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內文：

INTRODUCTION：

1. Bisphosphonates are drugs used to suppress bone turnover, primarily through effects on osteoclasts.
2. The more potent nitrogen-containing bisphosphonates (NBPs) are favoured in clinical applications today. They are intravenously administered to prevent skeletal related events (SREs) associated with malignancy and severe forms of osteogenesis imperfecta.
3. Intravenous (IV) pamidronate and zoledronic acid are used in this clinical setting, often monthly in the initial treatment phase.
4. Less potent NBPs such as alendronate and risedronate are also administered orally and used in the management of nonmalignant bone disorders such as osteoporosis and Paget's disease of bone.
5. The value of alendronate and risedronate in the management of post-menopausal osteoporosis (PMO) has been compared to placebo and supplements of calcium and／or Vitamin D. Both reduce vertebral, non-vertebral and hip fractures by 16 to 45%.
6. More recently annual IV zoledronic acid has also been shown to be effective in reducing vertebral fractures, non-vertebral fractures and hip fractures by 70%, 25% and 41%, respectively.
7. Bisphosphonate use has been linked to jaw osteonecrosis, particularly the use of NBPs in the setting of malignancy.
8. Bisphosphonate associated jaw osteonecrosis (ONJ), the condition presents as an area of exposed bone in the maxillofacial region.
9. As ONJ is often refractory to treatment, prevention is critical. The condition may progress to secondary maxillary sinusitis, extraoral and intraoral fistula formation, bone sequestration, secondary paraesthesia and pathological fracture, causing significant morbidity.
10. ONJ is exclusively related to the oral cavity, except for rare cases reported in the external auditory canal, hip, tibia and femur, where the contributory role of concomitant glucocorticoid use in some of these cases is uncertain.
11. Risk factors that have been demonstrated to be statistically significant include duration of bisphosphonate exposure, number of infusions, zoledronic acid, dental extraction and advanced age.
12. While the frequency of ONJ in patients with a history of IV bisphosphonate exposure for malignancy is low, 0.88% to 1.15%, the risk of ONJ after a dental extraction in such patients is 6.7–9.1%, as estimated in an Australian population-based survey.
13. This presents a great concern to dental practitioners managing such patients, especially in the event that invasive procedures, such as tooth extraction, are indicated. The same study reported a lower frequency of ONJ in patients with an

oral bisphosphonate exposure history for osteoporosis, 0.01–0.04%, with a 0.09–0.34% risk of ONJ after a dental extraction.

14. The pathophysiology of ONJ is poorly understood, and in particular why the condition localizes to the jaws. As discussed in a recent review of bisphosphonates and alveolar bone, it is postulated that bisphosphonates accumulate in human jaws at higher levels than the skeleton generally, as bone turnover in the jaws has been demonstrated to be higher. The consequent oversuppression of bone turnover may compromise jaw healing, both in response to injury (e.g. tooth extraction)
15. The normal physiological microdamage from occlusion. the pathophysiology may potentially be multifactorial, also involving other factors such as oversuppression of angiogenesis, altered functioning of oral mucosal cells, microbial flora, an anti-inflammatory effect and a genetic predisposition.

REVIEW OF BISPHOSPHONATES IN DENTISTRY

➢ Orofacial conditions with similar presentations to ONJ

- Osteoradionecrosis

1. Osteoradionecrosis (ORN) is caused by radiotherapy to the orofacial structures creating hypoxic, hypocellular and hypovascular tissue. Both ONJ and ORN have necrosis of jaw bones as a common feature, and both are susceptible to secondary infection. The presence of bacteria, and Actinomyces species in particular, are frequently observed in cultures and histology from ONJ lesion specimens.
2. Hyperbaric oxygen therapy (HBO) has proven beneficial clinically to enhance ORN wound healing and to prevent ORN before surgery in irradiated jaws.
3. However, the clinical utility of HBO for ONJ remains to date inconclusive. As recently reviewed, whilst some case series observed no substantive benefit from HBO, other reports suggest HBO may be useful

- Conditions affecting bone turnover

1. oversuppression of bone turnover is central to ONJ pathophysiology.
2. However, jaw osteonecrosis has not been reported with most other drugs that reduce bone turnover, including hormone replacement therapy, strontium ranelate, calcitonin and selective oestrogen receptor modulators, though these drugs do have a different mechanism of action to bisphosphonates.
3. ONJ has some similarities with the condition ‘phossy jaw’, first observed in the 19th century in individuals exposed to white (yellow) phosphorous, which white phosphorous is converted to a compound similar to modern NBPs.

➢ Bisphosphonates in different clinical settings

- Implants

1. However, in a prospective three-year follow-up of 50 subjects receiving implants – half with a bisphosphonate exposure history and half without – no cases of ONJ were observed. These studies were underpowered by small sample sizes, and the bisphosphonate delivery was all oral, which has a weaker association with ONJ than the potent IV NBPs.
2. From the issue of ONJ, several studies were unable to definitively establish that implant failure rates were substantially affected by a bisphosphonate use history. A recent South Australian study estimated the risk of implant failure in patients receiving oral bisphosphonates to be 0.88%.
3. Topical applications of bisphosphonate on dental implants in dogs, with and without a calciumphosphate layer, promoted implant-bone contact and increased the amount of bone peripheral to implants. Despite these potential benefits, the toxic effects on the oral mucosa may potentially contribute to the development of

ONJ.

4. Studies have described ulceration of gastric mucosa and oral mucosa or tongue after taking oral bisphosphonates, largely in the context of incorrect administration.

● Periodontics

1. Periodontal disease has also been observed to be a precipitant of ONJ, as high as 41% in one study. The presence of periodontal disease may necessitate invasive periodontal procedures or dental extraction, and hence increase the risk of ONJ.
2. Administration of systemic bisphosphonates reduced alveolar bone loss in the majority of animal models of experimentally induced and naturally occurring periodontitis, but without significantly affecting clinical periodontal parameters.
3. The effects of bisphosphonates on periodontal clinical parameters in controlled clinical trials are somewhat inconclusive. Three trials demonstrated the efficacy of bisphosphonates in significantly improving clinical parameters, but two did not.
4. Thus, bisphosphonates have paradoxical effects in the oral cavity, having potential beneficial effects on periodontal disease, whilst also increasing the risk of ONJ.

● Orthodontics

1. To date there have been no case reports describing ONJ occurring specifically in the region of orthodontic treatment, but as orthodontic tooth movement involves both bone resorption and formation, bisphosphonates may potentially compromise orthodontic treatment.
2. It has also been proposed that patients discontinue their bisphosphonate therapy for a period of time prior to orthodontic treatment.
3. In contrast, experiments involving local administration of bisphosphonates in rats have suggested a potential positive role for topical bisphosphonates in orthodontic treatment, inhibiting undesirable movement of anchor teeth and inhibiting post-treatment relapse in a dose dependent manner.

● Endodontics

1. In patients with a bisphosphonate exposure history, and especially that administered intravenously, endodontic treatment is the preferred treatment over extraction to minimize ONJ risk.
2. Whilst endodontic treatment itself has not been identified as a precipitant of ONJ, care is advised to minimize the risk. In particular, atraumatic rubber dam placement and avoiding filing beyond the apex are advised, and apicectomy is contraindicated.

➢ Management of bisphosphonate associated jaw osteonecrosis

● Diagnosis

1. ASBMR defines a confirmed case of ONJ as an area of exposed bone in the maxillofacial region that did notheal within eight weeks after identification by a healthcare provider, in a patient who was receiving or had been exposed to a bisphosphonate, and had not had radiation therapy to the craniofacial region.
2. The American Association of Oral and Maxillofacial Surgeons staging system for bisphosphonate associated jaw osteonecrosis：

✧ At risk No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates

✧ Stage 0 No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms

(This may include oral swelling, infection, and non-healing extraction sockets where exposed bone is not present.)

✧ Stage 1 Exposed／necrotic bone in asymptomatic patients without evidence

of infection

✧ Stage 2 Exposed／necrotic bone associated with infection as evidenced by pain and erythema in region of exposed bone with or without purulent discharge

✧ Stage 3 Exposed／necrotic bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone resulting in pathological fracture, extraoral fistula, oral antral／oral nasal communication, or osteolysis extending to the inferior border of the mandible or the sinus floor

3. The ASBMR guidelines specify 10 potential differential diagnoses, including periodontal disease, gingivitis, mucositis, infectious osteomyelitis, sinusitis, periapical pathology due to a carious infection, temporomandibular joint disease, osteoradionecrosis, neuralgia-induced cavitational osteonecrosis and bone tumours.
4. Radiographs are considered essential to exclude differential diagnoses, particularly malignant lesions. A review of radiographic presentations of ONJ reported findings of osteosclerosis, osteolysis, dense woven bone, thickened lamina dura, subperiosteal bone deposition and failure of post-surgical remodelling, with or without bony sequestrum.

● Prevention

1. There is consensus across the guidelines that a comprehensive oral evaluation is recommended prior to initiating IV bisphosphonate therapy.
2. The AmDA also promotes oral evaluation as beneficial either before or early on in oral bisphosphonate therapy, the AAOMS recommend oral evaluation if oral bisphosphonates have been received in the last three months
3. Whilst patients who have received bisphosphonates for osteoporosis can usually be managed in general dental practices, when NBPs have been administered for malignancy, management should be under the care of a dental specialist in conjunction with the oncology team.
4. Once bisphosphonate therapy has commenced, patients should be reviewed every six months to ensure that oral health is optimum and encourage oral hygiene. All attempts should be made to maintain the dentition, by performing endodontics rather than extractions where necessary.
5. Elective dentoalveolar procedures (e.g. implants, orthodontics and periapical surgery) are not recommended whilst receiving IV bisphosphonates for malignancy
6. Implant placement in patients with an oral bisphosphonate history needs to be carefully considered, and the patient informed of the ONJ risk and the risk of implant failure.
7. Nonetheless, IV bisphosphonates are best ceased at least one month prior to invasive dental procedures, and not recommenced until healing is achieved (systemic condition permitting).

Table 2. Guidelines for cessation of oral and intravenous bisphosphonates prior to invasive dental procedures

Guideline	Bisphosphonate exposure history by route of administration	
	Oral	Intravenous
ASBMR[56]	No specific guidelines given	No guidelines given
AAOMS[57]	Less than 3 year duration: No change to dosing Less than 3 year duration and corticosteroids: Cease: 3 months prior Recommence: Osseous healing has occurred† More than 3 year duration: Cease: 3 months prior Recommence: Osseous healing has occurred†	No guidelines given
CCPG[60]	No specific guidelines given	Cease: 3–6 months prior Recommence: Full healing†
Mayo Clinic[62]	No guidelines given	Cease: 1 month prior Recommence: Full healing
MFA[64]	No guidelines given	Low/intermediate risk of SRE: Cease: 2–3 months prior Recommence: 2–3 months after or full healing

†If systemic condition permits.

8.

- Treatment

1. A conservative approach to management of established ONJ is favoured. The ASBMR guidelines advise antimicrobial rinses (e.g. chlorhexidine 0.12%) and systemic antibiotics if there is evidence of infection. Surgical treatment should be conservative or delayed and be limited to: (1) removal of sharp bony edges to prevent trauma to adjacent soft tissues; (2) removal of loose segments of bony sequestra without exposing uninvolved bone; and (3) segmental jaw resection for symptomatic patients with large segments of necrotic bone or pathological fracture.
2. Management is interdisciplinary and involves ongoing close monitoring. The Myeloma Foundation of Australia (MFA) recommends ceasing bisphosphonate therapy for at least three months on ONJ development. Recommencement of bisphosphonates is dependent on risk for SREs, but is best delayed until ONJ resolution. Recommencement of bisphosphonates should with either oral non-NBPs or a reduced frequency of IV NBPs.

CONCLUSIONS

1. Bisphosphonates have revolutionized osteoporosis treatment and confer considerable anti-fracture benefits that outweigh the small risk of ONJ.
2. In periodontology in particular, this is balanced against the risk of substantial risk of ONJ.
3. Numerous guidelines inform the clinician, both in regards to ONJ prevention, management and dosing schedules in cancer. Invasive dental procedures are certainly to be avoided wherever possible in patients with a history of bisphosphonate use, especially intravenous bisphosphonates for cancer. Cessation of oral and intravenous bisphosphonates is advised, both prior to invasive dental procedures and on development of ONJ.
4. Limited surgical debridement together with systemic and local antibiotics is the

favoured management of ONJ, however, healing is not assured.

5. Dental and medical practitioners cannot be reticent about the risks associated with bisphosphonate use and have a duty of care to be fully informed regarding their combined management of patients on bisphosphonates.