antimicrobial effects. The evidence reported to inform the current guidelines has grouped lasers into two main wavelength categories: lasers with a wavelength range of 2780-2940 nm and lasers with a wavelength range of 810-980 nm.

Available evidence. Evidence was available from five RCTs (total n=147) with a follow-up of ≥ 6 months and a single laser application. Only RCTs reporting mean PPD changes were considered and this recommendation is made in light of this approach to the systematic review.

Risk of bias. The majority of studies displayed unclear risk of bias.

Consistency. Studies differed in terms of laser type, tip diameter, wavelength, mode of periodontal treatment, number of treated sites, population and several possible combinations of these parameters.

Clinical relevance and effect size. There is insufficient evidence to recommend adjunctive application of lasers to subgingival instrumentation.

Balance of benefits and harm. The majority of the studies did not report on potential harm/adverse effects.

Economic considerations. Additional costs associated with adjunctive laser therapy may not be justified.

Patient preferences. Patient-reported outcomes were rarely reported.

Applicability. The majority of studies were conducted in university settings, included specifically selected populations and were undertaken in a number of different countries.

Are treatment outcomes with adjunctive antimicrobial photodynamic therapy (aPDT) superior to non-surgical subgingival instrumentation alone?

Evidence-based recommendation (2.5)
We **suggest not to use** adjunctive aPDT at wavelength ranges of either 660-670 nm or 800-900 nm in patients with periodontitis.
Supporting literature (Salvi et al., 2019)
Quality of evidence: 5 RCTs (n=121, wavelength range 660-670 nm and wavelength range 800-900 nm) with single aPDT application reporting 6-month outcomes. 3 RCTs reported mean PPD changes.
Grade of recommendation: Grade B -↓
Strength of consensus Consensus (1.3% of the group abstained due to potential CoI)

Background

Intervention. Adjunctive antimicrobial photodynamic therapy (aPDT) is an approach used to improve the antimicrobial effects of traditional root surface decontamination methods. It functions by attaching a photosensitising dye to the normally impermeable outer cell membrane of Gram-negative bacteria, and then uses laser light to generate reactive oxygen species through the membrane-bound dye to locally destroy those bacteria.

Available evidence. Evidence was available from five RCTs (n=121) with a follow-up of ≥ 6 months and a single aPDT application. Only RCTs reporting mean PPD changes were included in the meta-analysis and this recommendation is made in light of this approach to the systematic review.

Risk of bias. The majority of studies displayed unclear risk of bias.

Consistency. Substantial heterogeneity across the studies was identified, in terms of laser type, photosensitizer, wavelength, mode of periodontal treatment, number of treated sites, population and several possible combinations of these parameters.

Clinical relevance and effect size. No benefits were observed with the adjunctive application of aPDT.

Balance of benefits and harm. The majority of the studies reported on adverse events with no harm associated with the adjunctive application of aPDT.

Economic considerations. Additional costs associated with adjunctive laser therapy may not be justified.

Patient preferences. Patient-reported outcomes were rarely reported and there is no evidence supporting one approach over the other.

Applicability. All studies were conducted in well controlled university settings or specialist centres, included specifically selected populations and were undertaken in a number of different countries.

Intervention: Use of adjunctive host-modulating agents (local or systemic) to subgingival instrumentation

Does the adjunctive use of local statins improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.6)
We **recommend not to use** local administration of statin gels (atorvastatin, simvastatin, rosuvastatin) as adjuncts to subgingival instrumentation.
Supporting literature (Donos et al., 2019)
Quality of evidence: Twelve placebo controlled RCTs (n= 753), for 1.2% atorvastatin (6 RCTs, n= 180), 1.2% simvastatin gel (5 RCTs, n=118) and 1.2% rosuvastatin gel (4 RCTs, n= 122)
Grade of recommendation: Grade A - ↓↓
Strength of consensus Strong consensus (0% of the group abstained due to potential CoI)

Background

Intervention. Statins are known to have pleiotropic pharmacological effects in addition to their hypolipidemic properties. These include antioxidant and anti-inflammatory effects, the stimulation of angiogenesis, improvements in endothelial function, and the positive regulation of bone formation pathways (Adam & Laufs, 2008; Mennickent, Bravo, Calvo, & Avello, 2008; Petit et al., 2019). Recent evidence suggests that statins may also attenuate periodontal inflammation, as reflected by decreases in pro-inflammatory and increases in anti-inflammatory mediators within the gingival crevicular fluid (GCF) of patients with periodontitis (Cicek Ari et al., 2016).

Available evidence. 12 placebo-controlled RCTs (n= 753), all derived from the same research group, assessed the effect of local statin gels in adjunctive non-surgical therapy for infrabony or furcation class II defects. PPD reduction (primary outcome) was reported at 6 and 9 months for 1.2% atorvastatin (6 RCTs, n= 180), 1.2% simvastatin gel (5 RCTs, n=118) and 1.2% rosuvastatin gel (4 RCTs, n= 122). Meta-analysis was performed in 9 RCTs (n= 607).

Risk of bias. There was a moderate overall risk of bias in the studies analysed. Three out of 12 studies presented with a high risk of bias in at least one domain. One study was moderately underpowered. While pharmaceutical companies provided the statins in the included studies, the level of involvement of industry in the analysis and interpretation of the results is unclear.

Consistency. Meta-analysis of nine RCTs where statins had been applied to a single site per patient demonstrated that adjunctive local application of 1.2% statin gels in infrabony defects led to a mean difference in PPD reduction of 1.83 mm (95% confidence interval - CI [1.31; 2.36]) at 6 months and of 2.25 mm (95% CI [1.88; 2.61]) at 9 months. Only one study investigated locally delivered statins in class II furcation defects.

Clinical relevance. Although the mean estimates suggested a clinically meaningful benefit from adding statin gels to subgingival instrumentation, there was a large prediction interval for PPD reduction at 6 months (-0.08 mm to 3.74 mm) and the I_2 (95.1%) indicating wide heterogeneity of data and therefore caution needs to be adopted when assessing the efficacy of statins. Whilst the prediction interval at 9 months (1.16 mm to 3.34 mm) improved over 6-month results, heterogeneity (I_2 statistic) of 65.4% still indicated moderate inconsistency in results. Since the outcomes of the different statin gels were considered as one group during the meta-analysis, it is not possible to draw definitive conclusions on which statin offered higher efficacy.
Balance of benefits and harms. All studies included in the review reported that patients tolerated local statins well, without any complications, adverse reactions/side-effects, or allergic symptoms.
Economic considerations. There is an additional cost associated with the use of statins that is borne by the patient.
Ethical and legal considerations. The statin formulations included in the systematic review are "off-label" and an approved formulation with appropriate good manufacturing practice quality control (Good Manufacturing Practice, GMP) and patient's safety validation is not available.
Applicability. The same research group published all data within the RCTs, thereby restricting the generalizability of the results, which need to be confirmed in future larger (multicentre) RCTs by independent groups, with multi-level analyses to account for potential confounding factors (e.g. medical history, smoking history). In addition, future studies will need to clarify which type of statin is more effective.

Does the adjunctive use of probiotics improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.7)
We **suggest not to use** probiotics as an adjunct to subgingival instrumentation
Supporting literature (Donos et al., 2019)
Quality of evidence: Five placebo controlled RCTs (n= 176) testing preparations containing *L. ramnosus* SP1, *L. reuteri*, or the combination of *S. oralis* KJ3, *S. uberis* KJ2 and *S. rattus* JH145.
Grade of recommendation: Grade B -↓
Strength of consensus Consensus (0% of the group abstained due to potential CoI)

Background

Intervention. Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (FAO/WHO). It has been suggested that probiotics may alter the ecology of micro-environmental niches such as periodontal pockets, and as such they may disrupt an established dysbiosis. This may re-establish a symbiotic flora and a beneficial interaction with the host via several mechanisms including modulation of the immune-inflammatory response, regulation of antibacterial substances and exclusion of potential pathogens via nutritional and spatial competition (Gatej, Gully, Gibson, & Bartold, 2017). This guideline does not include evidence on the use of probiotics in supportive periodontal therapy.

Available evidence. Five placebo-controlled RCTs (n= 176) assessed the adjunctive effect of probiotics to subgingival instrumentation. 2 studies from the same group used a preparation containing *L. ramnosus* SP1 ($2x10^7$ colony forming units). Two other RCTs from another research group used a preparation containing *L. reuteri*. One study evaluated a combination of *S. oralis* KJ3, *S. uberis* KJ2 and *S. rattus* JH145. Meta-analysis was performed on PPD reduction (primary outcome) at 6 months.

Risk of bias. All studies had an overall low risk of bias. Two out of the 5 studies declared industrial sponsorship and three received the probiotics from industry.

Consistency. Meta-analysis of 5 RCTs demonstrated that, compared with placebo, treatment with probiotics resulted in a mean difference in PPD reduction of 0.38 mm (95% CI [-0.14; 0.90]) at 6 months. The confidence interval and I^2 statistic (93.3%) suggested considerable heterogeneity for the effect of the treatment with the different formulations

Clinical relevance. The mean estimated difference in PPD reduction between probiotics and placebo was not statistically significant and of limited clinical relevance (difference <0.5 mm). Moreover, two groups published four out of the five RCTs included each of them using a different probiotic formulation. Preparations containing *Lactobacillus reuteri* were the only ones to demonstrate improved PPD reductions.

Given that probiotics embrace a broad range of micro-organisms and types of preparations, combining such data within the same meta-analysis poses an interpretational challenge.

Balance of benefits and harms. All formulations appeared to be safe and patients did not report adverse effects.

Economic considerations. There is an additional cost associated with the use of probiotics that is borne by the patient.

Applicability. All studies were conducted in two countries and no conclusions can be drawn on the effectiveness of probiotics as adjuncts to subgingival instrumentation.

Does the adjunctive use of systemic sub-antimicrobial doxycycline (SDD) to subgingival instrumentation improve clinical outcomes?

Evidence-based recommendation (2.8)
We **suggest not to use** systemic sub-antimicrobial doxycycline (SDD) as an adjunct to subgingival instrumentation.
Supporting literature (Donos et al., 2019)
Quality of evidence: Eight placebo-controlled RCTs (14 publications, n=610). Meta-analysis on PPD reduction was performed in 5 RCTs (n= 484)
Grade of recommendation: Grade B - ↓
Strength of consensus Consensus (1.3% of the group abstained due to potential CoI)

Background

Intervention. Sub-antimicrobial doxycycline (up to 40 mg a day) is a systemic drug employed specifically for its anti-inflammatory as opposed to its antimicrobial properties. The formulation offers anti-collagenolytic activity, which may have utility in reducing connective tissue breakdown and augmenting healing responses following subgingival instrumentation in periodontitis patients.

Available evidence. Eight placebo-controlled RCTs (14 publications, n= 610) reported on the systemic use of a sub-antimicrobial dose of doxycycline (SDD) (up to 40 mg a day) in combination with subgingival instrumentation. Meta-analysis on PPD reduction (primary outcome) at 6 months post subgingival instrumentation was performed in five RCTs (n= 484).

Risk of bias. One study was considered to be at high risk of bias and the remaining studies presented some concerns in certain domains. Of the five studies included in meta-analysis, three declared industrial sponsorship, one was sponsored by the academic institution and the fifth did not declare funding.

Consistency. The systematic review included data from eight RCTs, but meta-analysis was performed in five RCTs that stratified pockets into moderate (4-6 mm) versus deep (≥7mm). The findings were consistent in all studies. The I^2 statistic was 0% (95% CI [0%; 64.1%]) for both moderate and deep pockets. Two out of five RCTs included did not report a power calculation.

The strict experimental protocols employed by the five studies included in the meta-analysis limits the generalisability of the outcomes.

Clinical relevance of outcomes and effect size. Additional PPD reductions reported following the use of SDD were 0.22 mm at 6-months and 0.3 mm at 9-months in moderate depth pockets. The mean prediction interval ranged from 0.06 mm to 0.38 mm at 6 months and from 0.15 mm to 0.45 mm at 9 months. At deep sites, the additional PPD reductions were more clinically relevant, with 0.68 mm mean additional PPD reductions at 6-months, and 0.62 mm at 9-months. The mean prediction interval ranged from 0.34 mm to 1.02 mm at 6 months and from 0.28 mm to 0.96 mm at 9 months. Percentage of pocket closure was not reported.

Balance of benefits and harm. Most studies in the SDD category did not report any serious adverse events or patient dropouts that were directly attributed to the medication. However, it is known that doxycycline may lead to elevations in liver enzymes, which was evident for some patients in the results of one RCT included in the systematic review (Caton et al., 2000, 2001). The sustainability of the benefits or adverse events beyond the study period are unknown.

Ethical considerations. Current health policies on antibiotic stewardship and related public health concerns surrounding increasing antibiotic resistance need to be taken into account. The systemic effects of a drug taken over a 6-9 months period during the initial phase of subgingival instrumentation require careful consideration when extrapolating outcomes from controlled research trials into general clinical practice.

Legal considerations. SDD is not approved or available in some European countries.

Economic considerations. There is a cost associated with the use of SDD that is borne by the patient.

Applicability. SSD is mainly effective in deep sites (≥7 mm), although SDD is used as a systemic rather than a site-specific treatment. The clinical significance in deep sites (0.68 mm at 6 months and 0.62 mm at 9 months) is small, given that re-treatment with non-surgical root debridement might yield additional PPD reductions, and local drug delivery systems may yield similar effect sizes. Moreover, the five studies that did stratify results based upon pocket depth did not present an *a priori* statistical plan powered to stratify results in that manner.

Does the adjunctive use of systemic/local bisphosphonates to subgingival instrumentation improve clinical outcomes?

Evidence-based recommendation (2.9)
We **recommend not to use** locally delivered bisphosphonate (BP) gels or systemic BPs as an adjunct to subgingival instrumentation.
Supporting literature (Donos et al., 2019)
Quality of evidence: Seven placebo-controlled RCTs (n= 348), on local delivery of 1% alendronate gel (6 studies) and 0.5% zolendronate gel (1 study); two placebo-controlled RCTs (n= 90) on systemic administration of BPs (alendronic acid and risedronate).
Grade of recommendation: Grade A -↓↓
Strength of consensus Strong consensus (0% of the group abstained due to potential CoI)

Background

Intervention. Bisphosphonates (BPs) are a class of anti-resorptive agents that act mainly by inhibiting osteoclast activity. BPs can also directly inhibit host degradative enzymes like matrix metalloproteinases released by osteoclasts and other cells of the periodontium. There is also evidence that BPs reduce osteoblast apoptosis, thus increasing bone density as an overall therapeutic outcome. It is therefore rational to speculate that BPs may benefit the management of inflammation-mediated alveolar bone resorption in periodontitis patients (Badran, Kraehenmann, Guicheux, & Soueidan, 2009).

Available evidence. Seven placebo-controlled RCTs (n= 348), all from the same research group, on local delivery of 1% alendronate gel (6 studies) and 0.5% zolendronate gel (1 study) in infrabony or furcation class II defects were identified.

A meta-analysis on PPD reduction at 6 months in five RCTs (n= 228) using either single or multiple sites per patient in infrabony defects was undertaken. Two placebo-controlled RCTs (n= 90) evaluated systemic administration of BPs (alendronate and risedronate).

Risk of bias. Of the nine studies included, two were at high risk of bias and seven presented some concerns in at least one of the domains of the risk of bias assessment tool. One study was underpowered. All studies on local BPs were published by the same research group. While pharmaceutical companies provided bisphosphonates for local application in the included studies, the level of involvement of industry in the analysis and interpretation of the results is unclear.

Consistency. Nine RCTs were available, two involving systemic administration of BPs. No meta-analysis was therefore undertaken for systemic BPs. Out of the seven RCTs involving local application of BPs, five were on infra-bony defects (4 employed 1% Alendronate gel and 1 study

used 0.5% Zolendronate gel), whilst two were undertaken on furcation class II defects (all using 1% Alendronate gel). A meta-analysis of five studies using single or multiple sites per patient demonstrated a significant benefit in terms of PPD reduction of 2.15 mm (95% CI [1.75; 2.54]) after 6 months from non-surgical periodontal therapy in infra-bony defects, with a low level of heterogeneity ($I^2 = 47.3\%$).

Clinical relevance. The results of the two studies on systemic BPs were poorly comparable as they were undertaken in different populations and involved different confounding factors (e.g. smoking).

Although the mean estimates suggested adjunctive benefits from adjunctive use of BP gels, the combined use of studies considering single and multiple sites per patient in the meta-analysis should be taken into consideration.

Balance of benefits and harm. both systemic and local BPs were well-tolerated in the studies reported in the systematic review and were not associated with severe adverse reactions.

Economic considerations. There is an additional cost associated with the use of bisphosphonates that is borne by the patient.

Ethical and legal considerations. The balance of recognized potential severe risks (e.g. osteochemonecrosis of the jaws) versus benefits, resulted in a consensus that systemic administration of BPs should not be recommended in the clinical management of periodontal bone loss. It is important to note that BP gel formulations are "off-label" and an approved formulation with appropriate quality control (GMP) and patient safety validation is not available.

Applicability. the same research group/centre published all data on locally delivered BPs, therefore the generalizability of the results requires substantiating in future larger (multicentre) RCTs, with multi-level analyses accounting for potential confounding factors (e.g. medical history, smoking history).

Does adjunctive use of systemic/local non-steroidal anti-inflammatory drugs to subgingival instrumentation improve the clinical outcomes?

Evidence-based recommendation (2.10)
We **recommend not to use** systemic or local non-steroidal anti-inflammatory drugs (NSAIDs) as an adjunct to subgingival instrumentation
Supporting literature (Donos et al., 2019)

Quality of evidence: Two placebo-controlled RCTs (n= 88) on local application (1% flurbiprofen toothpaste; irrigation with 200 ml buffered 0.3% acetylsalicylic acid); two placebo-controlled RCTs (n=133) on systemic applications (celecoxib, diclofenac potassium)
Grade of recommendation: Grade A -↓↓
Strength of consensus Strong consensus (1.3% of the group abstained due to potential CoI)

Background

Intervention. Periodontitis is an inflammatory disease in which altered immune-inflammatory responses to a dysbiotic biofilm drives connective tissue destruction and bone loss. It is reasonable therefore that non-steroid anti-inflammatory drugs (NSAIDs), may be effective as adjunctive periodontal therapies.

Available evidence. Two placebo-controlled RCTs (n= 88) on local application, one using 1% flurbiprofen toothpaste twice daily for 12-months, and a second using subgingival daily irrigation with 200 ml buffered 0.3% acetylsalicylic acid were identified. Two placebo-controlled RCTs (n=133) on systemic applications, one RCT using systemic celecoxib (200 mg daily 6-months) and another using a cyclical regime of diclofenac potassium (50 mg 2-months, then 2-months off, then 2 months on) were included. All studies reported on PPD reduction at 6 months. No meta-analysis was performed due to the limited number of studies identified and their heterogeneity.

Risk of bias. Two out of four studies were considered at high risk of bias. All studies on NSAIDs either did not provide information on sample size calculation or were underpowered. All studies declared industry funding.

Consistency. It was not possible to undertake a meta-analysis of local or systemic NSAID administration as an adjunct to subgingival instrumentation because the studies were heterogeneous (not comparable) in terms of the medication employed and the modality of administration.

Clinical relevance. Local NSAIDs did not enhance the clinical outcomes of subgingival instrumentation. Systemic NSAIDs exhibited limited clinical benefits, but their heterogeneity did not permit the drawing of clinically meaningful conclusions.

Balance of benefits and harm. No serious adverse events were reported.

Ethical considerations. Long-term use of systemic NSAIDs carries a well-known risk of unwanted side effects, which raises concerns over their use as adjuncts to subgingival instrumentation.

Economic considerations. There would be a cost to using NSAIDs which would ultimately transfer to the patient.

Applicability. We do not encourage everyday clinical use of systemic NSAIDs or to conduct future studies to test these medications in their current standard formulations or dosage regimes. No meaningful conclusions could be made regarding use of local NSAIDs. Based on the current limited evidence, local NSAIDs did not provide a clinical benefit.

Does the adjunctive use of Omega-3 polyunsaturated fatty acids (PUFA) improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.11)
We **recommend not to** use Omega-3 PUFAs as an adjunct to subgingival instrumentation.
Supporting literature (Donos et al., 2019)
Quality of evidence: Three placebo-controlled RCTs (n= 160) with 6-months administration of Omega-3 PUFAs.
Grade of recommendation: Grade A - ↓↓
Strength of consensus Consensus (0% of the group abstained due to potential CoI)

Background

Intervention. The recent discovery of pro-resolving lipid mediators by Serhan and colleagues [reviewed by (Serhan, 2017)], some of which are produced by the metabolism of two major omega-3 polyunsaturated fatty acids (PUFAs), namely eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) to E- and D-resolvins respectively, raises the potential for essential dietary PUFAs as adjunctive host-modulating therapeutics for non-surgical periodontal treatment. However, few studies have investigated their efficacy in human trials.

Available evidence. Three placebo-controlled RCTs (n= 160) with 6-months administration of Omega-3 PUFAs. Heterogeneity in study designs precluded a meta-analysis. One RCT investigated low dose omega-3 PUFAs (6.25 mg eicosapentaenoic acid -EPA and 19.9mg docosahexaenoic acid -DHA) twice daily for 6-months; a second study employed high dose omega-3 PUFAs (3 g) in combination with 81 mg aspirin daily for 6-months; a third study used 1 g omega-3 PUFAs twice daily for 6-months. All studies provided PPD reduction data at 6 months post subgingival instrumentation. No meta-analysis was performed due to the limited number of studies identified and their heterogeneity.

Risk of bias. One out of three studies were considered to be at high risk of bias. One study reported industry support, one was supported by a University and one did not disclose the funding source.

Consistency. No meta-analysis could be performed due to the low number of available studies and study heterogeneity in terms of proposed regime and formulation.

Clinical relevance. Since the three RCTs used different doses and preparations of omega-3 PUFAs and one out of three studies combined omega-3 with 81 mg Aspirin, it was not possible to draw clinically meaningful conclusions from the data.

Balance of benefits and harm. No adverse events were associated to the use of omega-3 PUFAs and they are essentially a relatively safe dietary supplement.

Economic considerations. There would be a cost to using omega-3 PUFAs which would ultimately transfer to the patient.

Applicability. There is insufficient data to support or refute the use of omega-3 PUFAs, either as a monotherapy or as a combined therapeutic adjunct to subgingival instrumentation. The combination of omega-3 fatty acids and low dose aspirin also warrants further assessment of its use as an adjunct in the management of periodontitis.

Does the adjunctive use of local metformin improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.12)
We **recommend not to use** local administration of metformin gel as adjunct to subgingival instrumentation.
Supporting literature (Donos et al., 2019)
Quality of evidence: Six placebo-controlled RCTs (n= 313) on locally delivered 1% metformin gel
Grade of recommendation: Grade A - ↓↓
Strength of consensus Strong consensus (0% of the group abstained due to potential CoI)

Background

Intervention. Metformin is a second-generation biguanide used to manage type 2 diabetes mellitus. There is evidence suggesting that metformin decreases inflammation and oxidative stress and may also have an osteogenic effect by increasing the proliferation of osteoblasts and reducing

osteoclast activity (Araujo et al., 2017). It is therefore plausible that this medication may be beneficial in treating a chronic inflammatory disease like periodontitis.

Available evidence. Six placebo-controlled RCTs (n= 313) from the same research group investigated locally delivered 1% metformin gel as an adjunct to subgingival instrumentation. All studies reported on PPD reduction at 6 months post subgingival instrumentation and a meta-analysis was undertaken combining the 6 RCTs.

Risk of bias. Four out of six studies presented some concerns of risk of bias in most of the domains. All studies were published by the same research group. While pharmaceutical companies provided metformin, the level of involvement of industry in the analysis and interpretation of the results is unclear.

Consistency. Meta-analysis of six studies (four considering single sites per patient and two considering multiple sites per patient) indicated that 1% metformin gel as adjunct to subgingival instrumentation led to an improved PPD reduction of 2.07 mm (95% CI [1.83; 2.31]) at 6-months. Heterogeneity between the studies was low ($I^2 = 43\%$).

Clinical relevance. All studies reported a benefit in terms of PPD reduction when 1% metformin gel was used as an adjunct to subgingival instrumentation. However, studies using single and multiple sites per patients were combined.

Balance of benefits and harms. All studies included in the review reported that patients tolerated local metformin gel well, without any complications, adverse reactions/side-effects, or symptoms of hypersensitivity.

Ethical and legal considerations. The metformin formulation included in the systematic review is "off-label" and an approved formulation with appropriate quality control (GMP) and patient safety validation is not available.

Economic considerations. There is an additional cost associated with the use of metformin that is borne by the patient.

Applicability. the same research group published all data on local metformin; therefore, the generalizability of the results needs to be confirmed in future larger (multicentre) RCTs, with multi-level analyses accounting for potential confounding factors (e.g. medical history, smoking history).

Intervention: Use of adjunctive chemical agents to subgingival instrumentation

Does the adjunctive use of adjunctive chemotherapeutics (antiseptics) improve the clinical outcome of subgingival instrumentation?

Expert consensus-based recommendation (2.13)
Adjunctive antiseptics **may be considered**, specifically chlorhexidine mouth rinses for a limited period of time, in periodontitis therapy, as adjuncts to mechanical debridement, in specific cases.
Supporting literature (da Costa, Amaral, Barbirato, Leao, & Fogacci, 2017)
Grade of recommendation Grade 0 - ↔
Strength of consensus Consensus (6.3% of the group abstained due to potential CoI)

Background

Intervention. In order to control gingival inflammation during periodontal therapy, the adjunctive use of some agents has been proposed. Chlorhexidine mouth rinses have been frequently tested in this indication, and frequently used in different clinical settings.

Available evidence. In the systematic reviews of the present European Workshop, the role of antiseptics in active periodontal therapy has not been directly addressed. However, some evidence is available based on studies on the role of chlorhexidine use after subgingival instrumentation (da Costa et al., 2017).

In addition, other factors should be considered:

- It is unclear whether this should be a general recommendation for initial therapy.
- It may be necessary to optimize mechanical plaque control before considering adjunctive chlorhexidine as an adjunct to subgingival instrumentation.
- Specific considerations can be made when used in conjunction with full-mouth disinfection approaches and/or with systemic antimicrobials.
- The medical status of the patient.
- Adverse effects (staining) and economical costs should be considered.

Intervention: Use of adjunctive locally administered antiseptics to subgingival instrumentation

Do adjunctive locally administered antiseptics improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.14)
Locally administered sustained-release chlorhexidine as an adjunct to subgingival instrumentation in patients with periodontitis **may be considered**.
Supporting literature (Herrera et al., 2020)
Quality of evidence: 9 RCTs, 6-9 months. 718/719 patients. High risk of bias and heterogeneity among studies.
Grade of recommendation Grade 0 - ↔
Strength of consensus Consensus (10.5% of the group abstained due to potential CoI)

Background

Intervention. There is insufficient evidence on the benefits of locally administered sustained-release antiseptics as an adjunct to subgingival debridement in patients with periodontitis.

Available evidence. The systematic review (Herrera et al., 2020) revealed results from studies on products containing chlorhexidine (Periochip n=9, Chlosite n=2). One product (Periochip) demonstrated statistically significantly greater PPD reduction following single or multiple applications as an adjunct to subgingival debridement on short-term follow-up (6-9 months) (weighted mean difference - WMD=0.23, 95% CI [0.12; 0.34], $p<0.001$ and significant heterogeneity). There are no long-term data available. No significant differences were found regarding CAL. Data on BOP were insufficient and no data on pocket closure or on number needed to treat (NNT) were provided.

Risk of bias. High risk of bias and heterogeneity among studies.

Clinical relevance and effect size. Effect size estimated for all PPD categories indicates an increased effect of about 10% in PPD reduction.

Balance of benefit and harm. No increase in adverse effects or differences in patient-reported outcome measures (PROMs) were observed.

Economic considerations. The cost for the product and the limited availability of products in European countries need to be considered.

Intervention: Use of adjunctive locally administered antibiotics to subgingival instrumentation

Do adjunctive locally administered antibiotics improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.15)
Specific locally administered sustained-release antibiotics as an adjunct to subgingival instrumentation in patients with periodontitis **may be considered**.
Supporting literature (Herrera et al., 2020)
Quality of evidence: PPD-reduction (6-9 months): Atridox n=2 ,19/19 patients; Ligosan: n=3, 232/236 patients; Arestin: n=6, 564/567 patients. High risk of bias and heterogeneity in the majority of studies.
Grade of recommendation Grade 0 - ↔
Strength of consensus Consensus (7.8% of the group abstained due to potential CoI)

Background

Available evidence. Of the products available on the European market, the systematic review (Herrera et al., 2020) revealed statistically significantly improved PPD reduction of locally applied antibiotics as an adjunct to subgingival debridement on short-term follow-up (6-9 months) for Atridox (2 studies, WMD=0.80; 95% CI [0.08; 1.52]; p=0.028), Ligosan (3 studies, WMD=0.52; 95% CI [0.28; 0.77]; p<0.001) and Arestin (6 studies, WMD=0.28; 95% CI [0.20; 0.36]; p<0.001). No significant adjunctive long-term effect was evident. Statistically significantly improved CAL change for products used as an adjunct to subgingival debridement on short-term follow-up (6-9 months) was identified for Ligosan: (n=3, WMD=0.41, 95% CI [0.06; 0.75]; p=0.020) and Arestin: (n=4, WMD=0.52; 95% CI [0.15; 0.88]; p=0.019). Long term data did not show significant improvement of CAL for any product. Data on BOP and pocket closure were insufficient. No information on NNT was provided. Estimated effect size indicates an increased effect of 10-30% in PPD reduction.

Risk of bias. High risk of bias and heterogeneity in the majority of studies.

Balance of benefit and harm. No increase in adverse effects or differences in PROMs were observed. Harm vs benefit considerations on the use of antibiotics need to be considered.

Economic considerations. High economic costs and limited availability of products in European countries need to be considered.

Intervention: Use of adjunctive systemically administered antibiotics to subgingival instrumentation

Does adjunctive systemically administered antibiotics improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.16)
A. Due to concerns about patient´s health and the impact of systemic antibiotic use to public health, its routine use as adjunct to subgingival debridement in patients with periodontitis is **not recommended**. B. The adjunctive use of specific systemic antibiotics **may be considered** for specific patient categories (e.g. generalized periodontitis stage III in young adults).
Supporting literature (Teughels et al., 2020)
Quality of evidence RCTs (n=28) with a double blind, placebo controlled, parallel design. Risk of bias was low for 20 of the studies, while 7 studies had a high risk. PPD reduction at 6 months; MET+AMOX: n=8, 867 patients. PPD reduction at 12 months; MET+AMOX: n=7, 764 patients, MET: n=2, 259 patients.
A. Grade of recommendation Grade A - ↓↓ ***B. Grade of recommendation*** Grade 0 - ↔
A. Strength of consensus Consensus (0% of the group abstained due to potential CoI) ***B. Strength of consensus*** Consensus (0% of the group abstained due to potential CoI)

Background

Available evidence. While the results from the meta-analysis (Teughels et al., 2020) revealed a statistically significantly improved outcome for systemically administrated antibiotics as an adjunct to subgingival debridement, the effect was confined to a limited group of antibiotics. A significantly improved PPD reduction at the 6 months follow-up was observed for metronidazole (MET) and amoxicillin (AMOX) (n=8; WMD=0.43, 95% CI [0.36; 0.51]). Analysis of 12 month-data revealed a significant adjunctive effect for MET+AMOX (n=7; WMD=0.54, 95% CI [0.33; 0.74]) and MET (n=2; WMD=0.26, 95% CI [0.13; 0.38]). The adjunctive use of MET+AMOX and MET resulted in a statistically significant additional percentage of pocket closure at 6 and 12 months. Statistically significantly greater CAL gain and BOP reduction for MET+AMOX at 6 and 12 months. The adjunctive effect of MET+AMOX on PPD reduction and CAL gain was more pronounced in initially deep than moderately deep pockets. There are no relevant data on the long

term (>12 months) effect of using systemic antibiotics as an adjunct to subgingival debridement. NNT was not assessed.

Risk of bias. Low risk of bias and low heterogeneity among studies.

Consistency. High consistency of results.

Clinical relevance and effect size. Effect size estimation on PPD reduction as opposed to subgingival debridement alone indicates an increased effect of about 40-50%.

Balance of benefit and harm. While the MET+AMOX combination had the most pronounced effects on the clinical outcomes among the different types of systemic antimicrobial therapy, the regimen was also associated with the highest frequency of side effects. Global concerns regarding the overuse of antibiotics and the development of antibiotic resistance must be considered. Benefit vs. harm analysis includes considerations on the overall use of antibiotics for the individual patient and public health. Systemic antibiotic regimens have shown long lasting impact on the faecal microbiome, including an increase in genes associated with antimicrobial resistance.

Applicability. Due to concerns to patient´s health and the impact of systemic antibiotic use to public health, its routine use as adjunct to subgingival debridement in patients with periodontitis is not recommended. Based on the available evidence, however, its adjunctive use may be considered for special patient categories (e.g. generalized periodontitis stage III in young adults).

Clinical recommendations: Third Step of Therapy

The treatment of stage III periodontitis should be carried out in an incremental manner, first by achieving adequate patient's oral hygiene practices and risk factor control during the first step of therapy and then, during the second step of therapy by professional elimination (reduction) of supra and subgingival biofilm and calculus, with or without adjunctive therapies. However, in periodontitis patients, the complete removal of subgingival biofilm and calculus at teeth with deep probing depths (≥6 mm) or complex anatomical surfaces (root concavities, furcations, infra bony pockets) may be difficult and hence, the end points of therapy may not be achieved, and further treatment should be implemented.

The individual response to the second step of therapy should be assessed after an adequate healing period (periodontal re-evaluation). If the endpoints of therapy [no periodontal pockets > 4 mm with bleeding on probing or deep pockets (≥6 mm)] have not been achieved, the third step of therapy should be implemented. If the treatment has been successful in achieving these endpoints of therapy, patients should be placed in a SPC program.

The third step of therapy is, therefore, aimed at treating those sites non-responding adequately to the second step of therapy with the purpose of getting access to deep pocket sites, or aiming at regenerating or resecting those lesions, that add complexity in the management of periodontitis (infrabony and furcation lesions). It may include the following interventions:

- Repeated subgingival instrumentation with or without adjunctive therapies
- Access Flap Periodontal Surgery
- Resective Periodontal Surgery
- Regenerative Periodontal Surgery

Surgical approaches are subject to specific, additional patient consent and specific risk factors/presence of medical contra-indications should be considered. The individual response to the third step of therapy should be assessed (periodontal evaluation) and ideally the endpoints of therapy should be achieved, and patients should be placed in SPC. These endpoints of therapy may not be achievable in all teeth in severe stage III periodontitis patients.

Intervention: access flap procedures

The first relevant question to evaluate the relative efficacy of the surgical interventions in the third step of therapy, for the treatment of periodontitis stage III patients with residual pockets after the second step of periodontal therapy, is whether access flap procedures are more efficacious than subgingival re-debridement for achieving the end points of therapy [probing depth (PD)≤4 mm without BOP].

How effective are access flaps as compared to repeated subgingival instrumentation?

Evidence-based recommendation (3.1)
In presence of deep residual pockets (PPD ≥ 6 mm) in patients with periodontitis stage III after the first and second steps of periodontal therapy, **we suggest** performing access flap surgery. In presence of moderately deep residual pockets (4-5 mm), **we suggest** repeating subgingival instrumentation.
Supporting literature (Sanz-Sanchez et al., 2020)
Quality of evidence: 13 RCTs (500 patients) with moderate to high risk of bias. 5 studies were restricted to pockets associated with intrabony defects. Limited number of studies presented data for quantitative analyses. High consistency of results.
Grade of recommendation Grade B - ↑
Strength of consensus Consensus (1.4% of the group abstained due to potential CoI)

Background

Available evidence. Statistically significantly greater PPD reduction was observed in access flaps (AF) than in subgingival debridement at 1 year. The difference was more pronounced at initially deep sites (PPD ≥ 6 mm) (4 studies, WMD=0.67, 95% CI [0.37; 0.97], at 1 year; WMD=0.39; 95% CI [0.09; 0.70] at >1 year). The relative effect was 27.5%. These differences in PPD reduction also occurred in pockets associated with infrabony defects (4 studies; WMD=0.49, 95% CI [0.11; 0.86]). No statistically significant differences in CAL gain at initially deep pockets were observed between procedures. However, CAL gain was significantly greater in the subgingival debridement group at initially moderately deep pockets, and AF resulted in statistically significantly more attachment loss at sites with initial PPD ≤ 4 mm. Statistically significantly higher percentage of shallow pockets was achieved with AF than with subgingival debridement (3 studies, WMD=11.6%, 95% CI [6.76; 16.5]). The need of re-treatment (4 studies) was 8-29% in