# Step 2 for the Treatment of Periodontal Diseases

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Treatment of Periodontitis: Step 2 of Therapy- Adjunctive Therapies
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**Abstract:**
Step two of periodontal therapy primarily aims at the non-surgical, mechanical disruption of the sub-gingival biofilm and removal of plaque retentive factors allowing a shift from disease to health. Numerous therapeutic agents have been proposed as adjuncts to non-surgical periodontal therapy, generally through either aiding disruption of the dental plaque biofilm or though alteration of the host immune response. This article reviews the British Society of Periodontology's implementation of the S3 guidelines in relation to adjunctive therapies.

**Clinical relevance:**
Recommendation of adjunctive therapies in the treatment of periodontitis requires careful consideration of the available evidence as well as the wider effects of the proposed therapy.

**Five key words:**
Periodontitis, adjunctive therapies, antimicrobial resistance, non-surgical periodontal therapy, immune modulation

**Conflicts of interest:**
The authors declare that they have no conflicts of interest.

**Informed consent:**
There was no use of any images or personal information of any individuals in this article. Informed consent was not required.

## 1.1 Introduction

The desired outcome of periodontal treatment is disruption of a dysbiotic dental plaque biofilm, including bacteria and bacterial metabolites and toxins, leading to a return to healthy, non-pathogenic biofilm, and resolution of dysbiosis induced inflammation.

Step two of periodontal therapy primarily aims at the non-surgical, mechanical disruption of the sub-gingival biofilm as well as removal of plaque retentive factors (PRFs), allowing the shift in the microbiome-host interaction leading to disease resolution (1). This stage is conditional on patient engagement with improvements in oral hygiene and risk factor control as part of the first step of periodontal therapy. There are a number of potential adjunctive therapies that can be administered alongside mechanical plaque removal with aims to facilitate the disruption of the subgingival biofilm or to alter the host immune response. In this manuscript, we will discuss the use of therapies adjunctive to non-surgical subgingival instrumentation, as part of step two of periodontal therapy.

The British Society of Periodontology and Implant Dentistry's (BSP's) implementation of the S3 guidelines published in 2021(2) evaluates the evidence surrounding adjunctive therapies and the aim of this paper is to provide a comprehensive summary of the recommendations on the use of various treatment adjuncts in a UK healthcare setting.

Adjuncts can be categorised into four broad groups and the recommendations are summarised below (Table 1):

1. Physical and chemical agents
2. Host modulating agents (local/systemic)
3. Subgingival locally delivered antimicrobials
4. Systemic antimicrobials

Table 1: Summary of recommendations regarding the use of various adjunctive therapies considered in step 2 of periodontal therapy.

| **Physical and chemical agents** | |
|---|---|
| Lasers | Suggest not to use |
| Antimicrobial photodynamic therapy (aPDT) | Suggest not to use |
| Adjunctive chlorhexidine mouthwash | May be considered for a limited time in certain cases |
| **Host modulating agents** | |
| Local administration of statins | Recommended not to use |
| Probiotics | Suggest not to use |
| Systemic sub-antimicrobial doxycycline (SDD) | Suggest not to use |
| Locally delivered bisphosphonates (BPs) gels or systemic BPs | Recommended not to use |
| Systemic or local non-steroidal anti-inflammatory drugs (NSAIDs) | Recommended not to use |
| Omega-3 polyunsaturated fatty acids (PUFAs) | Recommended not to use |
| Local administration of metformin gel | Recommended not to use |
| **Subgingival locally delivered antimicrobials** | |
| Locally delivered sustained release chlorhexidine | May be considered |
| Locally administered sustained-release antibiotics | May be considered with caution in relation to antimicrobial resistance |
| **Systemic antimicrobials** | |

| | |
|---|---|
| Systemically administered antibiotics | Not recommended in routine use, may be considered for specific patient categories |

## 2.1 Physical and chemical agents

Subgingival instrumentation through ultrasonic or hand instruments aims to remove soft and calcified plaque deposits to re-establish a healthy biofilm and to prevent further accumulation of plaque. Various physical and chemical adjuncts have been investigated for their use in eliminating or disrupting the subgingival biofilm.

### 2.1.1 Lasers and photodynamic therapy

Lasers, an acronym for "Light Amplification by the Stimulated Emission of Radiation", are gaining popularity in dentistry and work by emitting focussed beams of a specific wavelength of light. Within dentistry, lasers have a wide range of potential uses. Lasers in dentistry are categorised by method of laser production; for example, neodymium yttrium aluminium garnet (Nd-YAG) or erbium chromium: yttrium scandium gallium garnet (Er, Cr: YSGG) and hence the wavelength of light produced(3). Of interest, in relation to non-surgical periodontal therapy, is the potential to break up calcified deposits and antimicrobial activity.

While lasers independently act directly on the target site, antimicrobial photodynamic therapy works by activation of a photosensitiser through a light source of a specific wavelength (including lasers), causing release of reactive oxygen species (ROS) which then act on the target, usually bacteria(4). Reactive oxygen species are a group of free radicals containing oxygen and capable of causing cell death through various different mechanisms. In aPDT, the plaque is first treated with a chemical photosensitising agent, followed by exposure to light (5), generating the release of ROS with the aim of killing plaque bacteria.

A systematic review of five studies investigating the effects of lasers in periodontal therapy concluded that there was insufficient evidence to support the use of lasers as a periodontal adjunct. This is, in part, due to the high heterogeneity between studies, arising from the various different types of lasers available for dental treatment. Review of studies evaluating aPDT similarly identified significant heterogeneity between laser type, photosensitiser and outcome measures amongst other factors. Almost all studies evaluating both lasers and aPDT failed to report on residual PPD, an important outcome measure to consider when recommending or suggesting a change to clinical practice. Additionally, as most studies were undertaken in Universities or specialist centres, it is difficult to understand the applicability of the results in general practice(6).

### 2.1.2 Chlorhexidine mouthwash

Chlorhexidine, a bisbiguanide with a broad spectrum of activity against both bacteria and fungi is commonly used as a 0.2% chlorhexidine digluconate prescription free mouthwash. Though commercially available mouthwashes ordinarily have limited use in terms of plaque control due to the lack of mechanical plaque disruption provided from a mouth rinse, chlorhexidine differs in its ability to adsorb onto various surfaces including the salivary pedicle and exhibit significant substantivity prolonging its antimicrobial action(7).

A systematic review and meta-analysis of the use of chlorhexidine mouthrinse identified that there was a statistically significant, but clinically small reduction in probing depth following adjunctive use of the mouthwash alongside PMPR(8). Though there is consistency Chlorhexidine can be recommended in appropriate cases and for limited time (1-2 weeks), to

avoid staining and taste disturbance. Appropriate cases include patients where mechanical plaque control would cause discomfort, for example after surgery, acute instances of oral pain, or patients at risk of oral mucositis. It is not acceptable as a replacement for effective mechanical plaque removal and should be used in conjunction with patient education and behaviour change techniques.

## 2.2 Host modulating agents

Though the defining factor in the development of periodontal diseases is the composition of the dental plaque biofilm(9), the progression of the disease is driven by the complex host immune response to the biofilm microbiota(10). The increased genetic susceptibility to periodontal diseases is associated in part with the variation in expression of genes associated with host inflammatory pathways(11) and perhaps it is this subgroup of patients who would benefit the greatest from immune modulation in addition to biofilm removal for treatment or prevention of periodontitis.

Various host modulating agents have been researched for use in periodontology, usually agents that already have a clearly defined use for other inflammatory conditions in the human body. The aim of these agents is to reduce the host inflammatory response that is key to the tissue destruction observed in periodontitis.

### 2.2.1 Statins

Statins are a group of medications used primarily for hypercholesterolaemia. The mechanism of action of statins against cholesterol is through inhibition the synthesis of cholesterol(12), though statins have been discovered to have multiple functions at various sites of the human body, including anti-inflammatory effects, effects on bone formation and even potential tumour cell growth reduction of cancer cells(12). Within periodontology, localised use of statin gels within periodontal pockets has been investigated as an adjunct to non-surgical therapy, primarily for its anti-inflammatory effects.

A meta-analysis of the literature revealed that the topical application of 1.2% statin gels (atorvastatin, rosuvastatin and simvastatin) to infrabony defects and furcation defects resulted in improved periodontal pocket depth (PPD) reduction compared to placebo, when used in combination with NSPT(13). Despite this, all studies evaluated originated from the same research group; further research is required confirming the existing results before the use of adjunctive topical statin gels can be widely recommended. Additionally, all formulations evaluated were used ‘off label’. Further understanding of the potential side effects or health risks of topical statin gels is required.

### 2.2.2 Probiotics

Probiotics are gaining interest as modulators of human health as we continue to gain understanding of the wide ranging impact of the human microbiome on health and disease. Probiotics are, in the most basic terms, live bacteria with anticipated beneficial action on health. The proposed mechanism of action of probiotics as a periodontal adjunct are wide ranging, but include encouraging the formation of a healthy biofilm through competition with pathogenic species and immune modulation through interactions with the host(14). The most widely researched probiotic strain *Lactocaseibacillus rhamnosus* GG (LGG), though primarily investigated for its effects on gastrointestinal health, has been researched for any effect on periodontal health (15).

A meta-analysis of five RCTs investigating different probiotic preparations showed that only studies evaluating *Lactobacills reuteri* in combination with NSPT resulted in improved clinical outcomes. There were no improvements observed in any of the other probiotic preparations (*Lactobacillus rhamnosus* SP1, or a combined preparation of *Streptococcus oralis* KJ3, *Streptococcus uberis* KJ3 and *Streptococcus rattus* JH145)(13). The BSP's implementation guidelines also considered a double blind, placebo controlled RCT evaluating the effects of *L.reuteri* or placebo lozenges as an adjunct to NSPT, this time concluding no benefit of the addition of probiotic consumption on periodontal treatment outcomes(16). Overall, the current literature does not support the use of probiotics as an adjunct to NSPT.

### 2.2.3 Systemic sub-antimicrobial doxycycline

Doxycycline, a tetracycline antibiotic, when used at sub-antimicrobial doses can illicit an anti-inflammatory response in the body. The background behind sub-antimicrobial dose doxycycline (SDD) is based on studies demonstrating matrix metalloproteinase (MMP) inhibition observed following SDD (17). MMPs have a significant role in periodontitis, activating an immune response resulting in localised tissue destruction(18).

Of the studies evaluated, following use of systemic SDD, a greater reduction in pocket depths was observed compared with placebo, with a greater effect seen in deeper pockets, with a mean reduction of 0.68mm at 6 months(13). This effect, though consistent throughout studies is small and the relevance of this needs to be considered. The available literature does not support the recommendation to use SDD as an adjunct to sub-gingival instrumentation.

### 2.2.4 Locally delivered bisphosponates

Bisphosphonates (BP)will be familiar through its role modulation of bone remodelling, used for management of osteoporosis at low doses and reduction of cancer metastasis in high doses, all associated, at various levels of risk, with medication related osteonecrosis of the jaw (MRONJ). BPs, like many of the drugs discussed in this paper, have pleotropic effects. Of most interest in periodontology is the potential for bisphosphonates to reduce inflammation(19).

Most studies investigating the use of BPs evaluate the use of locally administered topical BP gel. Though some effect in reducing PPD have been observed, these are all observed from the same study group(13). More research is required, including multi centre studies to fully understand the potential benefits of topical BPs in periodontal treatment, particularly understanding the risks of MRONJ, which cannot be understated for its potentially significant and severe negative effects on quality of life(20). Additionally, the preparations of BP gels used was 'off label' thus a full understanding of potential side effects and harms to health is not known.

### 2.2.5 Non-steroidal anti inflammatory drugs (NSAIDs)

Both systemic and topical NSAIDs have been investigated for their effects on periodontitis, including a flurbiprofen toothpaste, irrigation with acetylsalicylic acid and systemic administration of celecoxib and diclofenac.

Studies evaluating the effectiveness of an NSAID toothpaste or NSAID daily supragingival irrigation did not identify any improvement in PPD compared to a placebo. Systemic administration investigated in two studies revealed a greater PPD reduction in the NSAID groups compared with placebo 6 months(13).

Topical NSAIDs are not recommended as there is no clear clinical evidence of their use. While systemic NSAIDs may have a benefit evident at 6 months, longer term studies have not been completed. Additionally, administration of systemic NSAIDs are associated with unwanted side effects(21). Thus, NSAIDs are not recommended for use as an adjunct to sub-gingival instrumentation.

### 2.2.6 Omega-3 polyunsaturated fatty acids (PUFAs)

Polyunsaturated fatty acids (PUFAs) encompass a number of types of molecules, some of which are essenatial to human health. The most common of these molecules are omega-3 (n-3) PUFAs and omega-6 (n-6) PUFAs. These molecules are obtained by the human body through dietary sources as they cannot be made intrinsically. Omega-3 PUFAs have been suggested to have numerous beneficial effects on the human body(22). There are numerous studies investigating the effects of Omega-3 PUFAs in vitro, but systematic reviews evaluating the clinical effects of PUFAs on cardiovascular disease(23), dementia (24), depression(25) and cystic fibrosis (26) fail to identify evidence at a high enough quality to indicate clinical significance.

Similarly, though PUFAs appear promising in their anti-inflammatory activity in vitro(27), there are limited studies investigating the effects of PUFAs on periodontal disease in human studies. Of these studies, low dose supplementation of omega-3 PUFAs did not show any difference in PPD reduction compared with placebo(28). Though higher doses (1000mg twice daily)(29) and doses of omega-3 PUFAs in combination with aspirin(30) did show statistically significant improvements in PPD compared to placebo, full understanding of the size and clinical relevance of the effect requires further studies.

### 2.2.7 Metformin

Metformin, the first line medication for type II diabetes mellitus has also been found to improve bone quality through stimulation of osteoblast differentiation(31) and has therefore gained interest in periodontology, with the drug being seen as a potential topical adjunct to periodontal therapy (32-34). It has also known to have direct anti-inflammatory effects through numerous mechanisms(35).

Formulations of metformin as a topical 1% gel have been developed and investigated for their use as a periodontal adjunct, both for its anti-inflammatory effects and modulation of bone remodelling. Studies identified in a systematic review and meta analysis (13)that the use of metformin gel as an adjunct to non surgical periodontal treatment in infra bony defects resulted in an increased PPD reduction and infrabony defect depth compared with placebo(33, 34, 36, 37), though further studies from different research groups would be required before wide recommendation of metformin gel as a topical adjunct. As with other drugs discussed in this paper, the preparation of metformin gel used in the studies evaluated was used ‘off label’, hence a full understanding of the safety of its use in this preparation is not available.

## 2.3 Subgingival locally delivered antimicrobials

### 2.3.1 Locally administered sustained release chlorhexidine

Certain antimicrobial agents have been developed in preparations that permit a sustained release acting in a localised area, i.e. a periodontal pocket. The most common of these is either a chlorhexidine or doxycycline preparation.

While chlorhexidine mouthwash has good evidence to support its use in oral disinfection, localised, sustained delivery of chlorhexidine at specific sites has the advantage of targeting persistent deep pockets where it is difficult to maintain a high concentration of an antimicrobial through other means such as irrigation or mouthrinsing. PerioChip is a preparation of chlorhexidine digluconate within a gelatin matrix, facilitating placement in a

subgingival pocket. It has demonstrated a statistically significant reduction in PPD as an adjunct to non-surgical therapy with an effect size of about 10%, but there is no available evidence on the long-term effects of this(38). Locally administered sustained release chlorhexidine may be considered in specific cases on the basis that there are reports of improvement in PPD and the lack of reported adverse effects, but further evidence, including more studies with more detailed data on the effects, including long term results are required.

### 2.3.1 Locally administered sustained release antibiotics

Locally administered sustained release antibiotics include Atridox 10% gel(doxycycline), Ligosan 14% gel(doxycycline) and Arrestin 'microspheres' (minocycline). These are all in the tetracycline class of antibiotics and are effective at reducing bacteria associated with periodontal disease(39). The topical method of administration reduces or eliminates the risk of unwanted side effects of tetracyclines, including tetracycline staining.

A systematic review evaluating studies using locally administered sustained release antibiotics of the tetracycline class identified that topical application of such products resulted in an increased reduction of PPD with the greatest difference seen with Atridox. The effects observed with locally administered antibiotics were greater than that seen for locally administered chlorhexidine. Long term effects are less clear(38).

The S3 guidelines suggest that locally administered sustained release antibiotics may be considered as an adjunct to sub gingival instrumentation. The decision to use these must be considered very carefully in the context of antimicrobial resistance.

## 2.4 Systemic Antimicrobials

The two most commonly prescribed systemic antibiotics for periodontal conditions are metronidazole and amoxicillin. Studies evaluated in the development of the S3 guidelines show significant reductions of periodontal pocket depths (PPD) following use of either metronidazole or amoxicillin alone, or both metronidazole and amoxicillin used concurrently(40).

A significant and incredibly important disadvantage to the use of systemic antimicrobials is the worldwide threat to human health of antimicrobial resistance. The use of systemic antimicrobials in periodontitis must be considered carefully in balance with side effects and AMR. Though systemic antibiotics can effectively reduce or eliminate the pathogenic microbiota in the periodontal pocket, resulting in improved clinical outcomes, antibiotic resistance is rapidly increasing and is a significant threat global public health.

Clear differences have been observed in antimicrobial resistance of the subgingival microflora of periodontitis patients when comparing patients from a country of low antibiotic use to one of high antibiotic use(41). Further, systemic administration of antibiotics clearly have systemic effects, including significant disturbance of the gut microbiome(42). The impact of disturbance of the gut microbiome is wide ranging including associations with inflammatory conditions (43) and cancer(44).

For public health concerns and concerns of lasting and potentially significant detrimental effects for individuals, systemic antibiotics cannot be recommended as an adjunct to non surgical therapy in routine use. Where there is severe and rapidly progressing disease, antibiotics may be considered.

## 3.1 Conclusion

The majority of patients with gingivitis and periodontitis can be successfully treated by standard methods of plaque removal, involving primarily patient focussed OHI and behaviour change accompanied by professional mechanical plaque removal(45). Adjunctive therapies have been researched generating various degrees of quality of evidence. Though based on a sound theoretical base and supported by in vitro and animal studies, evidential outcomes of certain adjuncts do not currently translate into sufficient clinical improvement, in balance with any unwanted outcomes, to justify its use.

Certain cases may justify the use of adjuncts with strong evidence base, this includes patients with rapidly progressing disease despite maintenance of excellent oral hygiene or patients who are temporarily unable to maintain mechanical plaque removal. The S3 guidelines limits these adjuncts to chlorhexidine mouthwash and systemic antibiotics in carefully selected cases. A summary of recommendations is illustrated in Figure 1.

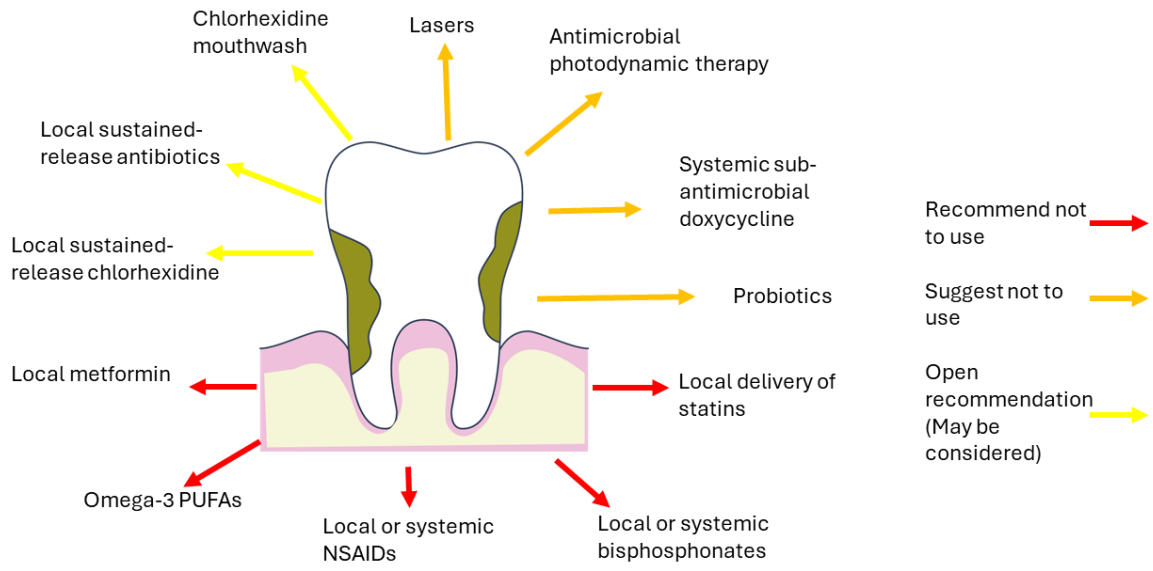


*Figure 1 Summary of recommendations*

While some adjuncts have shown to be effective in selected individual studies Larger, multi-centre trials are required to fully understand the overall treatment effect for wide recommendation of use.

Many of the potential adjuncts discussed in this paper have a common theme: reducing the risk of antimicrobial resistance (AMR), either through means of eliminating bacteria without the use of antimicrobials, or through modulation of the host response to bacteria, reducing the potential need for antimicrobial use. With AMR an increasing risk to the persistence of human life on our planet, careful consideration of the use of antimicrobials and further research into alternative methods for bacterial elimination or host modulation in relation to the progression of periodontal disease are essential.

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