### Expert Committee recommendation

The Expert Committee endorsed listing of amoxicillin and phenoxymethylpenicillin on the core list of the EML and EMLc as first-choice treatment for progressive (systemically complicated) apical dental abscess. These antibiotics are also recommended as first-choice treatment of apical dental abscess in medically compromised patients. Amoxicillin and phenoxymethylpenicillin are classified as Access group antibiotics (Section 6.2.1).

### Background

Antibiotics are the most widely prescribed category of medicines used by general dental practitioners, a group which was shown to be responsible for 7-11% of all antimicrobials prescribed, and for 45% of all prescriptions of metronidazole (1, 2). Studies have also shown a wide variation in the prescribing habits suggesting inappropriate use of antibiotics in this setting (3-8). Dentoalveolar infections are polymicrobial in nature, mostly strictly anaerobic gram-positive cocci and gram-negative rods mixed with facultative anaerobic flora (9-12). The types of infections where antibiotics may be used include periodontitis, pulpitis, pericoronitis, acute necrotizing ulcerative gingivitis, and periodontal abscesses. The choice of antibiotics is typically empirical in the treatment of these infections. Drainage and removal of the cause of the infection is key in infections such as abscesses, with antibiotics to be considered in certain patients such as those with systemic illness or immunocompromised individuals.

### Summary of evidence

The application presented the results of a search undertaken for systematic reviews and meta-analyses of systemic antibiotic...
therapy for dental infections. A total of 20 systematic reviews were included covering chronic periodontitis, apical periodontitis and acute apical abscess, and irreversible pulpitis. Chronic periodontitis Although patient important outcomes such as pain or quality of life would have been optimal, the outcomes reported in the literature for periodontitis were surrogate markers of activity such as reduction in probing depth, improvement in clinical attachment level, and bleeding on probing. Microbiological outcomes were disregarded as they were not considered to be of high patient importance. The scope of the identified systematic reviews ranged from assessment of the overall effect of antibiotics, to assessment of specific antibiotics or specific subpopulations such as diabetics or smokers. SRs of any antibiotics for any patients A systematic review and network meta-analysis of 14 RCTs of systemic antibiotics for patients with periodontitis reported that using metronidazole or a combination of amoxicillin and metronidazole as an adjuvant to scaling and root planing (SRP) improved clinical attachment gain and reduction in probing depth compared to no antibiotics (13). A greater gain in clinical attachment level (MD 1.08 mm) and reduction in probing depth (1.05 mm) was noted with metronidazole, and clinical attachment level (0.45 mm) and probing depth (0.53 mm) with amoxicillin/metronidazole. These antibiotics showed a better effect than doxycycline. A systematic review of 14 RCTs compared systemic antibiotics in combination with scaling and root planing compared to SRP alone (14). They found that systemic antibiotics significantly improved pocket depth reduction and clinical attachment gain. Results suggested that metronidazole with amoxicillin was the most potent combination. A systematic review of systemic antibiotics for non-surgical periodontal therapy identified a single eligible RCT in which benefit was noted in probing depth reduction (0.9 mm) and clinical attachment gain (0.7 mm). However, the authors concluded that findings were insufficient at this time and larger RCT with longer follow up was needed (15). SRs of amoxicillin with metronidazole A systematic review of 20 RCTs comparing efficacy of amoxicillin and metronidazole as an adjuvant to SRP compared to SRP alone found a beneficial effect of adjunctive antibiotic therapy for probing depth reduction (0.86 mm, 95% CI 0.65 to 1.07 mm) and clinical attachment level gain 0.75 mm (95% CI 0.40 to 1.09) (16). Another systematic review of six 6 RCTs evaluated the effectiveness of amoxicillin and metronidazole as an adjunct to full mouth SRP compared to full mouth SRP alone. Adjunctive antibiotic treatment was associated with significant clinical attachment gain (0.42 mm; 0.23, 0.61) and probing depth reduction (0.58 mm; 0.39, 0.77) (17). A systematic review of 6 RCTs that assessed the effect of adjunctive antibiotics for refractory periodontitis found greater reduction in probing depth and in loss of clinical attachment level with antibiotics compared to debridement alone across all studies, however a meta-analysis was not conducted. The authors concluded that no firm conclusions could be drawn due to the low quality of the evidence (18). A systematic review of 18 RCTs found no clinically important difference between amoxicillin plus metronidazole compared to no antibiotics as an adjunct to non-surgical treatment of periodontitis (19). SRs of metronidazole alone A systematic review of 3 RCTs that assessed metronidazole as an adjuvant to scaling and root planing found benefit of the antibiotic with respect to probing depth reduction (0.18 mm; 0.09-0.28) and clinical attachment (0.10 mm; 0.08-0.12) (20). Another, older systematic review of 8 RCTs also found that metronidazole may offer a benefit for periodontitis in pockets of 4 mm and greater, but only for short term outcomes (21). SRs of azithromycin Two systematic reviews (6 and 14 RCTs) comparing azithromycin as an adjuvant therapy for SRP to SRP alone both reported significant beneficial effects of azithromycin for outcomes of probing depth, clinical attachment level and bleeding on probing (22, 23). SRs of doxycycline A systematic review of 3 RCTs assessed the long-term efficacy of systemic low-dose (subantimicrobial-dose) doxycycline (SSD, 20 mg twice daily) as an adjunctive treatment to SRP compared to SRP alone (24). Significant reductions in probing depth reduction (0.9 mm; 0.43-1.37), clinical attachment gain (0.88 mm; 0.08-1.67), changes in plaque index, gingival index and gingival crevicular fluid at the 9 months mark were observed with adjunctive doxycycline. The authors concluded that the evidence supported a 3-month course of low-dose doxycycline. However, two of the studies were conducted by the same author, and all three studies were conducted in Turkey, potentially limiting the generalizability of the finding. The two studies driving the effect were both evaluated as being at high risk of bias. SRs in smokers Three systematic reviews of trials of antibiotic therapy in smokers with chronic periodontitis yielded variable findings of no benefit (25), inconsistent findings (26) and statistically significant benefit of questionable clinical relevance (27) associated with adjunctive antibiotic therapy. SRs in diabetics Two systematic reviews of trials of antibiotic therapy in diabetic patients both reported benefits associated with antibiotic therapy for the outcome of probing depth reduction, but not for other outcomes (28, 29). Apical periodontitis and acute apical abscess A Cochrane systematic review and meta-analysis of 2 RCTs (62 participants) comparing penicillin to placebo (with surgical intervention and analgesics) found no significant differences for pain or swelling between groups. The authors concluded that there were insufficient data to determine the effects of systemic antibiotics (30). Another systematic review of 8 RCTs comparing antibiotics to placebo or no pharmacotherapy for acute apical abscesses and found no benefit of antibiotics as an adjuvant to surgical intervention. However, a single identified study showed a benefit of azithromycin over amoxicillin-clavulanic acid in terms of reduction of pain, with no benefit for the co-primary outcome “absence of infection” (31). Irreversible pulpitis A Cochrane systematic review of systemic
antibiotics for pulpitis was based only on one small trial which included the use of penicillin for which there was a lack of significant differences in outcomes between groups (32).

**Guidelines**

The application presented the results of a search undertaken of clinical practice guidelines for recommendations on the use of antibiotics for dental infections. Chronic periodontitis A 2015 clinical practice guideline developed by an expert panel convened by the American Dental Association on the prevention and treatment of periodontal diseases in primary care recommended use of systemic subantimicrobial-dose doxycycline (20mg twice daily for 3-9 months) as an adjunct to SRP. The recommendation was made based on moderate evidence of a small net benefit in clinical attachment level from 11 RCTs (813 participants). There was also a weak recommendation for other systemic antimicrobials as adjunct therapy to SRP which showed a similar effect size as SSD but more significant risk for harm based on 24 RCTs (33). 2014 Guidelines published by the Scottish Dental Clinical Effectiveness Program recommended against the use of antimicrobials for chronic periodontitis or peri-implantitis due to a lack of convincing evidence (34). Apical periodontitis and acute apical abscess The European Society of Endodontology position statement recommended against the use of antibiotics in patients with acute apical periodontitis and acute apical abscess and emphasized the importance of surgical drainage. However, a recommendation for adjunctive antibiotics was made for the following patient groups: medically compromised patients (not defined in detail) and patients with systemic involvement (fluctuant swelling, temperature >38 degrees C, malaise, lymphadenopathy, trismus), and patients with progressive infections where referral to oral surgeons may be necessary (rapid <24h severe infection, cellulitis, spreading infections, osteomyelitis). They also recommended against antibiotic treatment in patients with chronic apical periodontitis with a sinus tract. In the subgroup of patients with an indication for antibiotics treatment, penicillin VK (phenoxymethylpenicillin) was the first choice, while amoxicillin, amoxicillin+clavulanic acid, and metronidazole were recommended after 48-72hours if penicillin VK fails. Further listings include clindamycin, clarithromycin, azithromycin for penicillin allergic patients. Duration should be re-assessed after 2-3 days, with a statement that 3-7 days if often sufficient (35). The Canadian Collaboration on Clinical Practice Guidelines in Dentistry (CCCD) also recommend against the use of antibiotics for acute apical periodontitis and acute apical abscess as no benefit had been shown over drainage alone. They suggest that antibiotics may be helpful in the setting of systemic complications (fever, lymphadenopathy, cellulitis), diffuse swelling or in patients with medical indications. There is a statement that no antibiotic can be recommended over another, and that antibiotics may be used if drainage is not possible (36). Irreversible pulpitis The European Society of Endodontology position statement recommends against the use of antibiotics for the treatment of irreversible pulpitis (35).

**Rationale for antibiotic selection**

Periodontitis The application stated that the overall evidence on antibiotics as an adjunct to SRP for periodontitis was limited, conflicting, and in general at high risk of bias. Where benefits had been shown, the summary estimates tended to be small to modest and as such of questionable clinical benefit. Also, recommendations in the two clinical practice guidelines identified were conflicting. It seems reasonable to conclude that the majority of patients likely do not benefit significantly from adjunctive systemic antibiotics, and as such the potential negative effects are outweighing the potential benefits. There might be a subgroup of patients who may clinically benefit from adjunctive antibiotics, but the current evidence does not allow drawing firm conclusions what these subgroups might be. It does not seem that large treatment effects can be seen in smokers or diabetics, and as such these groups should not be treated any differently from others. If, in a specific patient there is a perceived potential benefit with antibiotic treatment, low-dose long-term doxycycline which may have the least ecologic impact, or short-term courses with amoxicillin/metronidazole seem to be the most promising regimens. Apical periodontitis and acute apical abscess The systematic reviews identified in the application provided no evidence supporting the routine use of antibiotics for apical periodontitis and acute apical abscess. The identified guidelines also recommend against the use of antibiotics for the majority of patients, emphasizing the importance of source control and drainage. However, the guidelines recommend antibiotic use for subgroups of patients at risk for complicated/severe infections that may not get under control with drainage alone. In the absence of convincing evidence preferring one antibiotic regimen over the other, we agree with the European guideline listing phenoxymethylpenicillin or amoxicillin, with the potential of adding metronidazole if first line treatment fails. For penicillin allergic patients, the use of clindamycin seems to be the best option given the microbiology of periodontal infections. Irreversible pulpitis There is insufficient evidence to support the use of antibiotics for irreversible pulpitis. Guidelines do not support antibiotics for this indication.

**Committee considerations**