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Questioning dual antimicrobial therapy as first line in recent Australian Therapeutic Guidelines

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Questioning dual antimicrobial therapy as first line in recent Australian Therapeutic Guidelines

International efforts to tackle the development and spread of infections resistant to antibiotics have led to a drive towards the use of narrow-spectrum antibiotics wherever possible. Until a recent change in Therapeutic Guidelines: Oral and Dental Version 3 (TG3),¹ Australia was ahead of the international dental community in this respect, with phenoxymethylpenicillin monotherapy recommended for most acute spreading odontogenic infections.² We welcome the comprehensive nature of the new guidelines. However, we question the changed antibiotic regimen to dual therapy and the various combinations of antibiotics recommended.

Antibiotic resistance is a global public health problem. Antibiotic use is a key driver of antibiotic resistance – the more we use antibiotics, the more likely it is that resistance will develop.³ Broad-spectrum antibiotics select for a wider range of bacteria compared to narrow-spectrum agents.³ Antibiotic-resistant odontogenic infections are associated with longer hospital stays and poorer clinical outcomes.⁴ The key principle for clinicians is responsible prescribing, involving prescribing only when necessary, choosing an antibiotic with the narrowest, but appropriate spectrum to minimise the selection of antibiotic-resistant bacteria. Previous editions of Therapeutic Guidelines Oral and Dental² recommended that dentists use firstly, the narrow-spectrum phenoxymethylpenicillin for a spreading odontogenic infection, and then to only add metronidazole 48 hours later if clinically indicated with non-resolution. In direct contrast to the direction of the international dental community, the latest recommendations in TG3¹ have introduced metronidazole to be always prescribed in combination with phenoxymethylpenicillin; metronidazole with amoxicillin; or amoxicillin with clavulanic acid as first-line therapy for a spreading odontogenic infection without severe or systemic features.

Antibiotic prescribing guidelines differ worldwide. Nevertheless, first line prescribing recommendations in dental guidelines from the Faculty of General Dental Practice (United Kingdom (UK)),⁵ the Scottish Dental Clinical Effectiveness Program,⁶ and the United States (US) guidelines⁷ all recommend penicillin monotherapy, either amoxicillin or phenoxymethylpenicillin. The oral and dental health of the UK and US is similar to that in Australia with regard to the number of decayed, missing, and filled teeth, those edentulous

and access to oral health services.⁸⁻¹¹ Thus, it would be reasonable to assume that Australian dentists do not have clinically exceptional circumstances that require dual antimicrobial therapy as first-line treatment while at the same time susceptibility data demonstrate that this is unnecessary.

It is difficult to understand the shift in recommendation in TG3¹ to dual therapy as first-line treatment with an increased spectrum for spreading odontogenic infections without severe or systemic features. There is no evidence that there is a change in the spectrum to a more anaerobic infection if there is spread beyond the confines of the tooth and into the surrounding tissues. In fact there is evidence to show that the spectrum of bacteria in dentoalveolar and endodontic infections are the same.¹² Regardless of where the bacteria spread to (the periapical area, or a secondary space eg. buccal, canine space), they originated from the same source (the root canal system). There is a prevalence of anaerobic, Gram negative bacteria in deep space infections in those patients who require hospitalisation for severe odontogenic infections,⁴ however this is clearly not localised odontogenic infections with non-severe extra-oral swelling for which these recommendations address.

There is some evidence in the literature of increasing rates of resistance to penicillins in anaerobic bacteria, particularly *Prevotella* spp. However, there are no studies that report antibiotic susceptibility in representative target populations, an Australian dental patient in outpatient clinics. Various studies of anaerobic bacteria from patients in Russia,¹³ Romania¹⁴ and Europe¹⁵ report high rates of *Prevotella* spp. resistant to penicillin. However, the studied population and location of isolated bacteria are incomparable to a typical dental Australian patient presenting with a spreading odontogenic infection.

The fundamental principle of managing an odontogenic infection is to drain any suppuration and remove the source of the infection, either via extraction, endodontic treatment, or periodontal treatment. Active dental treatment is always required. Lesions progress beyond the confines of the tooth when the bacteria saturate the capacity of the body's defence mechanisms.¹⁶ There is always the potential that the spread of infection potentially can compromise airways, result in sepsis and significant morbidity.^{17, 18} Nevertheless, there is no evidence to show that the use of penicillin monotherapy in a non-severe extra-oral swelling with concurrent appropriate dental treatment is insufficient treatment that leads to hospitalisation.

A recent South Australian study undertook a retrospective assessment of severe deep space infections in hospitalised patients demonstrating an increased prevalence of anaerobic strains.⁴ Even though this cohort of patients is not comparable to the outpatient setting, penicillin resistance was observed in only 10.8% of isolates.⁴

Antibiotic resistance patterns vary by country,¹⁹ as the development of resistance and transmission of antibiotic-resistant genes depends on a range of factors including local antibiotic use (in humans, animals and agriculture), availability of antibiotics, and hygiene and infection control in healthcare facilities.²⁰ Susceptibility studies on bacteria commonly isolated from odontogenic infections in different countries across Europe, the USA, Brazil and Thailand between 2002 and 2014²¹⁻²⁴ have shown marked differences in patterns of susceptibility/resistance to antibiotics, such that nearly 50% of isolates in Spain were found to be resistant to metronidazole.²³ Guidelines for antibiotic use in dentistry should therefore be based on local resistance data where possible.

Antibiotics prescribed for dental conditions have a wider impact than just targeting the infection. Antibiotics taken orally are associated with dysbiosis, with a reduction in the number and diversity of microorganisms within the body's microbiome.²⁵ Metronidazole in particular increases the risk of intestinal enterococcal colonisation and expansion, and beta-lactam administration does not.²⁶ Antibiotic-related colitis, results from the selection of *Clostridioides difficile* in the gut. This condition can be life threatening and its link to dentists working in community settings has been established in the USA.²⁷ Dental antibiotics may be a risk to patient safety as well as to the population more generally through the development and spread of bacteria resistant to antibiotics, alterations in the gut microbiome, and adverse events such as antibiotic associated diarrhoea.

Based on principles of antibiotic stewardship to optimise antibiotic use and minimise adverse effects, the authors recommend that monotherapy (either phenoxymethylpenicillin or amoxicillin) be used initially as an adjunct to an operative dental procedure for acute spreading odontogenic infections, with the addition of metronidazole only if clinical improvement is not observed. There is a clear need for more local and relevant antibiotic susceptibility data to influence guideline recommendations. Where no applicable local data exist, the relevance and applicability of international studies should be employed with caution. Using broad-spectrum antibiotics through dual therapy as first-line guidance is not in

line with international dental guidelines. Moreover, clinical guideline recommendations should be based on Australian susceptibility data where possible.

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