

## Why worry about bisphosphonate-related osteonecrosis of the jaw?

A guide to diagnosis, initial management, and referral of patients

**Introduction.** Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a chronic condition of the oral cavity resulting in mucosal ulceration and exposure of underlying necrotic bone, and the ensuing secondary complications. As a relatively newly recognised condition, the epidemiology of BRONJ is poorly described. In a 2012 position statement by the UK Faculty of General Dental Practice, an estimated incidence of 10 patients per year per million population was stated.<sup>1</sup> This would indeed classify it as a rare condition, with a GP expecting to see only a handful of cases in their career. However, with increased numbers of patients on bisphosphonate (BP) therapy, all GPs should be aware of the risk factors for BRONJ and the pre-assessment advice they give to patients commencing BP therapy.

**What are bisphosphonates?** BPs inhibit the action of osteoclast cells, decreasing bone turnover and increasing bone density.<sup>2</sup> The mechanism by which BPs cause osteonecrosis is not proven but is probably due to a combination of decreased bone remodelling, poor wound healing, and an antiangiogenic effect leading to ischaemic changes and subsequent necrosis in response to a local traumatic insult.<sup>2</sup>

The main indications for the use of BPs are for the treatment of post-menopausal osteoporosis, steroid-induced osteoporosis, Paget's disease, and the complications of metastatic bone lesions and multiple myeloma, namely, hypercalcaemia and bony pain. It is outside the scope of this article to discuss BP indications in more detail and we assume GPs are familiar with these drugs.

**How do I know if a patient has BRONJ?** The following criteria should be met for a diagnosis of BRONJ: 1) current or previous BP treatment, 2) exposed necrotic bone lasting longer than 8 weeks, and 3) no history of radiation to the jaws.<sup>3</sup>

Patients with BRONJ usually present with ulceration of the oral mucosa with exposure



**Figure 1.** View into the mouth demonstrating an area of mucosal ulceration and exposed bone on the lower left alveolar ridge of the mandible, with signs of local tissue erythema and inflammation.



**Figure 2.** Same patient. View of the neck demonstrating an oro-cutaneous fistula of the left mandible.

of underlying necrotic bone (Figure 1). Mucosal erythema/swelling may precede the ulceration, with mobility of teeth local to this area. Pain and subsequent facial swelling can develop when the surrounding soft tissue becomes inflamed and infected. BRONJ progression results in increased necrotic bone ulceration, and complications include the formation of oro-cutaneous fistulae (Figure 2) and pathological fractures. The differential diagnosis for ulceration and exposed bone will include osteoradionecrosis (that is, has the patient had previous/recent radiotherapy?) and malignancy. *Any painless chronic ulcer with exposure of underlying bone is oral cancer until proven otherwise. As such, any malignant concern should prompt an appropriate referral.*

Risk factors for developing BRONJ are

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**Table 1. ASK–LOOK–DO management pathway for suspected BRONJ**

Ask	Look	Do
<ul style="list-style-type: none"> <li>• Which BP are they taking?</li> <li>• Why are they taking a BP?</li> <li>• Duration of BP therapy?</li> <li>• Recent dental extraction?</li> <li>• Symptomatic? That is, pain?</li> <li>• Other risk factors?</li> <li>• Previous radiotherapy?</li> <li>• Dental or OMFS input?</li> </ul>	<ul style="list-style-type: none"> <li>• Any mucosal ulceration?</li> <li>• Any exposed bone?</li> <li>• Signs of local infection?</li> <li>• Signs of soft-tissue swelling?</li> <li>• Signs of recent dental extraction?</li> <li>• Examine skin for fistula</li> <li>• Could it be oral cancer?</li> </ul>	<ul style="list-style-type: none"> <li>• Discuss the need for dental assessment before starting BP therapy</li> <li>• Prescribe antimicrobial mouth rinse (chlorhexidine)</li> <li>• Give antibiotics if signs of local inflammation/infection</li> <li>• Refer appropriately to OMFS team</li> </ul>

BP = bisphosphonate. OMFS = oral and maxillofacial surgery.

### Box 1. Risk factors for BRONJ

#### BP drug related

IV BP > oral BP  
 IV zoledronate > IV pamidronate > oral alendronate  
 Duration of BP therapy  
 BP for metastasis > osteoporosis

#### Patient factors

Age  
 Poor oral hygiene  
 Corticosteroid therapy  
 Other comorbidities (for example, diabetes)  
 Tobacco use

#### Local factors

Dentoalveolar surgery (dental extractions, dental implants, other gum/root dental surgery)  
 Mandible > maxilla (ratio 2:1)

listed in Box 1. Use of intravenous (IV) BPs has greater risk than oral BPs (0.88–3.1%<sup>4</sup> versus 0.01–0.04%),<sup>5</sup> as does duration of treatment and malignancy as an indication for BP use. The mean onset of BRONJ is 12–24 months for patients on IV BPs and 24–36 months for those taking oral BPs.<sup>5</sup> Most commonly, (>70% of cases) the causative risk factor is a dental extraction, which increases the risk of BRONJ more than seven-fold.<sup>3</sup>

*What should a GP do about a patient with BRONJ?* We present an ASK–LOOK–DO management pathway (Table 1). With BRONJ, prevention is the best cure. All patients about to start BP therapy should undergo a thorough dental assessment. Teeth that cannot be saved or have a poor prognosis should be extracted and any possible future dental treatment completed. This may involve liaising with the patient's dental practitioner, who may not be fully aware of the risks of these drugs. Patients should be encouraged to improve their risk factors, including smoking cessation, reducing alcohol intake, and improving oral hygiene. Although not evidence based, optimising other comorbidities such as diabetes is recommended.

If a patient presents with suspected BRONJ, the nature of the referral will depend upon the severity of symptoms. Asymptomatic BRONJ, that is, exposed bone with no pain or evidence of local infection, can be referred on a routine basis to the local oral and maxillofacial surgery (OMFS) department and in the meantime an antimicrobial mouth rinse, such as chlorhexidine 0.12% (Corsodyl®), can aid healing. If there is pain and evidence of local soft-tissue inflammation/infection, then an appropriate course of antibiotics (for example, co-amoxiclav) can be prescribed. Acute infection with facial or neck swelling, cutaneous sinus formation, or a possible pathological fracture should prompt immediate discussion with the on-call OMFS team. Any suspicion of malignancy

warrants an urgent 2-week-wait referral.

*What if a patient on BPs asks for advice on having dental treatment?* Dental extractions are not contraindicated in patients taking oral BPs but will normally be done in a specialist setting with a prophylactic antimicrobial mouth rinse. The risk of BRONJ increases after taking oral BPs for greater than 3 years. If this is the case then a 'drug holiday' is advised, whereby the BP is discontinued 3 months before and after any invasive dental procedure.<sup>3</sup>

For patients on IV BPs dental extractions should be avoided whenever possible. There is mixed evidence as to the impact of prophylactic pre- and postoperative antibiotics. For complex extractions antibiotics are routinely prescribed. There is no evidence that stopping IV BPs reduces the risk of BRONJ after dental extractions.

*Treatment of BRONJ in secondary care.* With the relatively recent discovery and ongoing research into this condition, treatment strategies are both controversial and complex.<sup>2</sup> Due to the loss of bone vascularity, the less surgery done the better. Apart from antimicrobial mouth rinses and antibiotics, other unlicensed medical treatments can include pentoxifylline, vitamin E and hyperbaric oxygen therapy, but it should be noted that evidence is both mixed and lacking. If a necrotic bony sequestrum is found, minimal surgical debridement is performed. Extensive debridement is difficult because of the lack of available soft-tissue coverage. In advanced cases microvascular reconstruction with bone and soft-tissue free-flaps may be required.

*Conclusion.* In summary, patients on IV BPs are at greater risk of BRONJ than those taking oral BPs, with risk increasing with duration of treatment and a malignant diagnosis. A GP diagnosing BRONJ can prescribe an antimicrobial mouth rinse and antibiotics if indicated, before referring appropriately. Any concern regarding spreading infection or secondary complications should prompt an urgent referral to the local OMFS unit, as should concern of oral malignancy. A thorough dental assessment by the patient's dental practitioner is mandatory before a patient is commenced on BP therapy.

#### Provenance

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#### Competing interests

The authors have declared no competing interests.

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#### Patient consent

The patient consented to the publication of this article and the images.

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