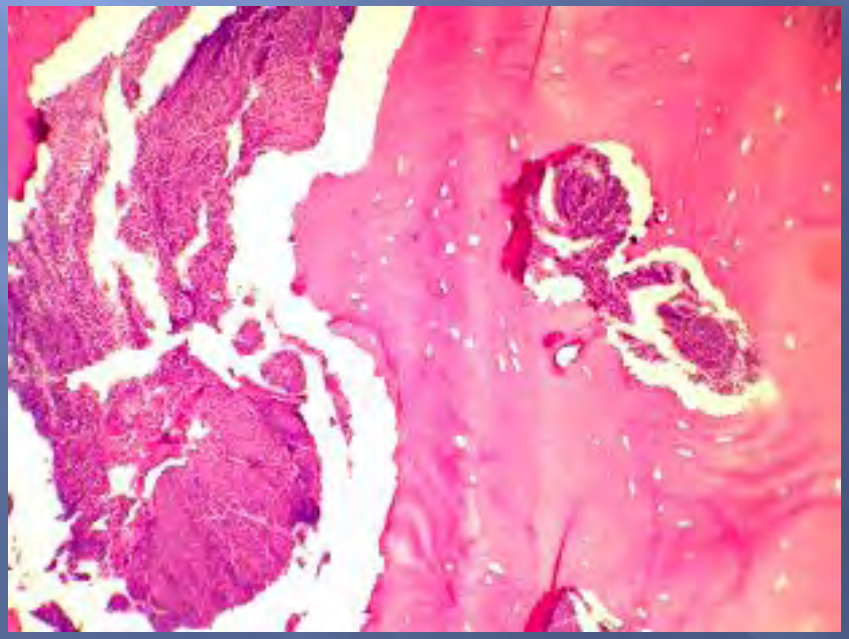


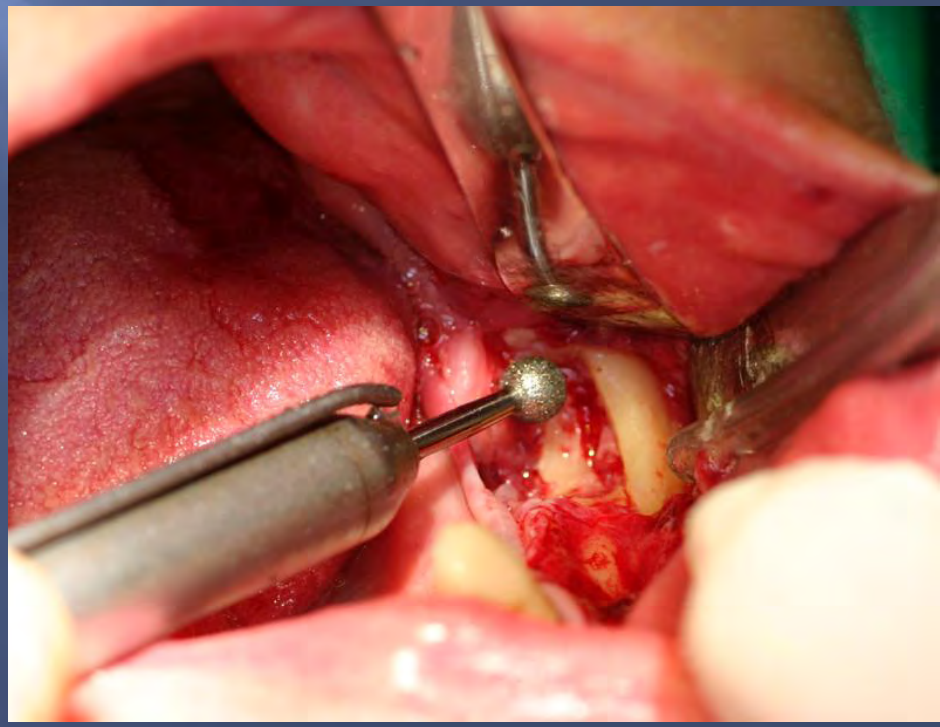


# 27.03.2008 Curettage of bony sequester



# 27.03.2008 Curettage of bony sequester



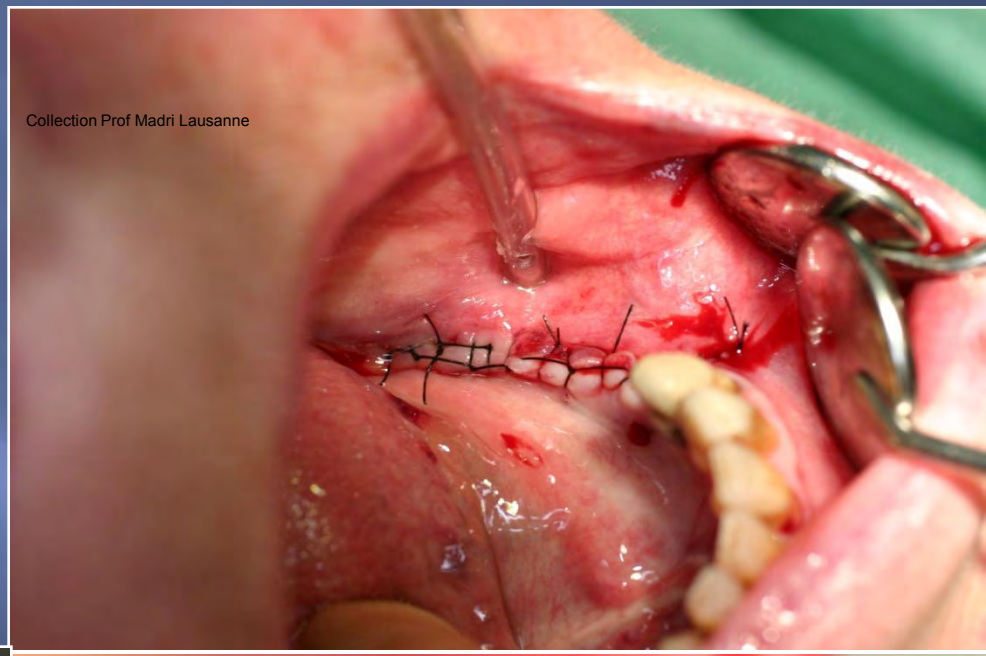


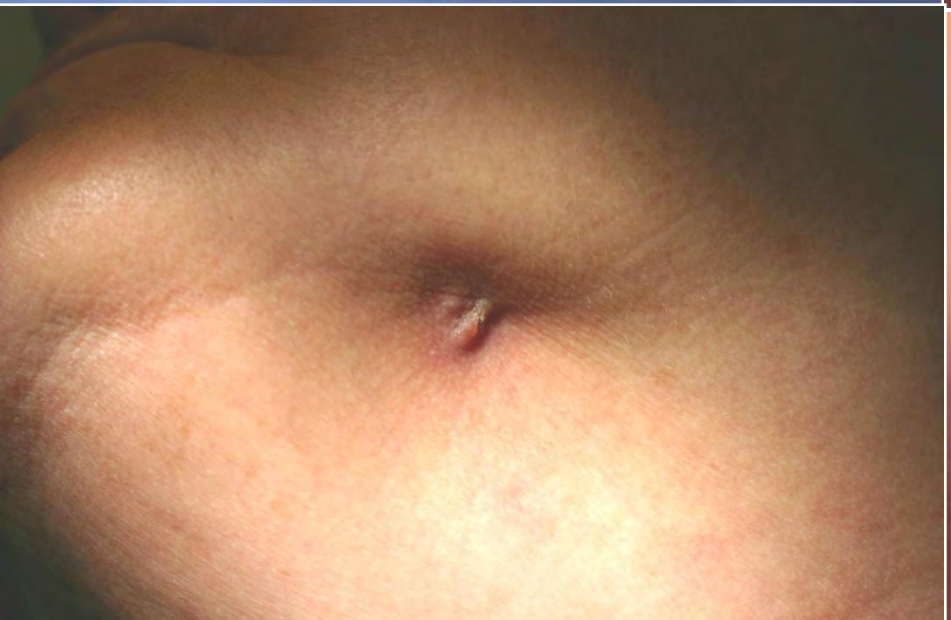
# Postoperative

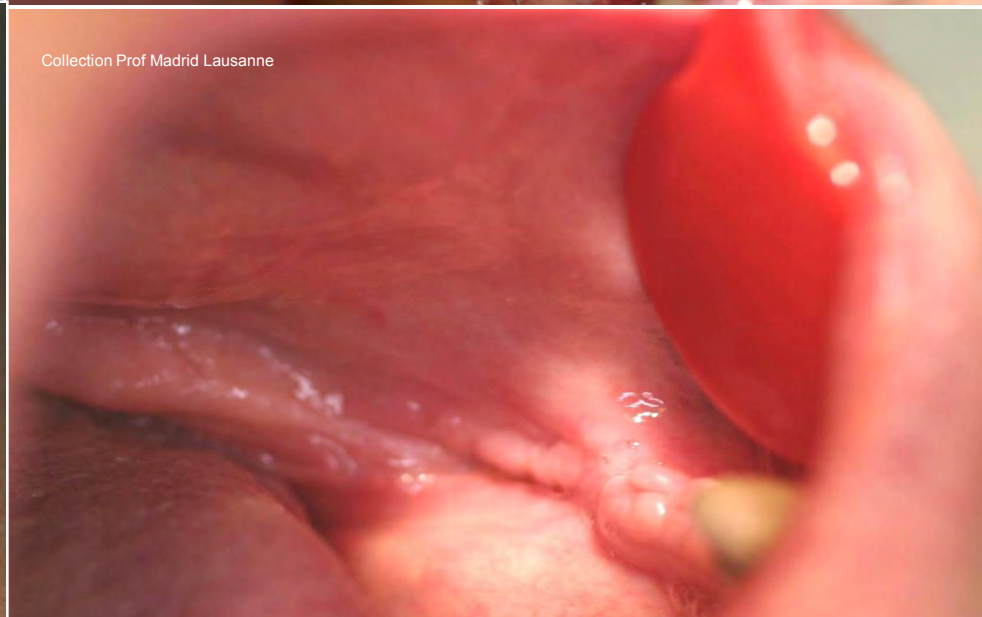
First intention healing →

30 days after surgery

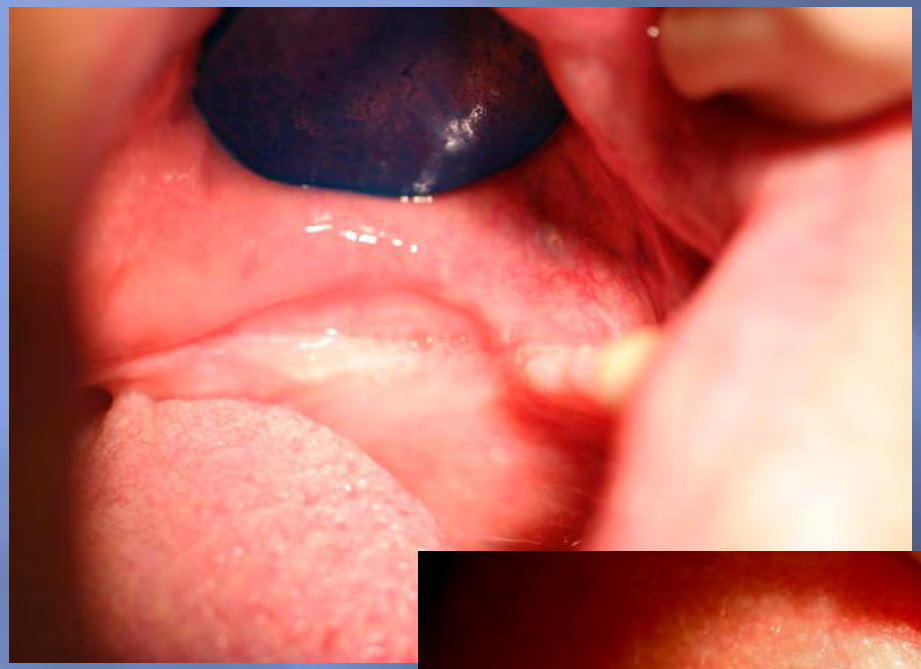
- Amoxicillin 3g/day
- Metronidazole 1.5g/day
- No denture wearing

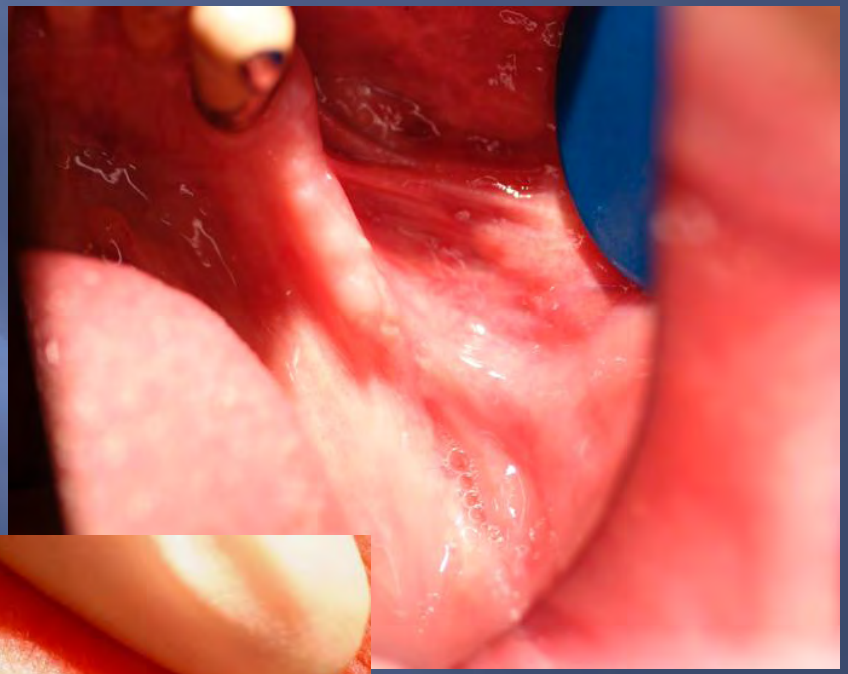


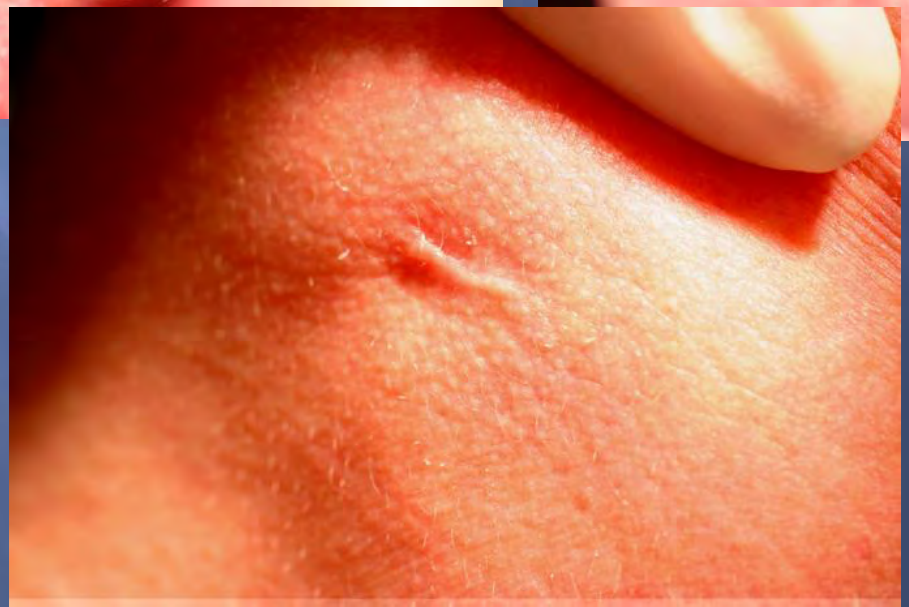





# Follow-up May 2009
# AB stopped in november 2008







# Management

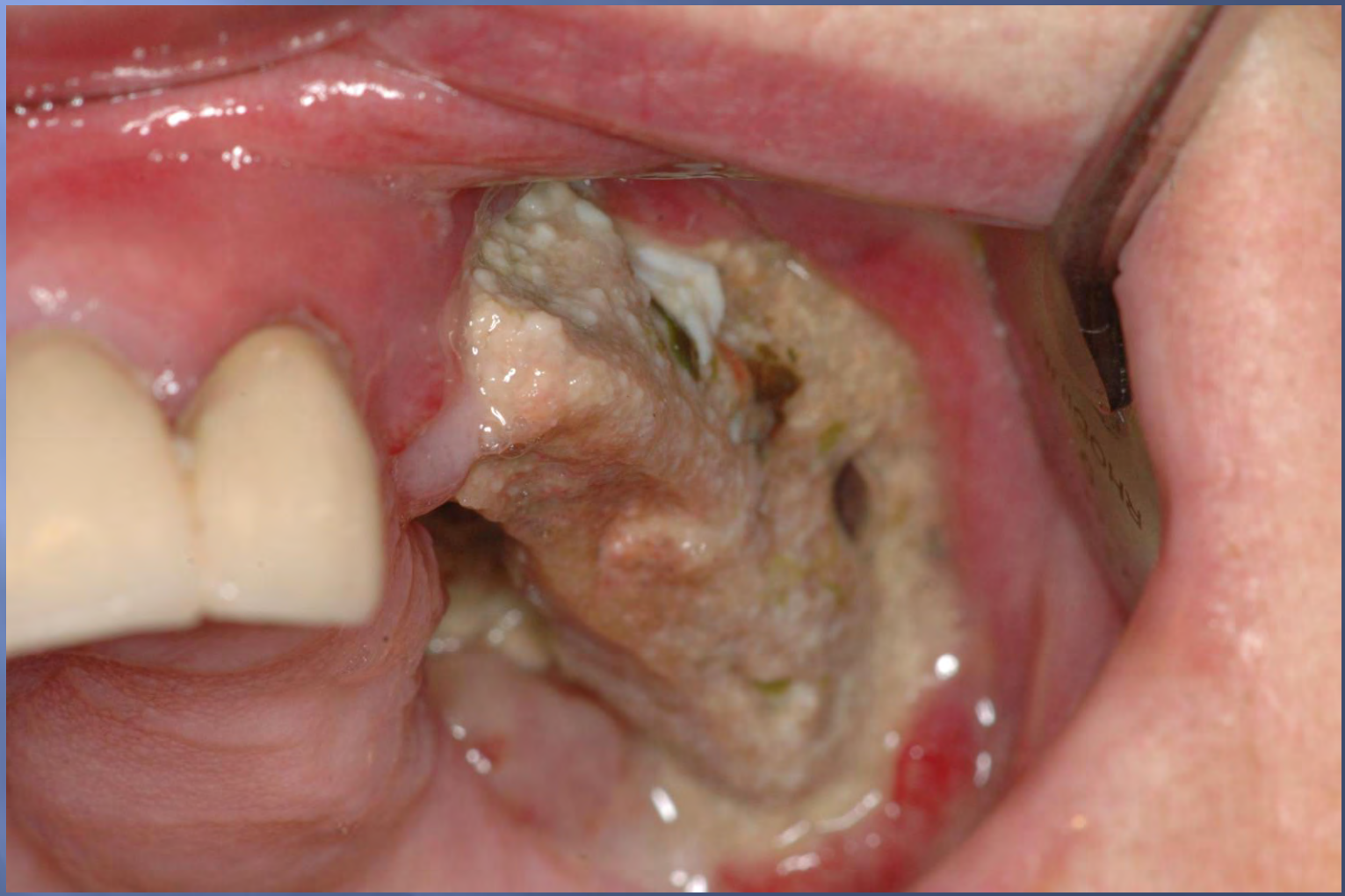
- Non-Conservative management of disabling BRONJ

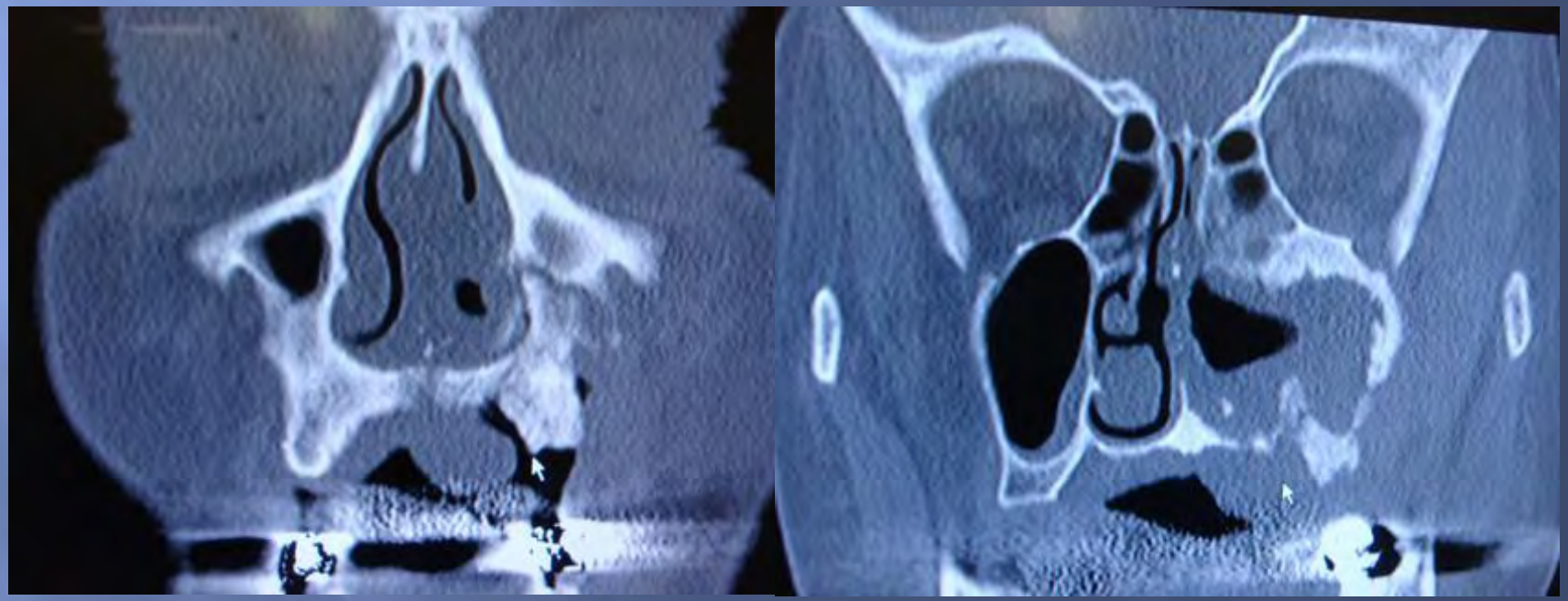
- Long course anbiotic therapy
  - Amoxicillin 3 g/d

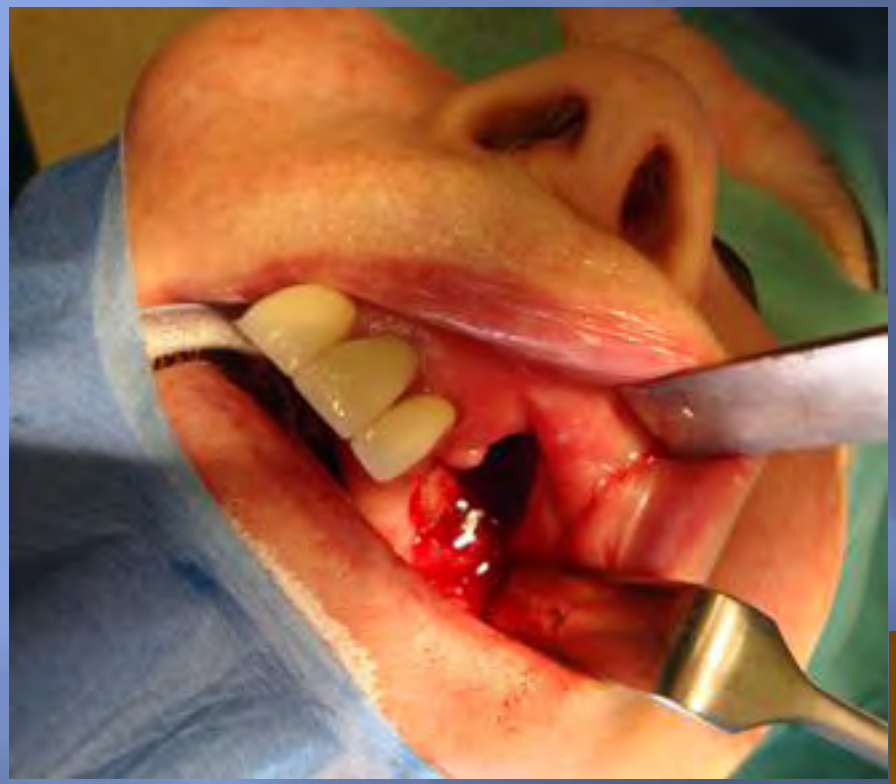
  Or:
  - Doxycyclin (Vibramycine): 200mg /d
  - Levofloxacin (Tavanic): 500mg /d
  - azithromycin (Zythromax): 250mg/d
- Professional dental hygiene every 3 months
- Large surgery to eliminate large portions of necrotic bone and control regional infection
- Exposition coverage by local flaps

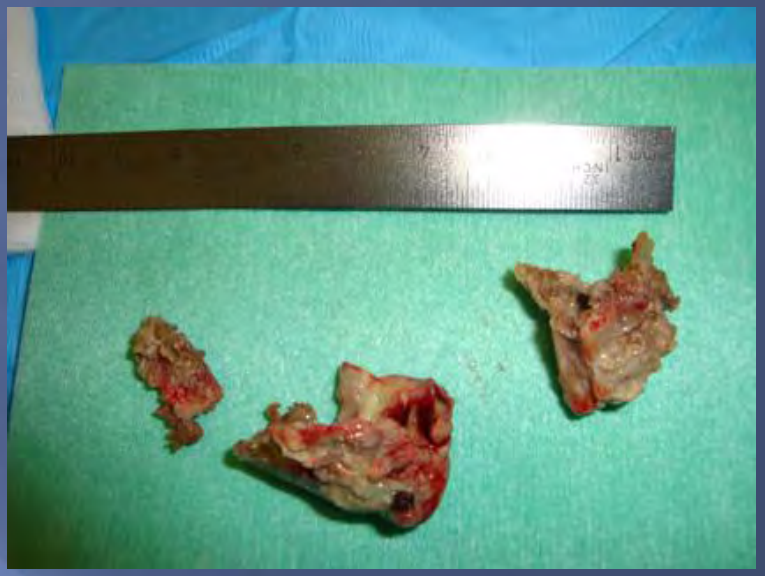
# Case report 3

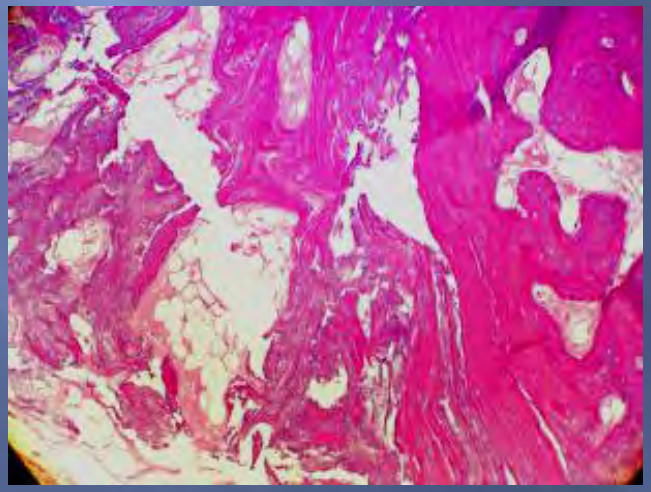
- Female 47 y
- Portugal
- Referred by ENT for « assessment »
- Breast cancer diagnosed in 2000
- Bone metastasis May 2004
- Started zoledronate without dental screening in June 2004- Stopped in September 2006
- Tooth extractions by her dentist in february 2007 in the left maxilla
- New tooth extractions in april 2007
- Referred by dentist to ENT for sinusitis june 2007
- June 2007- September 2007 several surgical treatments of sinusitis
- September 2007 decides to come to Lausanne

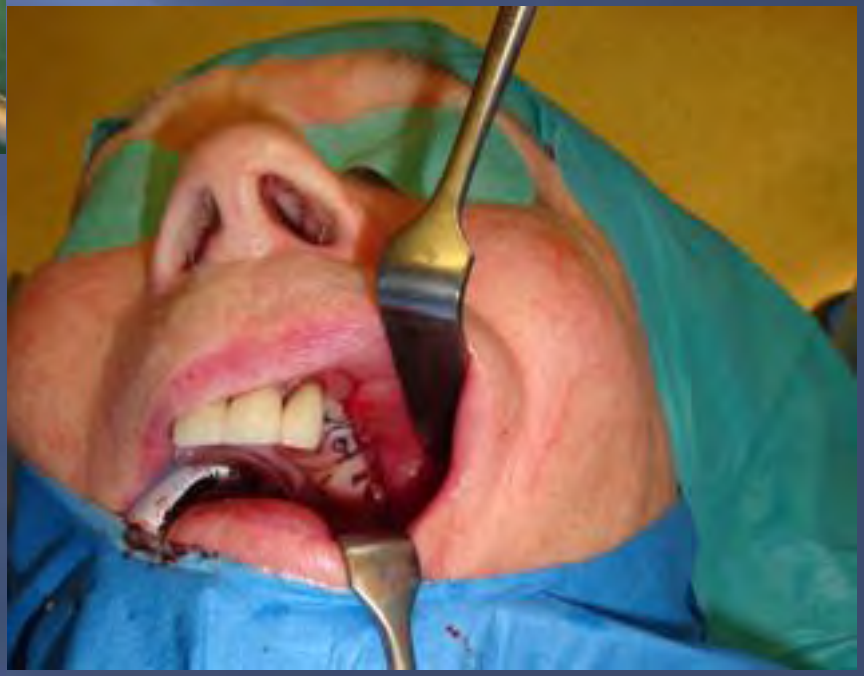








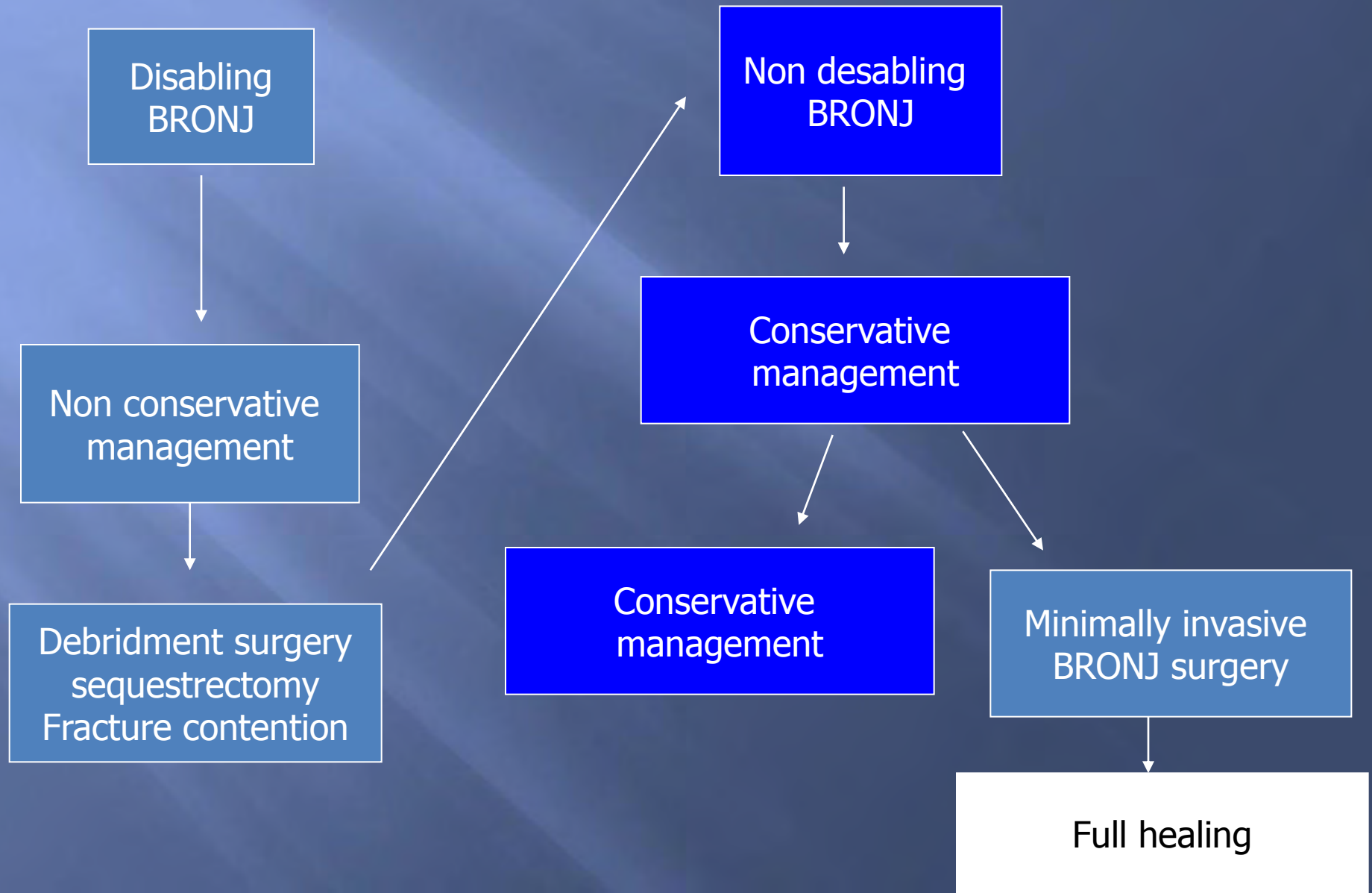




# Case report 3

- December 2007
- Surgical elimination of all necrotic bone and sinusal revision by Caldwell-Luc approach
- Vestibular flap to close oro-antral fistula
- Controlled every two months until december 2008.
  - No re-opening
  - No recurrence of osteomyelitis
  - On ciprofloxacin since september 2007 developped peripheral paresthesia in June 2008

# Lausanne flow-chart



# Management update – surgery

- 70-82% success rate with surgery & low level laser therapy (Nd;YAG laser)

*Vescovi 2008*

- Significant improvement between preop & postop staging with minimal resection of necrotic bone + local soft tissue closure

*Wutzl 2008*

- Case reports of radical surgery application

*Yarom 2007; Abu-Id 2007; Nocini 2008; Engroff 2008*

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# Hyperbaric oxygen

**Insufficient evidence to recommend**

*Marx 2003; Ruggiero 2004; Migliorati 2005; Shimura 2006; Marunick 2006; Freiberger 2007;Van Den Wyngaert 2007*

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# BRONJ – Other reported treatment options

- Laser therapy
- Platelet-derived growth factor
- Platelet-rich plasma
- Ozone therapy combined with surgery & antibiotics
- Slow extraction with orthodontic bands
- Systemic teriparatide

*Cheng 2005; Alessandro et al 2006; Vescovi et al 2007; Adornato et al 2007; Lee et al J 2007; Petrucci et al 2007; Harper 2007; Ruggiero 2008;*

# Drug holiday

# BP Drug holiday

- Counteract antiangiogenic effects of BPs
- Allow improvements in soft tissues & periosteum
- If discontinued for 4 half lives (approx 1-2 months) > 90% of drug clearance from high bone turnover areas
- Suggested that patients taking oral BPs could have a drug holiday of 3-6months before elective alveolar surgeries.

- No prospective data
- Evaluated on a case by case & risk/benefit basis
- No reports that support or oppose the discontinuation of BPs given iv once ONJ develops
- No scientific evidence to support the idea that discontinuing BP therapy will improve Tx outcomes
- Much could be lost in pathology for which drug originally prescribed - for little gain

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*Black 2006; Zahrowski 2007; AAOMFS 2007;Edwards 2008; Gomez Font 2008 Weitzman 2007; Gallego 2008; Edwards 2008*

# Other BP dosing regimes

3 year RCT of ZA versus placebo

- >7000 post-menopausal women with osteoporosis
- Yearly admin 5mg IV ZA associated with 1 case ONJ (same frequency as placebo)

2 year retrospective study

- 3 monthly ZA for MM ↓ risk of ONJ while maintaining anti-resorptive effect of drug

*Black 2007; Corso 2008*

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# Consensus Guidelines

*AAOMFS 2007; Canadian 2008;AAOM 2009*

## IV

- Consultation with oncologist
- Complete necessary dental Tx before start
- Non-urgent surgical Tx while on BPs consider stopping BPs for 3-6 mths pre-op & until surgical site healed
- If Tx urgent proceed & consider BP cessation during healing period
- Symptomatic teeth located within area of bone already exposed & necrotic - extraction should be considered because it is unlikely that it will exacerbate the established necrotic process

- **Symptomatic teeth that would otherwise require extraction should receive nonsurgical endo or perio Tx and left in situ**
- **Avoid implants**
- **Dental evaluation pre-Tx & continued 6-12 mthly**

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# Oral BPs – dental management

## Prevention

Before BP Tx

- Inform all patients
- Dental assessment
- Routine dental care
- Treat active oral infections & ↓ risk of further infections
- Allow time for epithelial healing post-surgery

Taking BPs

- Conservative dental Tx
- Interrupt BP in case of dental surgery→ decision on a case by case basis

## Treatment

BRONJ diagnosed

- Conservative management where possible
- Remove necrotic bone with minimal trauma to adjacent hard and soft tissue
- Topical antibiotic M/W
- ABx therapy
- Avoid extensive oral surgical procedures

*Adapted from AAOMFS 2007;*

*Canadian Consensus 2008; Rizzoli 2008*

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# Update – Implants

4

recent studies

All pts undergoing implant placement:

- Which drug?
- Dose?
- Duration prior to surgery?

Oral BP >3 yrs & taking prednisolone

- Alternative Tx options

*Bell 2008; Graham 2008*

*AAOMFS 2007*

prospective and retrospectives studies about safety of implant placement in patients treated by oral-BPs

*Madrid and Sanz, 2009*

| Study/ Year | Number of patients Test/control | Age range. (years) | Bisphosphonate/ Dosage | BP intake duration at implant placement | Number of implants Test/control | Follow-up duration (months) | BRONJ Number | Success rate in BP group | Success rate in control group |
|---|---|---|---|---|---|---|---|---|---|
| Jeffcoat MK 2006 propsective single-blind controlled study | 25/25 | ? | Alendronate Risedronate | 1 to 4 y | 102/108 | 36 | 0 | 100% | 99.2% |
| Fugazotto PA 2007 retrospective analysis | 61/ no control | 51 to 83 | Alendronate ( 52 patients) 70 mg/week (30) 35mg/week (22) Risedronate (9 patients) 35 mg/week (6) 70mg/week(3) | 1.25 patients 4 to 5 years 2.36 3 years and less<br>mean : 3.3 y | 169/no control | 12 to 24 | 0 ( 1 case of bone exposition not matching BRONJ criteria) | 100% | No control group |
| Bell BM and Bell RE 2008 retrospective analysis | 42/not communicated | Not communicated | Alendronate (34 patients) risedronate (6 patients) ibandronate (2 patients) doses :not communicated | Not communicated | 100/734 | 4 to 89 average 37 | 0 | 95% | 96.5% |
| Grant BT 2008 retrospective analysis | 89 patients under BP before implant surgery/1319 female patients with implant surgery | Mean :67.4 | Alendronate (66 patients) Risedronate (21 patients) Ibandronate (2 patients) | 38 months | 468/1450 | 48 | 0 | 99.5% | 99% |

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 bisphosphonate before/after placement |
|---|---|---|---|---|---|
| Migliorati CA 2006 | 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 adressed | No position |
| No author listed 2007 | American Dental Association Council on Scientific Affairs | Not addressed | - Should be considered carefully<br>- extensive implant placement or GBR at risk | Not recommended<br>To be considered :<br>In risky patients for risky procedures | Not adressed |
| No author listed 2007 | American Association of Oral and Maxillofacial surgeons | Should be avoided | -BP intake <3 y : no contraindication<br>-BP intake >3 y or <3y+corticosteroids : drug holiday recommended | Not addressed | Oral-BPs :<br>3 month before<br>3 months after |
| Khosla S 2007 | American Society of Bone and Mineral Reseach | Not recommended | Not contraindicated | Not addressed | -no data to suggest improvement of outcomes<br>-discontinuation of oral-BP unlikely to have adverse effect |
| Edward BJ 2008 | American Dental Association Council on Scientific Affairs | Not adressed | -Dentists should consider treatment options<br>-extensive implant placement or GBR at risk<br>-non surgical therapy of peri-implantitis | No evidence that antibiotics prevent BRONJ | Not recommended |
| Khan AA 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 :<br>3 to 6 months before procedure and until healing is achieved |

Madrid & Sanz, 2009

# Future

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# Alternatives to bisphosphonates or dosing regimes

**PROSTATE CANCER**

Endothelin receptor antagonists

Calcitriol PSMA antibody

Proteasome inhibitors

Thalidomide

Growth factor receptor inhibitors

**MULTIPLE MYELOMA**

Thalidomide

Lenalidomide

Bortezomib

(3mthly versus 1 mthly infusions of ZA to ↓ incidence of BRONJ

**OSTEOPOROSIS & BONE DISEASES**

Denosumab

ERT HRT SERM

Aromatase inhibitors ERD

Calcitonin PTH

Strontium ranelate

**CHANGES IN BP DOSING SCHEDULES**

Published guidelines for Osteoporosis & MM

Yearly IV Zolendronate for osteoporosis

**No ZA for early MM**

•Discontinue after 2 yrs

*Smith 2005; Cundy 2005; Capsoni et al 2006;*

*Lacy et al 2006; Corso 2007; Johnson 2007; Reginster 2008*

**PAGET'S DISEASE**

Recombinant osteoprotegerin

# Conclusions

- Important area of vigilance for GDPs, physicians, Oral Medicine & Oral Surgeons
- Minimally invasive surgery
- Collaboration
  - oncologists and oral surgeons
  - bone disease specialists and oral surgeons

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# Aknowledgements


- Prof Bertrand Jaques and Doctor Martin Broome Division de Chirurgie Maxillo-Faciale CHUV

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  Policlinique Médicale Universitaire

  Lausanne


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