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REVIEW ARTICLE

Europe's contribution to the evaluation of the use of systemic antimicrobials in the treatment of periodontitis

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1 | INTRODUCTION

Periodontitis is defined as the progressive destruction of the tooth-supporting apparatus.[1] Clinically, the disease causes increased periodontal pockets with inflammation, bleeding on probing, clinical attachment loss, and, radiographically, alveolar bone loss. Untreated, periodontitis causes tooth loss.

Periodontitis poses a significant threat to public health due to the following factors:

- It is one of the most common diseases in humans. The Global Burden of Disease 2010 study found an 11.2% global age-standardized prevalence (1990-2010) of severe periodontitis, making it the sixth most prevalent condition in the world,[2] whereas the 2015 study estimated 7.4%.[3] Besides severe forms of periodontitis, the prevalence of any type of periodontitis in adult populations can be around 50%.[4]
- It can cause tooth loss and disability, alter chewing function and esthetics, cause social inequity, and lower quality-of-life indicators.[5]
- It has been associated with different systemic diseases, such as diabetes,[6,7] and cardiovascular diseases.[8,9]
- It has been associated with increased medical expenditure.[10]

Periodontitis is caused by bacteria in supra- and subgingival dental plaque biofilms. Dental biofilms can become "dysbiotic,"[11] which dysregulates the host immune-inflammatory response, increasing dysbiosis and destroying periodontal tissues.[12] Philip Marsh proposed the "ecological" plaque hypothesis, which uses dysbiosis to explain the etiology of periodontal diseases: In health, host and microbiota are in balance, but they are out of balance in disease, causing dysbiosis.[13]

For the treatment of periodontitis, the European Federation of Periodontology S3-level clinical practice guidelines[14,15] recommend a step-by-step approach. Interventions in step 1 include professional and patient-based control of supragingival biofilms, together with risk factor control. Step 2 involves subgingival instrumentation with or without concomitant therapy.[14] Steps 1 and 2 may be successful in preventing further periodontal attachment loss in most initial and moderate cases. The final and crucial step is supportive periodontal care, which focuses on preventing disease progression.

Subgingival instrumentation, usually rendered as scaling and root planing, has been shown to have a significant clinical impact.[16] However, this nonspecific periodontal treatment is not adequate for all sites/patients.[17-19] Moreover, one of the features of grade C periodontitis is the "lack of expected response to standard bacterial control therapies."[1,20] This, along with the well-known limitations of subgingival instrumentation (deep pockets, furcation lesions, vertical defects, dentin hypersensitivity, gingival recession, inexperienced operators, etc), has historically led to the search for alternative or adjuvant therapeutic procedures.[21-23] To overcome those limitations, different treatment strategies (such as full-mouth

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disinfection), alternative instrumentation methods (eg, lasers, antimicrobial photodynamic therapy), or adjunctive therapies (like antimicrobials, probiotics, anti-inflammatory drugs, and antioxidant micronutrients) have been proposed and tested.[24]

Among the adjunctive therapies, the most widely evaluated and commonly used are topically, locally, or systemically applied antimicrobial agents.

Chlorhexidine mouthwash is the most common topically applied antimicrobial. When used with subgingival instrumentation, this chemical agent enhances clinical outcomes.[25] The European Federation of Periodontology clinical practice guideline indicates that its use may be considered adjunctive in step 2 of the treatment of periodontitis.[14]

Topically or locally delivered antimicrobial agents have advantages over systemic delivery if they have a sustained-release system: lower total dosage, fewer side effects, improved compliance, and reduced risk of bacterial tolerance to medications.[26] However, it also represents additional costs. Several studies and a few systematic reviews have examined the effects of local antimicrobials delivered in fibers, gels, chips, or microspheres, mostly in untreated patients but also in treated sites and patients with poor response or recurrent disease. Some of these studies ratio have shown significant additional benefits with the use of certain agents or devices, but their clinical value and cost-benefit ratio have been controversial.[27] In the systematic review for the European Federation of Periodontology clinical practice guideline for stages I-III periodontitis,[28] 50 randomized controlled trials reported in 59 papers with a minimum follow-up of 6 months were identified, and statistically significant benefits were observed for the different locally applied antimicrobials. After 6-9 months, the additional clinical benefits in probing depth reductions and clinical attachment loss changes were estimated (weighted mean difference) at 0.36 mm (95% confidence interval: 0.26-0.47) and 0.26 mm (95% confidence interval: 0.12-0.40), respectively. The European Federation of Periodontology clinical practice guideline suggested that subgingivally applied antiseptics (chlorhexidine) and antibiotics (doxycycline or minocycline) with sustained release may be considered adjuncts to subgingival instrumentation.[14]

This review will focus on systemically delivered antimicrobials. Thus, this narrative review will address how systemically delivered antimicrobials have been used to treat periodontitis and the extent to which European research has been involved.

2 | RATIONALE FOR THE USE OF ANTIMICROBIALS IN THE MANAGEMENT OF PERIODONTAL DISEASES

Since bacteria are essential to the onset and progression of periodontal diseases,[13] chemical or biological antimicrobial agents have long been recommended for their treatment.[29] However, the rationale for their use depends on the objective (prevent or treat), the disease (acute or chronic), and the delivery format or route of administration (local or systemic).

2.1 | Objective of the use of antimicrobials

Antimicrobials can be used in steps 2 and 3 of periodontitis treatment, and in primary and secondary prevention. However, the timing of the prescription can affect the antimicrobial type and delivery format or route.

Antimicrobials that are used for prevention are usually antiseptics that are delivered via toothpaste and mouthwash and are designed for long term use. They may prevent dental biofilm formation when used with mechanical biofilm control.[30] These agents may be useful in the primary and secondary prevention of gingivitis and periodontitis. Gingival indices are the main outcomes of randomized controlled trials assessing the efficacy of antimicrobials, so the studies focus on gingivitis.[31] However, the most relevant impact of their use would be the primary prevention of periodontitis and prevention of disease progression during supportive periodontal care.[32] According to the European Federation of Periodontology clinical practice guideline for the treatment of periodontitis in stages I-III,[14] the suggested antiseptic agents are chlorhexidine, triclosan with copolymer, stannous fluoride with sodium hexametaphosphate in dentifrices, and chlorhexidine, essential oils, and cetylpyridinium chloride in mouth rinses.[30-33]

Antimicrobials used in therapy are usually antibiotics, targeting bacteria in subgingival biofilms. This area can be reached directly, through the pocket entrance, with locally delivered antibiotics, or by following a systemic route with systemically delivered antibiotics.

Locally delivered antimicrobials need a release system that ensures a 24-h dosage.[26] Nonabsorbable fibers and absorbable gels are used for this. Chlorhexidine, metronidazole, tetracycline hydrochloride, doxycycline, and minocycline have been used for subgingival delivery. Some of these products have demonstrated statistically significant benefits over placebo,[28] but three main issues have limited their use:

- Generalized periodontitis may not be treatable locally with antimicrobials. Thus, the indication is limited to localized lesions in remaining pockets after therapy or localized recurrent active sites.
- Despite the rationale for finding suitable indications for locally delivered antimicrobials, few studies have focused on those indications, making it difficult to make strong recommendations or perform an adequate cost/benefit ratio.
- Locally delivered antimicrobial agents are expensive and with limited in availability in different countries, general recommendations are difficult to implement.

Systemically delivered antimicrobials are mainly used in therapeutical approaches, and antibiotics are used exclusively. Systemic

antibiotics can also be used in periodontics for prophylactical purposes, such as the prevention of infective endocarditis,[34] but that discussion is not within the scope of the present review.

2.2 | Nature of the disease

The course of periodontitis can be either acute or chronic. This determines whether to treat the disease with antimicrobials. Periodontal abscesses and necrotizing periodontal diseases are acute periodontal infections.[35] Systemic antimicrobial therapy can be used in both cases:[36]

- Incision, drainage, and debridement is the primary treatment for periodontal abscesses. If drainage is impossible due to the abscess's size or location, the patient's medical condition requires antibiotic prophylaxis; or if the periodontal condition is severe and includes fever and malaise, adjunct systemic antimicrobial therapy may be considered.
- In patients with temporarily or moderately compromised immune systems, superficial cleaning with a sonic/ultrasonic device, chlorhexidine mouthrinse, and limited mechanical hygiene is the first line of treatment for necrotizing periodontal diseases. If the disease is severe, feverish, and resistant to mechanical treatment and local antiseptics, adjunct systemic antimicrobial therapy may be considered.

In acute periodontal infections, systemic antimicrobial agents are prescribed with loading doses and lower dosages than in chronic conditions.[37] The prescription should be short term, with the aim of resolving symptoms or signs and controlling tissue destruction. This requires daily disease resolution control.

3 | EVALUATION OF SYSTEMIC ANTIBIOTICS IN THE TREATMENT OF PERIODONTAL DISEASES: HISTORICAL PERSPECTIVE AND EUROPEAN CONTRIBUTIONS

3.1 | From the 1960s to the 1980s: The pioneer studies

The use of antimicrobial agents in the management of periodontal diseases was suggested very early: After discovering the optical microscope, Antonie van Leeuwenhoek in the 17th-18th centuries advised rinsing with morning urine to reduce gingival inflammation.[38] In the early 1900s, some pioneers suggested using antimicrobials before mechanical or surgical treatments,[39] and even systemically[40] to reduce the risk of systemic disorders.

In the 1960s, different studies demonstrated that oral intake of antimicrobial agents provided acceptable drug levels in crevicular fluid[41] and saliva,[42] allowing these drugs to be used in the treatment of oral infections. This insight, combined with the emerging "specific plaque hypothesis",[43-45] provided initial scientific basis for the use of systemic periodontal antimicrobial therapy. Systemic periodontal antimicrobial therapy began to be scientifically evaluated, focusing on three main possible benefits: (a) to control bacterial deposits ingressed into periodontal tissues or residing in difficult access areas by mechanical means; (b) to reduce the need for periodontal surgery; and (c) to improve treatment results in terms of new attachment and/or periodontal regeneration.[46] Successful systemic periodontal antimicrobial therapy was also expected to produce a more predictable treatment outcome, especially in cases of "refractory" periodontitis; that is, cases with ongoing disease activity despite standard treatment rendered.

Since then, a large body of evidence has shown the clinical efficacy of systemic periodontal antimicrobial therapy. This was the basis for the first European Federation of Periodontology S3-level clinical practice guideline, which includes recommendations for using chemical adjuvants for the treatment of stage I-III periodontitis.

3.1.1 | Tetracyclines

Tetracycline hydrochloride was the first drug to demonstrate therapeutic crevicular fluid levels.[41] Crevicular fluid concentration was 2-10 times higher than in blood.[47] In the late 1970s, it was mainly tested as an adjunct to mechanical periodontal treatment,[22,43,48] but also in long-term use at 250 mg per day.[49,50] Tetracycline hydrochloride was considered a good option, since periodontal diseases were included in the list of oral or dental conditions in which tetracyclines could be useful,[21] and also due to its antimicrobial properties and mild side effects. Additionally, tetracycline hydrochloride inhibited host tissue collagenolytic enzymes and reduced collagen destruction in periodontitis.[51,52] In nonresponding sites, tetracycline hydrochloride was used based on the nonspecific plaque hypothesis,[53] to reduce anaerobes and provide additional clinical benefits.[54]

However, controlled clinical trials failed to show significant and predictable clinical benefits of tetracycline hydrochloride as an adjunct to mechanical periodontal therapy.[22,43,48] In addition, tetracyclines increased bacterial resistance,[17,55] were associated with mild but frequent side effects, which combined with problems with compliance with a four times a day regimen, lead to a decrease in the use of tetracycline hydrochloride for periodontitis.

Doxycycline and minocycline, tetracycline derivatives, have been the subject of multiple trials. Patient compliance benefits from once-daily dosing. Minocycline and doxycycline showed promising results in the 1990s, making them "the antibiotics most likely to be of value in the United States for the treatment of certain other forms of periodontitis."[46]

In the 1970s and the 1980s, two views on the role of bacteria in periodontal diseases were popular: the nonspecific plaque hypothesis and the specific plaque hypothesis.[44] The latter gained credit when a strong association was found between localized juvenile periodontitis and detection of *Aggregatibacter actinomycetemcomitans*.[45,56] *A.actinomycetemcomitans* persistence after mechanical

instrumentation or surgery was linked to periodontal breakdown by several researchers.[57-61] This observation led to the emergence of clinical periodontal microbiology in several European countries and became the basis for the rational use of systemic periodontal antimicrobial treatment.[62]

Although the initial explanation for subgingival instrumentation's limited efficacy was the pathogen's possible tissue invasion, the results after surgery cast doubt on this explanation. The first suggested strategy was to include systemic tetracycline in the treatment protocols for localized juvenile periodontitis.[22,60,63] However, 25% of treated patients relapsed, regardless of the professional periodontal maintenance protocol,[60] and systemic tetracycline did not prevent further periodontal attachment destruction.[63]

These observations initiated the use of doxycycline.[64,65] Metronidazole, which was also effective against periodontal anaerobes, was also evaluated in combination with mechanical treatment in *A. actinomycetemcomitans*–associated periodontitis.[66] The results showed that this antibiotic provided more predictable results in localized juvenile periodontitis patients than did tetracyclines.

3.1.2 | Metronidazole

In 1959, metronidazole, a nitroimidazole, was commercially available to treat protozoal infections (trichomoniasis, amebiasis). Shinn,[67] in 1962, reported in the *Lancet* that metronidazole helped seven Necrotizing gingivitis patients. Other necrotizing gingivitis studies confirmed these findings.[68] It was found that metronidazole was bactericidal mainly against anaerobes, including spirochaetes and gram-negative and gram-positive bacterial species. Since these bacteria were identified in the subgingival plaque in different forms of periodontal diseases, including necrotizing forms, the interest in metronidazole led to the publication of a number of clinical studies in the 1980s.

The first clinical trials of metronidazole for periodontal diseases were conducted in the United Kingdom,[67,68] Finland,[66] Sweden,[69] and the United States.[70] An important contribution was the series of studies by Walter J. Loesche and coworkers,[71,72] at the University of Michigan, demonstrating the clinical and microbiological effects of metronidazole in the treatment of "adult" periodontitis using scientifically sound double-blind protocols. They showed that metronidazole improved posttreatment clinical parameters like probing depth and clinical attachment loss better than mechanical treatment alone. Systemic metronidazole, added to scaling and root planing, reduced the number of teeth requiring periodontal surgery.[73] These studies have helped to rationalize the use of metronidazole for periodontitis. This research group also examined dosage, compliance, and medication course length. In one of Dr Loesche's last clinical publications, he reported on the 6-year follow-up of 34 patients who received systemic metronidazole and subgingival instrumentation. The number of teeth recommended for surgery before periodontal treatment decreased from 9.4 to 1.5. Half of those subjects maintained clinical benefits for 6.4 years without surgery.[74] Dr Loesche's concepts were elegantly presented and defended,[44] comparing the nonspecific and specific plaque hypotheses, as presented in Figure 1.

In Switzerland in the 1980s, ornidazole, a nitroimidazole, performed similarly to metronidazole.[75]

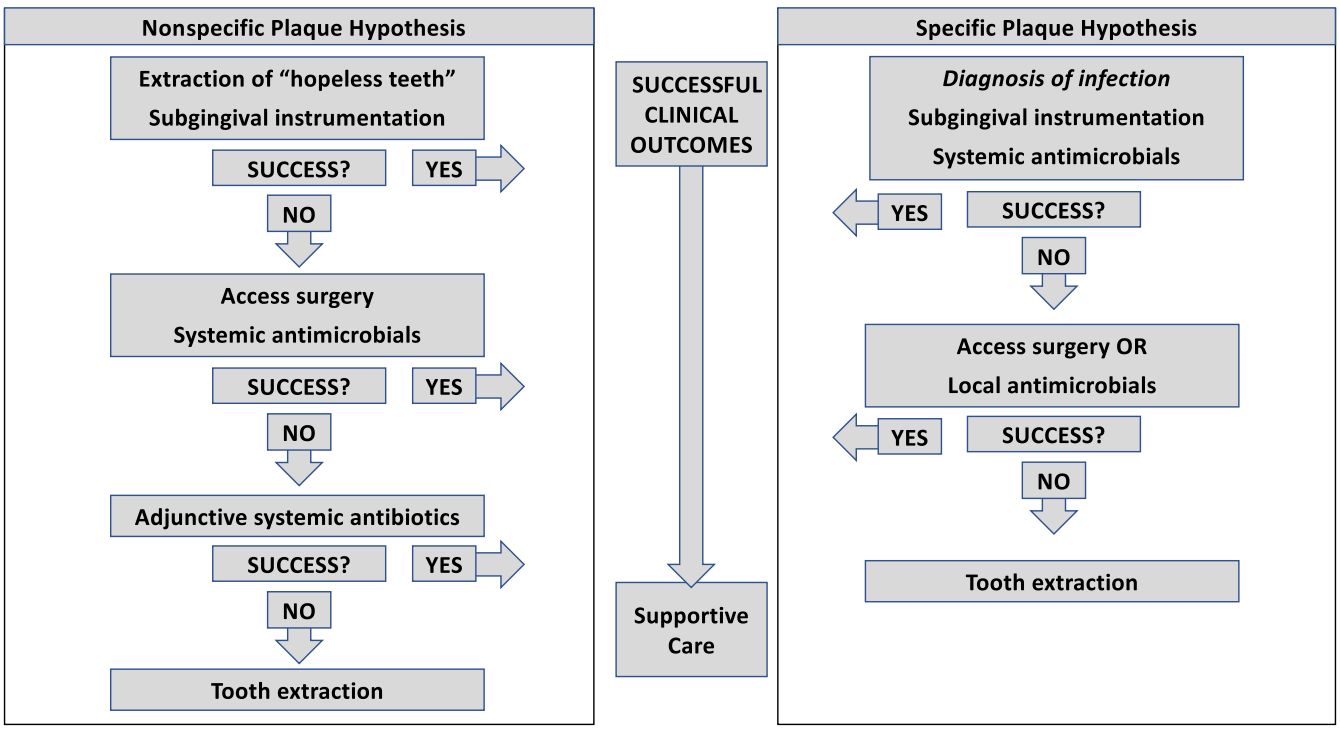

FIGURE 1 Treatment sequence and concept, based on the "specific plaque hypothesis" or the "nonspecific plaque hypothesis", according to Walter Loesche. Terminology and format have been adapted and modified from Loesche.[44]

Metronidazole combined with spiramycin was tested as an adjunct to mechanical periodontal therapy in Canada.[76]

3.1.3 | Penicillins

The most commonly used antimicrobials in medicine and dentistry are penicillins. They are indicated for the management of periodontal diseases, specifically to treat acute conditions.[77] However, owing to their importance in managing serious, life-threatening conditions, they were not considered a reasonable option in the treatment of periodontitis in the 1980s,[46] explaining why amoxicillin alone was not frequently evaluated as an adjunct to subgingival instrumentation. However, and after promising in vitro results, amoxicillin and clavulanate were tested in the 1990s in the United States[17,78] and in Europe.[79]

3.1.4 | Macrolides

Macrolides are frequently used as antimicrobials in medicine and dentistry. Erythromycin, the best-known antibiotic in this group,[80] was deemed inappropriate periodontics due to its antimicrobial profile and very low concentration in crevicular fluid.[81] Conversely, spiramycin and azithromycin have been studied in periodontal therapy[82-84] for different reasons, explained below.

Spiramycin was an interesting drug, since its concentration in saliva was higher than its serum concentration,[85] which made the drug a potential agent for the treatment of oral infections. However, spiramycin, like erythromycin, only kills gram-positive bacteria, so its antimicrobial profile was poor. It was not accepted in the United States, which limited research. Two Canadian randomized controlled trials in the late 1980s and early 1990s[82,83] suggested clinical benefits, which were confirmed in one of the first systematic reviews on the topic.[86] Following those two studies, the first European Workshop, based on systematic reviews, identified metronidazole, alone or in combination with amoxicillin, and spiramycin as the most relevant agents.[87]

Azithromycin has good pharmacokinetics and broad antimicrobial activity against periodontal bacteria. In the early 1990s, Finnish studies suggested bactericidal effects against *Porphyromonas gingivalis*[88] and *A. actinomycetemcomitans*,[89] which were later confirmed by others.[90] Italian researchers found high concentrations in inflamed tissues.[91] Azithromycin was first tested adjunctively in periodontitis therapy in a 1996 London clinical trial,[92] and it was later tested in the treatment of periodontal abscesses,[84] with comparable results to amoxicillin and clavulanate.

3.1.5 | Other systemic antimicrobials

Clindamycin, a lincosamide, has been tested as an adjunct to subgingival instrumentation for the same reasons as metronidazole, with the added benefit of achieving high bone tissue concentrations. It requires six-hourly dosing, making compliance more difficult. Clindamycin, like other antibiotics like β-lactams, can cause pseudomembranous colitis. Its effects on "refractory" periodontitis, in the United States,[17,93] and on "rapidly progressive" periodontitis, in Germany, have been studied.[94]

Ciprofloxacin and ofloxacin, quinolones, have been studied post-surgically, either in conventional periodontal therapy (in Germany)[95] or after membranes or other regenerative technologies, and in combination with metronidazole and/or doxycycline.[96,97] Moxifloxacin, another quinolone, has shown good activity against a panel of periodontal pathogens in vitro[98] and in a clinical study in aggressive periodontitis patients.[99]

3.2 | The 1990s: Europe takes the lead

3.2.1 | Research in Europe in the 1960s-1980s

Some of the most relevant studies in the initial scientific development of the use of systemic antimicrobials in the treatment of periodontitis were conducted in the United States. However, Europe and European researchers helped to develop this research area and produced interesting publications. In the gingivitis experimental model, Harald Löe's group tested topical vancomycin in the 1960s. Jan Lindhe and colleagues evaluated systemic tetracyclines for long-term use[50] and localized juvenile periodontitis.[60] Also, systemic metronidazole's clinical impact was examined.[69] Lars Heijl led Göteborg researchers in studying metronidazole, vancomycin, and clindamycin in Beagle dogs in the late 1970s and early 1980s.

Since the 1990s, researchers in Scandinavia, Switzerland, the UK, and the Netherlands have studied the effects of systemic antimicrobials on periodontics.

Leena Saxén and coworkers[64] tested doxycycline and metronidazole at the University of Helsinki, using microbiological evaluation as a treatment outcome. The application of systemic antimicrobial agents also included microbiological data, particularly the subgingival detection of *A. actinomycetemcomitans*.[66] Metronidazole, being bactericidal, initially provided clinical results that were insufficient, with different suggested explanations, such as the fact that the drug did not easily penetrate the bacterial wall of *A. actinomycetemcomitans* or that salivary and crevicular levels were not optimal.[100]

The University of Helsinki conducted the first in vitro azithromycin studies against periodontal pathogens.[88,89] The first randomized controlled trial on the adjunctive use of azithromycin in periodontitis therapy was conducted in the United Kingdom.[92]

Renvert and coworkers[101,102] published a famous case series in Sweden on the effects of subgingival instrumentation and periodontal surgery on *A. actinomycetemcomitans* detection. Those studies did not evaluate systemic antimicrobials, but they supported their use in treating *A. actinomycetemcomitans* periodontitis. In a randomized controlled trial in Stockholm, Sweden, complete healing was

observed in 30% of metronidazole patients, compared with 9% in the control group.[103]

Andrea Mombelli et al[75] did research at Bern University on the use of systemic antimicrobials and microbiology in periodontal and peri-implant diseases, including testing systemic ornidazole in 1989.

Groups in the United Kingdom pioneered first in observing metronidazole's periodontal effects in the 1960s,[67] and later in performing the first clinical study on azithromycin in periodontitis therapy.[92]

3.2.2 | Research in Europe in the 1990s: Amoxicillin plus metronidazole

Much of the initial research on systemic periodontal antibiotic therapy was focused on the detection and suppression of bacterial markers, such as *A. actinomycetemcomitans*, or strict anaerobic bacterial species, such as spirochetes and black-pigmented *Bacteroides* species, currently including *P. gingivalis* and *Prevotella intermedia*. One challenge in periodontics in the 1990s was the suppression of *A. actinomycetemcomitans* below detection levels in susceptible patients. These included not only localized juvenile periodontitis patients but also subjects with "rapidly progressive periodontitis" and "refractory" periodontitis with detectable subgingival *A. actinomycetemcomitans*.[104]

The Academic Centre for Dentistry Amsterdam, in the Netherlands, under the direction of the microbiologist A. J. van Winkelhoff, became an important research center for studies on the use of adjunctive antimicrobial therapy in the treatment of periodontitis. Following the concepts of the specific plaque hypothesis,[44] the association found between localized juvenile periodontitis and *A. actinomycetemcomitans*,[56] and the limited impact of mechanical therapy,[57,101,102] the use of adjunctive antimicrobials was strongly advocated in the treatment of *A. actinomycetemcomitans*–associated periodontitis. However, systemic tetracyclines, including doxycycline and minocycline, appeared unpredictable in their suppression of *A. actinomycetemcomitans*, resulting in significant recurrent disease activity in treated patients. This was then explained by the bacteriostatic nature of tetracyclines. Metronidazole, a bactericidal drug, performed better initially.[66]

Since periodontal monotherapies with systemic antibiotics as adjuncts to mechanical instrumentation had limited effect on subgingival *A. actinomycetemcomitans*, a new approach was needed. In 1989, van Winkelhoff et al[105] presented a case series of patients, including 11 localized juvenile periodontitis and 11 rapidly progressing periodontitis subjects, all subgingivally culture-positive for *A. actinomycetemcomitans*. After mechanical subgingival instrumentation, followed by 7 days of systemic amoxicillin and metronidazole, *A. actinomycetemcomitans* was eliminated in all but one patient. All patients showed clinical improvements (excluding one with severe diarrhea), resulting in lower probing depths and bleeding on probing. After 9-11 months, all 16 patients were culture-negative for *A. actinomycetemcomitans* and showed further clinical improvement.[105] This observation initiated further research, including studies on the nature of interactions between *A. actinomycetemcomitans* and the drugs. Pavicić and coworkers[106-109] found that metronidazole and amoxicillin act synergistically against *A. actinomycetemcomitans*: in the presence of amoxicillin, metronidazole's hydroxy metabolite could better penetrate the bacterial cell, enhancing its bactericidal effects and providing its synergistic effects. This synergy resulted in the killing of *A. actinomycetemcomitans* at levels far below the minimum bactericidal concentrations of both antibiotics. This explained subgingival *A. actinomycetemcomitans* suppression in almost all treated patients (see clinical studies), and the combination of amoxicillin and metronidazole was referred to later as "the van Winkelhoff cocktail."

Clinical studies were conducted after in vitro research on the combination of metronidazole and amoxicillin against *A. actinomycetemcomitans*:

- In 1992, 118 *A. actinomycetemcomitans* periodontitis patients treated with subgingival instrumentation and amoxicillin (375 mg) and metronidazole (250 mg) thrice daily for 7 days were culture-negative 3-9 months later.[110]
- In 1994, a case series of 48 patients with *A. actinomycetemcomitans* periodontitis treated with the same protocol reported no detectable subgingival *A. actinomycetemcomitans* in 47 patients. Tonsillar, salivary, and mucosal samples were culture-negative 2 years after active periodontal treatment.[111] Excellent clinical results accompanied these microbiological findings.
- In 1998, a similar study on 22 patients, followed for 35 weeks, focused on the impact of mechanical periodontal treatment, including the use of metronidazole and amoxicillin, on other periodontal pathogens, like *P. gingivalis*, *Tannerella forsythia*, or *P. intermedia*, although the patients were selected based on the presence of *A. actinomycetemcomitans*.[112]
- The first randomized controlled trial of this group, assessing amoxicillin plus metronidazole, was published in 2001 and included 49 patients with generalized severe periodontitis. The presence of *A. actinomycetemcomitans* was not an inclusion criterion. The test group showed statistically significant clinical benefits, and baseline *P. gingivalis* carriers responded better.[113]

Although the Academic Centre for Dentistry Amsterdam group's main contribution was the proposal and evaluation of the combination of amoxicillin and metronidazole, they also provided important information on the microbiological outcomes of periodontal therapy and searched for specific adjunctive antimicrobials for microbiologically specific types of periodontitis, such as *P. gingivalis* or *T. forsythia* periodontitis. Though metronidazole alone seems to work for *P. gingivalis* periodontitis,[113] it is unclear which antimicrobial may target *T. forsythia*.[114] The Academic Centre for Dentistry Amsterdam group also tested amoxicillin plus clavulanate in a 12-month randomized controlled trial with generalized adult

periodontitis patients and found no additional clinical or microbiological added benefits.[79]

The summary of 15 years of research is captured in a very elegantly written narrative review, published in 2005.[62] The existence of periodontitis as "true infections" associated with "exogenous pathogens" is the basis for the use of specific antimicrobial therapies targeting those exogenous pathogens. The best examples are *A. actinomycetemcomitans*, which can be managed with amoxicillin and metronidazole, and *P. gingivalis*, which showed very reasonable outcomes after treatment with metronidazole alone. Moreover, they suggested that microbiological diagnosis, if capable of detecting these pathogens, could help in tailoring specific treatments (Figure 2) and reduce the risk of "unsuccessful" outcomes, following the term used by Loesche (Figure 1).

3.2.3 | Research in Europe in the 1990s: Other studies

Amsterdam was an important but not the only place in Europe where relevant studies were produced and published. To evaluate the importance of Europe in the field, the studies selected by the systematic review on systemic antibiotics prepared for the 4th European Workshop in Periodontology[86] are used as reference: randomized controlled trials or controlled clinical trials, with at least 6 months' duration, published from the 1970s until the 21st century. The following findings are relevant (Table 1):

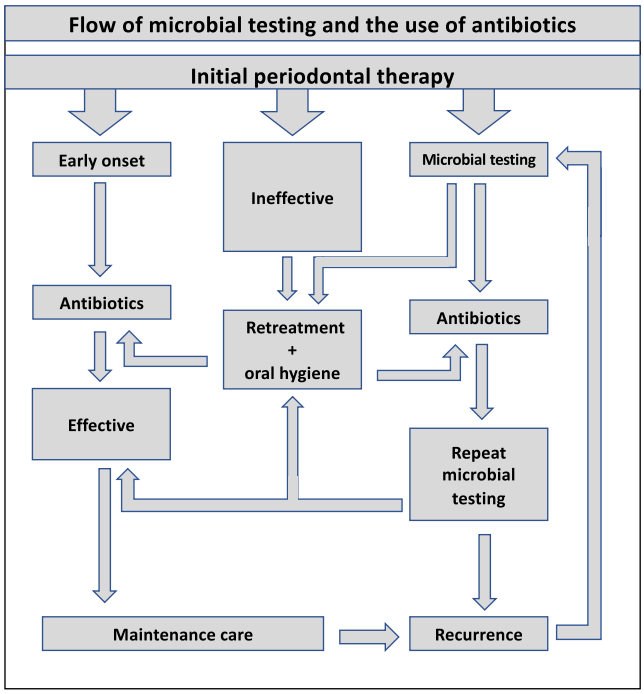

FIGURE 2 Treatment sequence, based on the concept of "true" infections and "exogenous" pathogens, according to A. J. van Winkelhoff and Edwin Winkel. Adapted and modified from van Winkelhoff & Winkel.[62]

- Before 1980, two papers on tetracycline reported on the same patient sample.[115,116]
- From 1980 to 1990, 10 papers were included: four from Canada, one on spiramycin,[82] one on spiramycin/metronidazole,[76] and two on doxycycline, but on the same patient sample;[117,118] three from Sweden, one on tetracycline[50] and two on metronidazole;[69,103] two from the United Kingdom on metronidazole, although reporting on the same patient sample;[119,120] and one from the United States, on metronidazole.[121] Overall, four studies were conducted in Europe and four in North America.
- From 1991 to 2001, 11 articles were considered: three from the United States, one on doxycycline[122] and two on clindamycin or amoxicillin and clavulanate in "refractory" cases;[17,93] one from Canada, on spiramycin;[83] two papers came from the United Kingdom, testing metronidazole, but reporting on the same patient sample;[123,124] two from Scandinavia, one from Sweden on amoxicillin plus metronidazole[125] and another from Finland on metronidazole or tetracycline;[66] two in Germany, one testing amoxicillin plus metronidazole[126] and the other comparing doxycycline, clindamycin, and metronidazole in "rapidly progressive" periodontitis;[94] one additional study came from the Netherlands, on amoxicillin and clavulanate.[79] Overall, four studies were conducted in North America and six in Europe.

Interestingly, by the turn of the century, Europe was taking the lead in the field: other drugs than tetracyclines and metronidazole were evaluated; microbiological outcomes were considered relevant, and specific forms of diseases were targeted in the studies, either clinically characterized ("aggressive" forms of disease, "refractory" periodontitis) or microbiologically defined (ie, presence of specific pathogens, proportions of spirochetes, proportions of resistant species).

3.3 | The 21st century: The impact of the workshops

3.3.1 | European and world workshops in the 20th century

In the last decades of the 20th century, the American Academy of Periodontology pioneered the organization of "workshops,"[127] which they called "world" workshops for unknown reasons, where experts discussed the available evidence and their own clinical experience, provided guidance to clinicians, requested additional research, or developed classifications, diagnostics, or treatment approaches. The third workshop, held in Princeton, New Jersey, on July 23-27, 1989, provided a new classification scheme.[128]

Two of the European participants of this "world" workshop, Niklaus Lang and Thorkild Karring, considered Europe ready to organize "European" workshops and founded the European Academy of Periodontology, which, together with the European Federation of Periodontology, organized the First European Workshop

TABLE 1 Studies selected by the systematic review on systemic antibiotics, prepared for the Fourth European Workshop in Periodontology.[86]

Publication year	Reference	Author, year	Country	Study duration	Drugs tested
1979	115,116	Helldén et al (1979), Listgarten et al (1978)	Sweden	25 weeks	Tetracycline
1983	50	Lindhe et al (1983)	Sweden	50 weeks	Tetracycline
1983	69	Lindhe et al (1983)	Sweden	50 weeks	Metronidazole
1984, 1986	119,120	Joyston-Bechal et al (1984, 1986)	UK	22 weeks, 3 years	Metronidazole
1984	121	Loesche et al (1984)	USA	15-30 weeks	Metronidazole
1987	76	Quee et al (1987)	Canada	6 months	Spiramycin
1989	82	Al-Joburi et al (1989)	Canada	24 weeks	Tetracycline, spiramycin
1990, 1991	117,118	McCulloch et al (1990), Kulkarni et al (1991)	Canada	7 months	Doxycycline
1990	103	Soder et al (1990)	Sweden	6 months	Metronidazole
1993	66	Saxén & Asikainen (1993)	Finland	6 months	Tetracycline, metronidazole
1993	17	Walker et al (1993)	USA	24 months	Amoxicillin/clavulanate, clindamycin
1994	83	Bain et al (1994)	Canada	24 weeks	Spiramycin
1994	93	Magnusson et al (1994)	USA	2 years	Amoxicillin/clavulanate, clindamycin
1998	126	Flemmig et al (1998)	Germany	12 mo	Amoxicillin/metronidazole
1998	125	Berglundh et al (1998)	Sweden	24 months	Amoxicillin/metronidazole
1998, 1999	123,124	Palmer et al (1998, 1999)	United Kingdom	24 weeks	Metronidazole
1998	122	Ng and Bissada (1998)	United States	24 weeks	Doxycycline
1999	79	Winkel et al (1999)	Netherlands	12 months	Amoxicillin/clavulanate
2001	94	Sigusch et al (2001)	Germany	24 months	Clindamycin, doxycycline, metronidazole
2000	224	Caton et al (2000)	United States	9 months	Low-dose doxycycline
2001	225	Golub et al (2001)	United States	36 weeks	Low-dose doxycycline

on Periodontology, at the Charter House in Ittingen (Thurgau, Switzerland), on February 1-4, 1993. Etiology, pathogenesis, classification, and diagnosis were covered at that workshop.[129] For subsequent workshops, the European Federation of Periodontology and the European Academy of Periodontology, or Workshop Committee, chaired by Professor Lang, organized the European Workshops. For years, European and "world" workshops ran concurrently.

In 1996, the Second European Workshop on Periodontology focused on the use of molecular biology in the diagnosis, prevention, and management of periodontal diseases,[130] whereas the 1996 "World" Workshop in Periodontics was subtitled "Improved Clinical Decision Making Using the Evidence-Based Approach".[131] This workshop covered a wide range of topics and is well remembered because there the term "periodontal medicine" was suggested for the first time.[132]

In 1999, the Third European Workshop on Periodontology conducted an evaluation of the field of implant therapy using a critical lens.[133] The American Academy of Periodontology organized the International Workshop for a Classification of Periodontal Diseases and Conditions, which developed the 1999 classification.[134]

The foundation for each of these 20th-century workshops was a set of meticulously written position papers that surveyed the relevant literature and were subjected to the scrutiny of their respective authors. During the group meetings, these articles were debated, revised, and, in the end, adopted to serve as the foundation for subsequent discussions. At the end of the meeting, the group consensus reports were discussed in plenary sessions to develop concluding remarks for the profession. But, with the turn of the century, a huge change would affect the 21st-century workshops as systematic reviews became popular, and this would have a clear impact on how workshops were designed and conducted and on how consensus was developed and reached.

3.3.2 | European workshops in the 21st century: The first workshop based on systematic reviews (2002)

The Fourth European Workshop on Periodontology[135] was a major game changer in the field of periodontology/periodontics, since it

covered periodontal practice for the first time on the basis of so-called "systematic reviews." This new approach to analyzing the body of work was taken in an attempt to achieve an unbiased approach to the analysis of the available scientific literature, and therefore, the highest level of scientific proof. The systematic reviews prepared for the workshops aimed to incorporate the most compelling evidence, which was typically derived from randomized controlled trials, which evaluated therapeutic or other management approaches. However, such randomized controlled trials were and are not always available in many disciplines of medicine, including periodontology. Consequently, the systematic reviews sometimes had to be based on a lower level of evidence, such as prospective or even retrospective cohort studies; case series were usually excluded from the systematic reviews. As a result systematic reviews were unable to answer all of the questions that a clinician might face in clinical practice. On the other hand, the process of doing a systematic review did, at least, provide an objective approach to extremely significant components of daily practice. With this in mind, the European Federation of Periodontology began the process of establishing a stable foundation for periodontal practice, and in 2002 all the consensus reports of the sessions focused on the clinical and scientific implications of the "status of the science of periodontology" in 2002.[135]

Whilst there were two very relevant narrative reviews[136,137] and some systematic reviews with meta-analyses[53,138] on the use of systemic antimicrobials in periodontitis patients in the scientific literature before the Fourth European Workshop on Periodontology, no evidence-based conclusions or recommendations could be drawn from them. Therefore, Herrera and co-workers' review,[86] prepared for the 4th European Workshop in Periodontology. It examined the clinical effects of adding systemic antimicrobials to subgingival instrumentation (most commonly, scaling and root planing), versus scaling and root planing alone or with a placebo in the treatment of "chronic" or "aggressive" periodontitis, according to the 1999 classification.

This review included only 6-month randomized controlled trials and controlled clinical trials. Owing to their short duration, none of the trials included reported tooth survival or loss, the primary endpoint for periodontal treatment efficacy. Instead, proxy variables—particularly clinical attachment loss and probing depth changes—were chosen as the primary outcomes.[139] The review used these two outcome indicators to compare systemic antimicrobials to scaling and root planing in treating periodontitis. Secondary outcome variables included bleeding on probing, gingival inflammation, plaque levels, tooth loss, new clinical attachment loss, and adverse pharmacologic and microbiological effects.

Because randomization, allocation concealment, and blinding were not well described, and because the 25 studies included revealed substantial heterogeneity in design, patient demographics, follow-up, antimicrobial type, and doses, pooling results was difficult, making it difficult to reach conclusions for clinical practice. These constraints limited the meta-analyses to five. Based on the findings of all the studies that were selected, scaling and root planing in combination with systemic antimicrobials showed improved clinical attachment loss and periodontal probing depth changes, particularly in deep pockets (clinical attachment loss range: 0.2-0.6 mm; probing depth range: 0.2-0.8 mm). The meta-analysis showed that spiramycin decreased probing depth in deep pockets ($n_{studies}=2$, weighted mean difference 0.40 mm, 95% confidence interval 0.1-0.7 mm), whereas amoxicillin with metronidazole increased clinical attachment loss in deep pockets ($n_{studies}=2$, weighted mean difference 0.45 mm, 95% confidence interval: 0.2-0.7 mm). Metronidazole also tended to show improved clinical attachment loss change in deep pockets. In general, the test groups outperformed the control groups for all periodontitis types and antimicrobials.

There was some evidence to show that the effectiveness of antimicrobials may be greater for severe or aggressive forms of periodontitis; however, this was not conclusive. The researchers concluded that systemic antibacterial adjunctive treatment may benefit patients with deep pockets, "progressive" or "active" disease, and specific microbiological profiles. There was evidence of potential side effects, most of which were mild to moderate and gastrointestinal. Additionally, most drugs' microbiological side effects were untested.

The workshop concluded that, based on the limitations of the systematic review and meta-analyses, it was difficult to make any general clinical recommendations regarding the use of systemic antimicrobials as adjuncts to SRP in the treatment of periodontitis.[87] It was suggested that, owing to their side effects and antimicrobial resistance, systemic antimicrobials should not be routinely used. Systemic antimicrobials may improve clinical outcomes for people with deep pockets, "active" sites, "aggressive" periodontitis, or certain microbiological profiles, especially when pockets are deep.

The workshop consensus report made three suggestions for future research:

- To reduce bias, randomized controlled trials need proper randomization, allocation concealment, and a placebo. They should last at least 6 months, and ideally a year. Disease and microbiological profiles must be established, and study populations must be properly selected. Systemic antimicrobial therapy discontinuation rates should be accurately recorded. Additionally, how skilled the operators are, whether anesthesia and what equipment was used, and how long each session lasted must be detailed. Supragingival biofilm control should be monitored and reported. Antimicrobial selection, dosage, duration, and compliance must be assessed.
- Clinical and microbiological side effects must be considered when using systemic antimicrobials based on risk/benefit.
- Long-term research should include tooth survival and clinical attachment loss. Pathogen decrease or elimination should be measured microbiologically.

As explained, this systematic review was published in 2002. One year later, systematic reviews were prepared for the 2003 American Academy of Periodontology World Workshop on Contemporary Science in Clinical Periodontics on host modulation, anti-infective agents, and tissue engineering.[140] One of them, authored by

Haffajee et al,[141] systematically explored the impact of "systemic anti-infective periodontal therapy." Although the approach and methodology were less strict than the European review, allowing for more studies but at a higher risk of bias and performing meta-analyses with substantial heterogeneity among the studies, the conclusions were similar to those achieved 1 year earlier.

3.3.3 | European workshops in the 21st century: Advances in etiology and pathogenesis (2005)

After the 2002 success, the European Federation of Periodontology dedicated the Fifth European Workshop on Periodontology to discussing new research in etiology, pathogenesis, and analytical epidemiology that leads to preventive strategies.[142] It also addressed public health and patient-centered benefits. Unlike the Fourth European Workshop on Periodontology, the fifth workshop's topics could not be covered solely by systematic reviews, so traditional reviews were also accepted, evaluated, and revised. Two of these reviews were important for treating periodontitis with systemic antimicrobials.

Philip Marsh's review[143] examined dental plaque's biological significance as a biofilm and its microbial populations. Biofilm-structured bacteria have increased antibiotic resistance due to their different structural organization and gene expression. Most biofilms host multiple species, leading to physical, metabolic, and molecular interactions. These interactions give bacteria more growth habitats, metabolic diversity and efficiency, and tolerance to environmental stress, antimicrobials, and host defenses. Thus, both the biofilm and microbial interactions between bacteria increase biofilm resistance and tolerance. This increased tolerance to antimicrobial agents also includes those found in toothpastes and mouthwashes.[144,145] For instance, when *Streptococcus sobrinus* was grown as a biofilm, chlorhexidine and amine fluoride had biofilm inhibitory concentrations 300 and 75 times higher, respectively, than the minimal bactericidal concentration (MBC) of planktonic cells.[146] Similarly, 10-50 times the minimal inhibitory concentration of chlorhexidine was required to eradicate *Streptococcus sanguinis* biofilms within 24 h.[147] The age of the biofilm was also found to play a significant role: 72-h *S. sanguinis* biofilms were more chlorhexidine resistant than 24-h ones.[148] Confocal microscopy of in situ–established natural biofilms showed that chlorhexidine affected only the exterior layers of cells in 24- and 48-h plaque biofilms,[149] suggesting quenching at the biofilm surface or a lack of penetration.

Oral bacterial biofilms resist antibiotics like amoxicillin, doxycycline, minocycline, and metronidazole better than planktonic cells do.[150-152] However, resistance depends on the organism, model system, and inhibitor. For instance, biofilms of *P. gingivalis* tolerated 160 times the metronidazole minimal inhibitory concentration for planktonic cells.[153] However, monospecies biofilms of *A. actinomycetemcomitans* or *P. gingivalis* treated with moxifloxacin did not show a similar increase in resistance.[154]

These discoveries have significant implications for periodontal practice, including decreased susceptibility to antimicrobial agents and pathogenic synergism.[155]

A second narrative review, prepared for the Fifth European Workshop by van Winkelhoff and Boutaga,[156] also impacted the use of systemic antimicrobials in the treatment of periodontitis. It focused on periodontal pathogen transmission, which has profound implications for the "true infection" and "exogenous pathogens" concepts.

In 2005, it was accepted that periodontitis tends to run in families. Pathogenic bacterial species, genetic susceptibility, behavioral traits, and environmental factors were thought to cause this. Communicable diseases are contagious infections. Not all pathogenic bacteria or diseases are communicable. For example, *S. sanguinis* infective endocarditis is a noncommunicable disease. Bacterial transmission prevention is crucial to the prevention of communicable diseases in a population. Thus, bacterial transmission research benefits public health. Diseases caused by a single microbial species (like whooping cough and rabies) or a small group of closely related species require transmission studies (such as malaria-causing *Plasmodium* species). The issue of transmission is particularly complicated in multifactorial diseases that are linked to a complex microbiota, such as infectious bowel diseases (Crohn and ulcerative colitis), vaginitis, and periodontal diseases.

Van Winkelhoff and Boutaga[156] investigated periodontal microorganisms' horizontal and vertical transfer. They concluded that most subgingival bacterial species are local to the oral and in 2002 cavity and that periodontitis caused by these bacteria might be viewed as an opportunistic infection. Since *A. actinomycetemcomitans* and *P. gingivalis* are rarely found in periodontal health in Western populations, periodontitis brought on by these bacteria might be viewed as an external, opportunistic infection.

A. actinomycetemcomitans, but not *P. gingivalis*, transmits vertically for localized juvenile periodontitis. Most studies found that *A. actinomycetemcomitans*–colonized children have one or two parents with the same genotype. These findings suggested that parents are the source of transmission. There are an infinite number of genotypes, so finding identical genotypes in family members may be a coincidence. *A. actinomycetemcomitans* vertical transmission was estimated at 30%-60% based on identical genotypes in children and parents. *P. gingivalis* may be transmitted only occasionally vertically by genotyping parent-child isolates.

According to research, spouses can horizontally transmit *A. actinomycetemcomitans* and *P. gingivalis* at 14%-60% and 30%-75%, respectively. The possibility of sibling transmission of *A. actinomycetemcomitans* cannot be ruled out. Periodontal pathogens can permanently colonize a person depending on the frequency of contact, number of organisms, oral health, local microbiota, immunological, and genetic factors. There is some weak evidence that living with a partner with periodontitis affects your periodontal health, but more data are needed to prove this and evaluate strategies for preventing the colonization of *A. actinomycetemcomitans* and *P. gingivalis*. One

potential strategy for the prevention of *A.actinomycetemcomitans*–associated periodontitis was the screening for and inhibition of transmission of specific virulent clones. However, *P.gingivalis* is typically found in adult patients, and its transmission appears to be mostly limited to adults. Thus, periodontal treatment that eliminates or significantly suppresses the pathogen in patients with good oral hygiene may prevent the horizontal spread of *P.gingivalis*.

The Fifth European Workshop on Periodontology concluded that family members could transmit periodontal pathogens, but the clinical effects were unclear.[155] Transmission prevention was also untested.

3.3.4 | European workshops in the 21st century: How systemic antimicrobials should be used (2008)

At the Sixth European Workshop on Periodontology (2008), on contemporary periodontics, five working sessions discussed and debated innovations in periodontal practice, including "antimicrobial therapy in periodontitis," periodontal tissue engineering and regeneration, critical issues in bone regeneration, peri-implant infections, and periodontal diseases and health. Herrera et al[157] performed a systematic review of systemic antimicrobials for periodontitis treatment. It addressed three clinical issues.

The first issue was whether systemic antimicrobials can affect dental biofilms without previous mechanical disruption. As mentioned before, Marsh[143] found that dental plaque behaves like a biofilm, indicating higher antimicrobial resistance. Mature biofilms also resist antimicrobials better. Herrera et al[157] systematically evaluated systemic antimicrobials as a monotherapy for periodontitis. They concluded that systemic antimicrobials as a monotherapy were not supported by the research reviewed, so they should not be advocated. Antimicrobials should only be used with mechanical instrumentation, and only in certain people and conditions owing to their risks.

The second issue was whether nonsurgical or surgical subgingival biofilm instrumentation affects the clinical outcomes of adjunctive antimicrobial therapy. Herrera and colleagues' previous systematic review[86] showed that systemic antimicrobials should be used adjunctively to subgingival instrumentation, but there was still debate on when to use them. The 2008 review by Herrera et al[157] found that there was not enough evidence to prescribe them after surgery and that there was no medical need for prophylactic antibiotics in periodontal surgery. Various earlier reviews suggested adding adjunct antimicrobials to the surgical protocol for subgingival microbial management to improve outcomes. However, a lack of research made this approach questionable.

The third issue was whether adjunctive antimicrobial therapy efficiency depends on subgingival biofilm debridement quality and the order of instrumentation and antimicrobial use. Indirect evidence suggests that debridement quality and antimicrobial prescription timing may affect clinical results. Thus, it was hypothesized that clinical outcomes would improve if the operator was more skilled, the instrumentation was done over a short period of time, and the antimicrobial was given right away. It was suggested that antimicrobials would be more effective if the biofilm was disturbed and had not yet reorganized.

Despite answering the questions, the studies were diverse, and other factors like antimicrobial dose, plaque control, and so on may have affected the findings. Based on this review, the workshop concluded that systemic antimicrobials should only be used in certain patients/conditions (eg, those with aggressive periodontitis, severe or progressing forms) owing to their side effects.[158] These side effects include systemic and microbiological side effects and bacterial resistance issues. Thus, the prescription requires individual assessment. To obtain the best results, the antimicrobial should be given under the safest and most effective conditions. Thus, systemic antimicrobials should be used with mechanical instrumentation in periodontal therapy. There was little evidence to determine the best supplementary instrumentation method (nonsurgical versus surgical). In addition, systemic antimicrobials with periodontal surgery were not supported by evidence. No evidence supported a specific approach for using adjunctive systemic antimicrobials with nonsurgical mechanical instrumentation. Indirect data suggested that antimicrobial intake should start the day instrumentation is finished, which should be done in a short period of time (ideally less than a week) and with an appropriate quality.

The workshop also suggested future research:

- Comparing systemic antimicrobials after scaling and root planing and periodontal surgery in well-designed randomized controlled trials. This should include determining the best phase of periodontal treatment for systemic antimicrobials: nonsurgical, cause-related, reevaluation, or surgical.
- Comparing antimicrobial intake after full-mouth instrumentation within 12-24 h with usual procedures in well-designed randomized controlled trials.
- Determining which periodontitis patients and clinical situations benefit most from systemic antimicrobial therapy, the most effective antimicrobials, doses, and route of administration.
- Randomized controlled trials should assess adverse effects, especially microbiological ones.

3.3.5 | European workshops in the 21st century: European workshops moved to Spain

The Sixth European Workshop was the last with Professor Lang as chair of the Workshop Committee. Mariano Sanz was selected to continue holding the torch, and he decided to move the venue of the workshops from Switzerland to a small palace village in the northern slopes of the mountains north of Madrid: Real Sitio de San Ildefonso, also known as La Granja, in Segovia province, Spain. The first

workshop in La Granja was the Seventh European Workshop on "The biology of periodontal and peri-implant diseases", in November 2010.[159] From 2010 onwards, European workshops were organized on a yearly basis, except in 2015, and on two occasions together with the American Academy of Periodontology (in 2012, dealing with the association of periodontitis and systemic diseases, and in 2017, for the development of the 2018 classification). However, it was not until the 16th European Workshop, the first workshop organized to produce a clinical practice guideline, that systemic antimicrobials regained attention.

The impact of the 2002, 2005, and 2008 European workshops was crucial for the advancement of this topic. However, many randomized controlled trials and systematic reviews were published in parallel.

3.4 | The 21st century: The impact of randomized clinical trials

Many European randomized controlled trials, sometimes in collaboration with other countries, have made significant contributions to the field since 2000, following the 2002, 2005, and 2008 European workshops' research recommendations.

Similar to Section 3.2.3, this section considers randomized controlled trials from the systematic review presented at the 2019 European Workshop[160] (Table 2). The inclusion criteria were more stringent than the 2002 European Workshop,[86] requiring exclusively placebo-controlled, parallel studies of at least 6 months: 34 articles were included, reporting on 28 different studies. As three were published before 2002 and have already been presented,[82,83,125]

TABLE 2 Studies selected by the systematic review on systemic antibiotics, prepared for the 16th European Workshop in Periodontology.[160]

Publication year	References[a]	Author, year	Country	Study duration (months)	Drugs tested
1989	82	Al-Joburi et al (1989)	Canada	6	Spiramycin
1994	83	Bain et al (1994)	Canada	6	Spiramycin
1998	125	Berglundh et al (1998)	Sweden	24	Amoxicillin/metronidazole
2002	161	Rooney et al (2002)	United Kingdom	6	Amoxicillin/metronidazole, amoxicillin, metronidazole
2005	162	Guerrero et al (2005)	United Kingdom	6	Amoxicillin/metronidazole
2008	226	Haas et al (2008)	Brazil	12	Azithromycin
2009	164	Cionca et al (2009)	Switzerland	6	Amoxicillin/metronidazole
2010	227	Mestnik et al (2010)	Brazil	12	Amoxicillin/metronidazole
2010	169	Oteo et al (2010)	Spain	6	Azithromycin
2011	170	Basegmez et al (2011)	Turkey	6	Minocycline
2011	228	Heller et al (2011)	Brazil	12	Amoxicillin/metronidazole
2011	229	Pradeep and Kathariya (2011)	India	9	Clarithromycin
2011	230	Sampaio et al (2011)	Brazil	12	Azithromycin
2012	165	Aimetti et al (2012)	Italy	6	Amoxicillin/metronidazole
2012	231	Casarin et al (2012)	Brazil	6	Amoxicillin/metronidazole
2012	171	Emingil et al (2012)	Turkey	6	Azithromycin
2012	232	Feres et al (2012)	Brazil	12	Amoxicillin/metronidazole, metronidazole
2012	172	Han et al (2012)	Turkey	6	Azithromycin
2012	233	Pradeep et al (2012)	India	6	Ornidazole
2013	234	Preus et al (2013)	Norway	60	Metronidazole
2015	235	Ardila et al (2015)	Colombia	6	Moxifloxacin
2015	236	Harks et al (2015)	Germany	24	Amoxicillin/metronidazole
2016	167	Cosgarea et al (2016)	Romania	12	Amoxicillin/metronidazole
2016	237	Martande et al (2016)	India	12	Azithromycin
2016	238	Taiete et al (2016)	Brazil	6	Amoxicillin/metronidazole
2017	239	Andere et al (2017)	Brazil	6	Clarithromycin
2017	240	Borges et al (2017)	Brazil	12	Amoxicillin/metronidazole
2018	241	Morales et al (2018)	Chile	9	Azithromycin

[a]If more than one reference, only the first publication of the series is quoted.

the present analysis will focus on the remaining 25 studies. Europe was the "world center" of research in this field up until 2005, but since then, and especially since 2008, Brazil has taken over with nine randomized controlled trials. Two more came from South America (Colombia and Chile) and three from India. The remaining 11 studies were performed in Europe. Surprisingly, both the United States and Canada disappeared from the list. Within Europe, Turkey took the lead (three studies), followed by the United Kingdom (two), with one study each being performed in Italy, Germany, Norway, Romania, Spain, and Switzerland.

3.4.1 | The United Kingdom studies on amoxicillin and metronidazole

The first two randomized controlled trials, published in the 21st century, were performed in Bristol[161] and at the Eastman Dental Institute in London.[162]

Before 2002, several studies showed that adjunctive systemic amoxicillin and metronidazole helped treat periodontal diseases. However, these antimicrobials had never been compared individually or together. The Bristol trial examined the adjunctive benefits of amoxicillin and metronidazole alone or combined. This four-arm trial included patients with advanced chronic periodontitis. After quadrant scaling and root planing, all patients received either amoxicillin (250 mg) and metronidazole (200 mg), metronidazole alone, amoxicillin alone, or a placebo three times a day for 7 days. All groups showed improvement in clinical parameters. The amoxicillin plus metronidazole group had the greatest effects, and the placebo group had the smallest. Metronidazole or amoxicillin alone were also better than a placebo. Microbiological results showed that amoxicillin plus metronidazole outperformed a placebo and metronidazole alone for total aerobes and anaerobes after 1 month. The antibiotic groups had fewer *P. intermedia* than the placebo group. This study found that amoxicillin and metronidazole enhanced scaling and root planing treatment of advanced chronic periodontitis.[161]

The most influential study of this decade was a 6-month London study on amoxicillin and metronidazole in generalized aggressive periodontitis.[162] Forty-one participants received a 7-day course of systemic amoxicillin plus metronidazole or a placebo as adjuncts to nonsurgical periodontal treatment in this randomized, placebo-controlled, clinical trial. Clinical and microbiological parameters were measured. Amoxicillin plus metronidazole improved the primary outcome variable more than a placebo did after 6 months. Since that article was published, it has been assumed that amoxicillin plus metronidazole has been almost mandatory for aggressive periodontitis, with consequently empiric drug selection. A secondary analysis almost 10 years later[163] found that the adjunctive antimicrobials in the primary analysis were unaffected by the baseline microbiological state. However, exploratory subgroup analyses showed that baseline *A. actinomycetemcomitans* carriers had better clinical outcomes. Thus, all patients benefited from the evaluated supplementary antibiotic regimen, but those with *A. actinomycetemcomitans* at baseline may benefit more.

3.4.2 | Additional studies on amoxicillin and metronidazole

Amoxicillin and metronidazole were given to chronic periodontitis patients after full-mouth periodontal instrumentation within 48 h, by Andrea Mombelli's group (Geneva, Switzerland),[164] in a 6-month randomized controlled trial. Twenty-five participants received metronidazole and amoxicillin for 7 days; 26 received a placebo. Metronidazole and amoxicillin improved clinical outcomes at 6 months. The test patients had fewer persistent pockets greater than 4 mm and bleeding on probing that required additional treatment. Six months after full-mouth debridement and antibiotics, 0.4 (SD = 0.8) pockets remained, compared with 3.0 (SD = 4.3) in the control group. The protective risk of antibiotics against more than one pocket deeper than 4 mm and bleeding on probing per individual after 6 months was 8.85. These findings indicated that systemic metronidazole and amoxicillin treatment significantly reduced the need for additional treatment.

Aimetti et al[165] at the University of Torino, Italy, studied the clinical and microbiological effects of systemic metronidazole and amoxicillin combined with the one-stage full-mouth disinfection protocol in patients with generalized aggressive periodontitis. The test group received amoxicillin-metronidazole for 7 days, while the control group received a placebo. In addition to clinical parameters, polymerase chain reaction was used to test moderate- and deep-pocket subgingival plaque samples for periodontopathogens. Both regimens improved clinical and microbiological indicators, but the test group had the most positive effects. The test group had better probing depth reductions, clinical attachment loss gains, and *A. actinomycetemcomitans*, *Treponema denticola*, and *T. forsythia* prevalence than the control group.

In 2015, Harks et al[236] questioned whether systemic antibiotics affect periodontitis progression based on several randomized controlled trials showing clinical and microbiological benefits of metronidazole and amoxicillin adjuvant use. In a German multicenter randomized controlled trial of patients with moderate to severe periodontitis, researchers examined the effects of empiric adjunctive systemic amoxicillin and metronidazole for 7 days on clinical attachment loss and the long-term effects of adjunctive antibiotics on periodontitis progression. After 27.5 months, the main outcome was the percentage of sites with further attachment loss of greater than 1.3 mm. Standardized treatment included mechanical instrumentation, antibiotics or a placebo, and 3-month maintenance. Both treatments slowed periodontitis. However, empiric supplementary systemic antibiotics reduced attachment loss slightly more, but significantly compared with placebo. This suggests that therapists should consider the patient's total periodontal disease risk before prescribing adjunctive antibiotics.

Owing to the concerns about antimicrobial resistance development, several European clinical trials sought better treatment regimens or alternatives to systemic antimicrobials to reduce resistance development. Two clinical trials examined the clinical efficacy of shortening systemic antibiotic treatment. The first study examined the efficacy of 3- or 7-day systemic amoxicillin and metronidazole as an adjunct to scaling and root planing in patients with severe chronic periodontitis (one site with probing depth of at least 6 mm per quadrant) undergoing nonsurgical periodontal treatment.[166,167] A total of 102 patients were randomly divided into three equal-sized groups and treated with either scaling and root planing within 24 h plus placebo (group A), scaling and root planing plus amoxicillin/metronidazole (both 500 mg, three times daily) for 3 days (group B), or scaling and root planing plus placebo (group C). Probing depth, clinical attachment loss, bleeding on probing, full-mouth plaque, and gingival bleeding index were measured. The main outcome variable was the number of sites with probing depth of 6 mm or more. All three treatment procedures showed statistically significant improvements over baseline for all clinical measures at 3, 6, and 12 months. At 6 months, group B and group C had statistically significant reductions in the mean number of sites with probing depth greater than 6 mm compared with the placebo group. Only the 3-day antibiotic group had significantly fewer sites with probing depth of at least 6 mm at 12 months. The three treatment groups reduced probing depth of at least 6 mm sites similarly. At 12 months, significantly more patients in both antibiotic groups had a lower risk of disease progression (four sites or fewer with probing depth of at least 5 mm) than the placebo group. In severe chronic periodontitis patients, nonsurgical periodontal therapy with systemic amoxicillin/metronidazole for 3 or 7 days improved clinical outcomes more than nonsurgical therapy alone, regardless of duration.

In a more recent study, not included in the 2020 systematic review, the same group of researchers compared a 3-day systemic antibiotic protocol, adjunctive to subgingival instrumentation, with a 7-day protocol in aggressive periodontitis (stage III/IV grade C).[168] Fifty systemically healthy patients were randomly assigned to group A (subgingival instrumentation plus amoxicillin/metronidazole, 500 mg of each, three times daily for 3 days, followed by placebo three times daily for 4 days) or group B (same protocol, but 500 mg of each drug three times daily for 7 days). Clinical, microbiological, and immunological parameters were assessed at baseline and 3 and 6 months, and patients reported outcomes 2 weeks later. The proportion of residual sites with probing depth of at least 6 mm at 6 months was the primary outcome variable. The 3-day antibiotic regimen was noninferior to the 7-day antibiotic protocol for the primary outcome variable. Both antibiotics had comparable clinical benefits. Regardless of therapy, all periodontopathogens and proinflammatory host-derived markers were significantly reduced. These findings suggest that, in patients with stage III/IV, grade C periodontitis, a 3-day systemic administration of amoxicillin and metronidazole adjunctive to subgingival instrumentation may result in noninferior clinical outcomes after 6 months with fewer adverse events than a 7-day protocol.

3.4.3 | Studies on azithromycin and minocycline

Systemic azithromycin was added to scaling and root planing to treat chronic periodontitis caused by *P. gingivalis* in Spain in 2010.[169] *P. gingivalis*–periodontitis patients were randomized to test or placebo groups. The experimental group received scaling and root planing and 500 mg of azithromycin daily for 3 days, while the control group received scaling and root planing and a placebo. At baseline, 1, 3, and 6 months, microbiological and clinical data were collected. Systemic azithromycin was more effective than scaling and root planing plus placebo at reducing *P. gingivalis* detection in *P. gingivalis*–periodontitis patients.

In Istanbul, Turkey, Basegmez et al[170] examined the clinical and immunologic effects of systemic minocycline on chronic periodontitis. Besides nonsurgical periodontal therapy, 20 patients received systemic minocycline for 2 weeks, and another 20 received a placebo. Clinical parameters and gingival crevicular fluid were collected at baseline and the first, third, and sixth months. Both groups' measurements improved significantly. Minocycline significantly reduced probing depth, relative clinical attachment loss, matrix metalloproteinase-8, and prostaglandin E_2 levels at all times. They concluded that minocycline improved periodontal therapy and host-modulated inflammatory mediators.

Over a 6-month period at Ege University in Izmir, Turkey, azithromycin was tested in combination with nonsurgical periodontal therapy on clinical and microbiological parameters, as well as matrix metalloproteinase-8 and tissue inhibitor of metalloproteinases-1 levels in gingival crevicular fluid, in patients with generalized aggressive periodontitis.[171] This randomized controlled trial randomly assigned aggressive periodontitis patients to azithromycin (500 mg once daily for 3 days) or a placebo. Clinical parameters, gingival crevicular fluid samples, and microbiological samples were collected from single-rooted teeth with probing depth greater than 6 mm. Clinical, microbiological, and gingival crevicular fluid matrix metalloproteinase-8 levels improved over 6 months. After 1 month the azithromycin group had more deep pockets resolved than the placebo group did. At 6 months, neither group differed. They concluded that, in patients with generalized aggressive periodontitis, adjunctive azithromycin did not improve clinical, microbiological, or gingival crevicular fluid biological markers compared with nonsurgical periodontal treatment.

Simultaneously, the group released the results of a similar study involving severe generalized periodontitis patients.[172] The design resembled that of the previously described study.[171] In this trial, both the azithromycin and placebo groups improved clinical indicators similarly and statistically significantly. *A. actinomycetemcomitans*, *P. gingivalis*, *T. forsythia*, *P. intermedia*, and total bacteria decreased significantly over the 6-month period in both groups, whereas *Fusobacterium nucleatum* was reduced significantly in all visits in the azithromycin group and was lower than in the placebo group. At posttreatment and 2-week visits, azithromycin and placebo reduced matrix metalloproteinase-8 levels significantly. These findings showed that adjunctive azithromycin did not improve nonsurgical periodontal treatment in patients with severe generalized chronic periodontitis, similar to aggressive generalized periodontitis.

3.4.4 | A long-term study on metronidazole

In Oslo, Norway, Preus et al[234] tested the hypothesis that traditional scaling and root planing or same-day full-mouth-disinfection with or without metronidazole had the same 5-year clinical outcome. After a 3-month oral hygiene phase, 184 periodontitis patients were randomly assigned to one of four treatment regimens: full-mouth disinfection plus metronidazole or placebo, scaling and root planing plus metronidazole or placebo. A biannual supportive periodontal care followed active therapy. A total of 161 patients recorded clinical attachment loss, probing depth, bleeding on probing, and plaque over 5 years. Full-mouth disinfection decreased the highest clinical attachment loss recording by 0.12 mm, whereas metronidazole increased it by 0.17 mm (not statistically significant). The highest probing depth readings were 0.00 mm and 0.05 mm, respectively. Although single-level analyses showed statistically significant differences, they could not be confirmed by other analyses and were too small to recommend metronidazole for severe periodontitis treatment owing to its risk of adverse effects on patients and the environment.

4 | EVALUATION OF SYSTEMIC ANTIBIOTICS IN THE TREATMENT OF PERIODONTAL DISEASES: CONTEMPORARY PERSPECTIVES

4.1 | The impact of systematic reviews

Since the turn of the millennium, European researchers have published a variety of systematic reviews, with or without meta-analysis, on the adjunctive effects of systemic antimicrobials in periodontitis treatment. Some of the ones published in the last 10 years are quoted here.[160,173–197] Although there are more published reviews than primary research, it would be impractical to characterize all of them. It is essential to recognize that systematic reviews and meta-analyses are becoming increasingly important in the context of health care.

Strong research can help health-care decision-makers follow best practices and eliminate variations in care. However, incorporating research into clinical practice is time-consuming, so clinicians need easy access to evidence.[198,199] In an ideal world, clinical decisions should be based on the latest evidence. Health-care professionals would have to read too many articles each day to keep up with the growing number of health research publications. Systematic reviews aim to solve this problem. They synthesize research to inform and aid this process.[198,200,201] This improves evidence access.

Clinical practice guidelines are often based on systematic reviews.[199] However, despite their importance, there is currently no evidence that scientifically shows the true impact of systematic reviews on daily clinical practice. Funding agencies can require a systematic review as a prerequisite for conducting additional research in order to establish that there is a need for it, and health-care policymakers do use systematic reviews to direct health care.[202] For example, in Belgium, the Federale Overheidsdienst Service Public Fédéral public health organization used systematic reviews and meta-analysis to develop evidence-based practice guidelines for a more effective dentist antibiotic policy.[203] Belgian outpatient antibiotic prescribing ranked eighth in Europe in 2018. Dentists prescribed 6% of these antibiotics. The Belgian Health Care Knowledge Centre, an independent research center that provides scientific advice on topics related to health care, published a report in 2019 proposing a more effective antibiotic policy.[204] Public authorities, universities, professional associations, and others request the topics for the Belgian Health Care Knowledge Centre and, one of these was a dentist's evidence-based practice guideline. This guideline aims to reduce variability between dental practices and improve patient-dentist communication, such as explaining when antibiotics are not appropriate. Belgian Health Care Knowledge Centre researchers collaborated with a multidisciplinary group of clinicians and Belgian dental faculty to develop this guideline.[203] Dentists, national and international scientific and professional associations, and government agencies like the Rijksinstituut voor Ziekte- en Invaliditeitsverzekering, the Medicine Agency, and the Belgian Antibiotic Policy Coordination Committee are implementing the guidelines (Belgian Commission for the Coordination of Antibiotics Policy). Another example is the European Federation of Periodontology S3-level evidence-based treatment guideline for stages I-III periodontitis implementation in Taiwan[205] and China.[206]

However, the clinician must understand the structure and characteristics of systematic reviews and meta-analyses to accurately and clinically apply their findings.[199] Systematic reviews use explicit methods to limit bias, to draw trustworthy and accurate conclusions, to easily deliver the information needed to health-care providers, researchers, and policymakers, to help reduce the time it takes to implement research findings, to improve results generalizability and consistency, and to improve accuracy.[207] Like any other type of research, the value of a systematic review depends on what was done, what was found, and how well the findings were reported. Systematic reviews, like other publications, have varying reporting quality, making it hard for readers to assess their pros and cons.[202] Systematic reviews and meta-analyses are the most reliable methods for answering a research question, but they have their drawbacks. Location and selection of studies, heterogeneity, loss of important outcomes, inappropriate subgroup analyses, conflict with new experimental data, and duplication of publication are some of these limitations.[199]

4.2 | The impact of the European Federation of Periodontology clinical practice guideline

4.2.1 | The systematic review on systemic antimicrobials

The 16th European Workshop on Periodontology (2019) aimed to develop an S3-level clinical practice guideline for stages I-III periodontitis. The European Federation of Periodontology prepared this clinical practice guideline following the methodological guidelines of the Association of Scientific Medical Societies in Germany and

the Grading of Recommendations Assessment, Development, and Evaluation. The rigorous and transparent process included synthesis of relevant research in 15 specifically commissioned systematic reviews, evaluation of the quality and strength of the evidence, formulation of specific recommendations, and consensus by leading experts and a wide range of stakeholders. The clinical practice guideline used a preestablished stepwise approach to treat periodontitis (stages I, II, and III), which is gradual and includes a variety of therapies.

Teughels et al[160] reviewed the adjunctive effect of systematic antimicrobials in periodontal therapy. This review included only placebo-controlled, parallel, double-blind studies with at least 6 months of follow-up and analyzed antimicrobials separately to overcome some of the limitations of previous reviews. Most of them only examined mean changes in full-mouth probing depth, clinical attachment loss, and bleeding on probing, which may hide the most clinically significant effects of systemic antimicrobials in deeper sites. Full-mouth probing depth, clinical attachment loss, and bleeding on probing often have small differences, making clinical decision-making difficult. The review included data on full-mouth probing depth decrease, clinical attachment loss gain, initial moderately deep and deep pockets, pocket closure percentage, and residual pockets. The latter two outcomes were not included in previous systematic reviews or meta-analyses. Twenty-eight randomized controlled trials (34 papers) were included, in which antimicrobials were used as adjuncts to subgingival instrumentation for up to 6 months and 1-year posttreatment. The meta-analysis of 24 randomized controlled trials showed that systemic antimicrobials in the active phase of periodontal therapy increased full-mouth probing depth reduction (weighted mean difference 0.448 mm, primary outcome variable) and clinical attachment loss gain (weighted mean difference 0.348 mm, secondary outcome variable) at 6 months, compared with the control groups. Their benefits lasted at least 1 year (probing depth: weighted mean difference 0.485 mm; clinical attachment loss: weighted mean difference 0.285 mm, $P < 0.05$). However, most trials had a 6-month follow-up, which hampered this analysis.

Since evidence quality varied across antimicrobials, their effects were assessed separately. Overall, metronidazole plus amoxicillin was the most effective treatment. Adjunctive metronidazole plus amoxicillin outperformed debridement alone in all clinical outcomes, including probing depth reduction and clinical attachment loss gain in the full mouth and initially moderately deep and deep pockets, percentage of pocket closure (from probing depth of at least 4 mm to periodontal probing depth of at least 3 mm), frequency of 4, 5, 6, and 7 mm pockets, and sites with bleeding on probing.

The evidence supporting the advantages of the adjunctive use of metronidazole and azithromycin was rated as moderate, although the results for metronidazole were more reliable. Despite the fact that only two studies with a low risk of bias evaluated metronidazole, the results were consistent in demonstrating the benefits of this antimicrobial in reducing mean PD in the full mouth (at 1 year), in moderately deep and deep sites (at 6 months and 1 year), and in improving the percentage of pocket closure at 6 months and 1 year of follow-up. In contrast, the seven studies on azithromycin yielded mixed results. The overall clinical impact showed a statistically significant increase in full-mouth clinical attachment loss in favor of azithromycin at 6 months, but the studies' findings varied greatly on this parameter. The clinical impact on full-mouth clinical attachment loss was sustained at 1 year, and azithromycin significantly lowered probing depth in initially deep pockets. The few 1-year studies were inconsistent: for full-mouth clinical attachment loss, two of the three trials with data showed little or no benefit for this antibiotic (0.02 or 0.15 mm), whereas a single study with a high risk of bias had the greatest impact (1.0 mm).

Clarithromycin, minocycline, and moxifloxacin had limited evidence. These antimicrobials had no additional benefits at 6 months, and 12-month data were unavailable.

Within the limitations of this systematic review, systemic antimicrobials, specifically metronidazole plus amoxicillin, as adjuncts to subgingival instrumentation, result in statistically significant greater probing depth reductions, higher percentages of pocket closure, lower frequencies of pockets equal or deeper than 4, 5, 6, and 7 mm, clinical attachment loss gains, and bleeding on probing reductions. The additional PD reduction and CAL gain elicited by metronidazole plus amoxicillin, and to a lesser extent by metronidazole and azithromycin, are more pronounced in that are initially deep than moderately deep. These clinical effects are maintained up to 12 months after their use. There is currently no evidence above 2 years of follow-up for the benefits of systemic antimicrobials as adjuncts to SRP. There were also no indications that the effect of systemic antimicrobials is different between aggressive and chronic periodontitis patients. Among the different types of systemic antimicrobials, the use of metronidazole plus amoxicillin was associated with the largest frequency of side effects. Metronidazole and azithromycin had a significant impact on some outcome measures, but smaller than metronidazole plus amoxicillin in terms of magnitude.

4.2.2 | The clinical practice guideline

As mentioned, the European Federation of Periodontology developed an S3-level clinical practice guideline for periodontitis (stages I-III) in 2020 based on strictly validated procedures, providing a uniform and evidence-based approach.[14] The recommendations stressed the importance of using scientific data to support clinical decisions when treating periodontitis stages I to III. Thus, its main objective was to promote the best evidence and/or expert consensus-based recommendations for periodontal care therapies. These recommendations aim to improve European periodontal care, reduce tooth loss from periodontitis, and improve systemic health and quality of life. A recommendation on the use of systemic antibiotics with subgingival instrumentation was included in the guideline (Figure 3): "Due to concerns about patient's health and the impact of systemic antibiotic use on public health, its routine use as an adjunct to subgingival debridement in patients with periodontitis is not

recommended." Thus, despite the clinical benefits observed in the systematic review, their use is strongly discouraged. This was based on widespread concerns about antibiotic misuse and the emergence of antibiotic resistance. The overall use of antimicrobials for the patient as a whole as well as for public health are taken into account in benefit versus harm analyses. Systemic antibiotics have long-term effects on the fecal microbiome, including antimicrobial resistance gene upregulation. Its systematic usage as a supplemental treatment for subgingival instrumentation in patients with periodontitis is therefore not advised due to concerns about the patient's health and the effect of systemic antibiotic use on public health. However, given the information at hand, its adjunctive usage for particular patient types may be taken into consideration (eg, generalized periodontitis stage III in young adults).

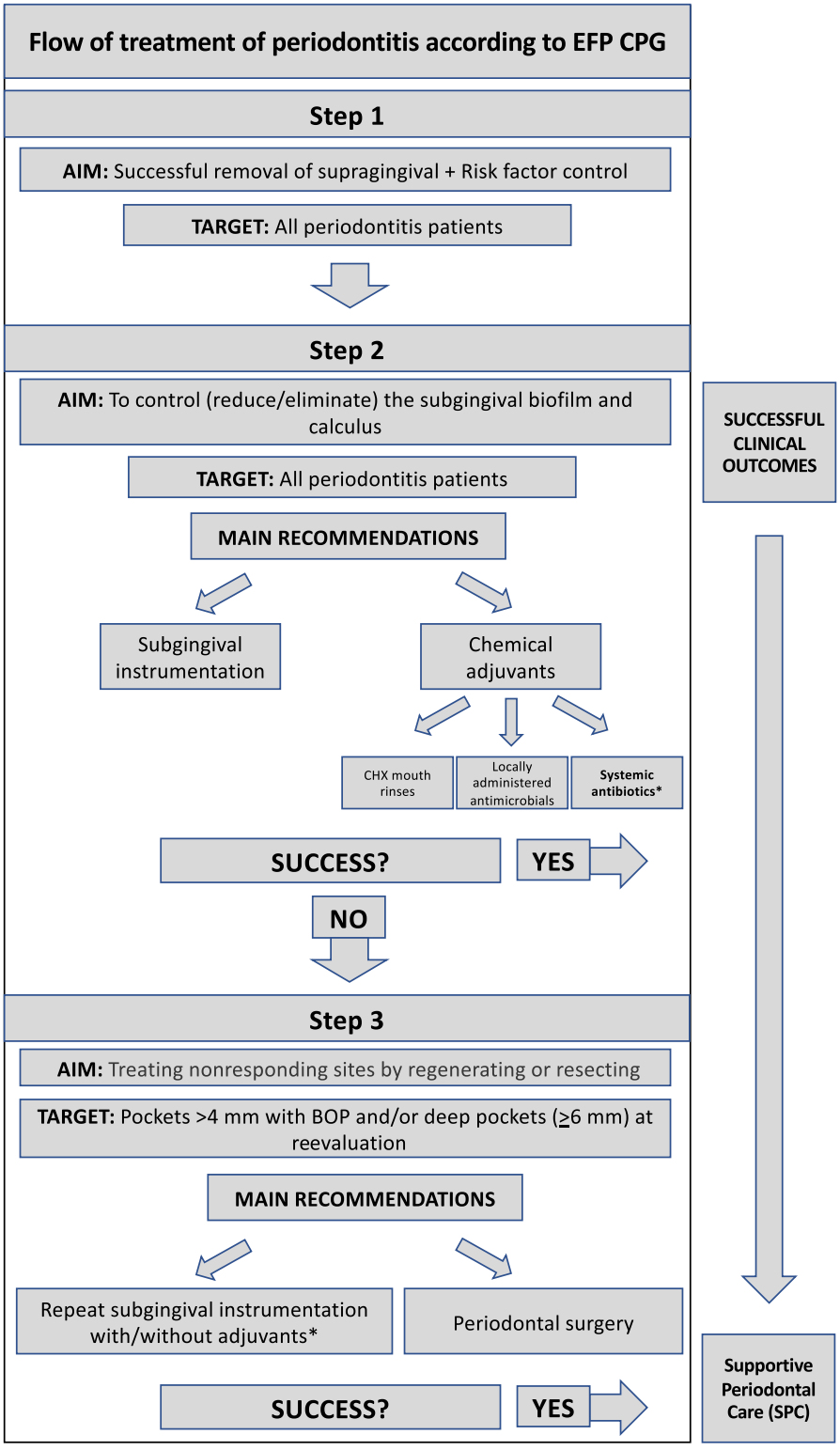

FIGURE 3 Treatment sequence according to the European Federation of Periodontology (EFP) clinical practice guideline (CPG) for the treatment of periodontitis in stages I-III.[14] BOP, bleeding on probing; CHX, chlorhexidine. *The adjunctive use of specific systemic antibiotics may be considered for specific patient categories (eg, generalized stage III periodontitis in young adults).

Thus, the second part of the recommendation is open: "The adjunctive use of specific systemic antibiotics may be considered for specific patient categories (e.g. generalized periodontitis stage III in young adults)." For "specific systemic antibiotics," systemically administered antimicrobials as an adjuvant to subgingival debridement improved outcomes statistically, but only a small subset of antimicrobials did so. Metronidazole plus amoxicillin reduced probing depth better at 6 months ($n_{studies}=8$; weighted mean difference 0.43, 95% confidence interval 0.36-0.51). In the 12-month data analysis, metronidazole plus amoxicillin ($n_{studies}=7$; weighted mean difference 0.54, 95% confidence interval 0.33-0.74) and metronidazole ($n_{studies}=2$; weighted mean difference 0.26, 95% confidence interval 0.13-0.38) had a significant adjunctive effect. Metronidazole plus amoxicillin and metronidazole closed a statistically significant percentage of pockets at 6 and 12 months. Metronidazole plus amoxicillin significantly increased clinical attachment loss gain and decreased bleeding on probing at 6 and 12 months. Moreover, metronidazole plus amoxicillin had a greater effect on probing depth decrease and clinical attachment loss gain in initially deep pockets than in moderately deep pockets. Systemic antibiotics as a supplement to subgingival instrumentation over 12 months were not studied. The studies had low heterogeneity and bias risk and strong consistency. Compared with subgingival instrumentation, probing depth reduction was 40%-50% greater. The metronidazole and amoxicillin combination had the greatest clinical effects, but it also had the most side effects.

5 | AND THE FUTURE?

Systemic antimicrobials used with subgingival instrumentation have been discussed previously. They may improve clinical outcomes for at least 1 year, according to convincing, high-quality evidence.[160] However, the use of antimicrobials, especially systemic ones, is controversial, especially given the dramatic rise in antimicrobial resistance and its extremely negative consequences. Thus, exploring the future of systemic antibiotics in periodontitis treatment requires weighing the pros and cons and identifying a critical need.

5.1 | The negative consequences of using systemic antimicrobials

Systemic antimicrobials, like all drugs, have side effects. They are the main cause of antimicrobial resistance, so rational and limited use is mandatory.

Unwanted or side effects are common consequences of systemic antimicrobial intake. In a recent systematic review[160] of randomized controlled trials, 25 of the studies included reported adverse events and/or patient reported outcomes, and 21 reported some of the following events: "nausea/stomach upset/vomiting," "diarrhea/gastrointestinal disturbance," "metallic taste," "oral ulceration," "dizziness," "fever," "headache," "periodontal abscess," "general unwellness (eg, irritability)," and "allergic reactions." The study groups using amoxicillin and metronidazole had the highest frequency of those events (0%-36.36%) compared with the placebo group (0%-20%).

Drugs vary in adverse event frequency and severity:[208] For penicillins, they are usually mild and in frequent, except for some hypersensitivity reactions; tetracyclines and macrolides are also very safe, with some gastrointestinal problems; clindamycin and metronidazole, although generally safe, have been associated with antibiotic-associated colitis and other, less relevant, gastrointestinal problems, as well as nausea, headache, anorexia, and vomiting, especially when combined with alcohol (known as the Antabuse-like effect).[209] Peripheral neuropathies and some carcinogenic risks have been suggested.[210]

Systemic antimicrobial intake generates resistant strains and global antibiotic resistance. Alexander Fleming stated this in his 1945 Nobel Prize speech. Selective pressure from widespread and unconscious use accelerates resistance development. Bacterial resistance and the lack of new antimicrobial drugs are major public health issues that could threaten global health.[211] To illustrate this, a report requested by the European Centre for Disease Prevention and Control made an estimation of the magnitude of the problem in the European Union and in the European Economic Area:[212] in 2015, 671 689 infections with antibiotic-resistant bacteria were estimated, with 33 110 attributable deaths and 874 541 disability-adjusted life-years. The burden was highest in infants and older people, and it had increased since 2007.

Systemic antimicrobial overuse and misuse lead to the development of specific drug-resistant and multidrug-resistant bacteria.[211,213] In populations with higher frequencies of systemic antimicrobial exposure, periodontal pathogens have higher antimicrobial resistance profiles.[214-216] Based on the foregoing, systemic antimicrobial prescriptions should be controlled and used optimally. The "Proposals for EU Guidelines on the Prudent Use of Antimicrobials in Humans"[217] were created for this purpose. Among the general recommendations made for all health professionals, the following are listed:

- "Ensure that appropriate microbiological samples are taken before starting antimicrobial treatment.
- Avoid antimicrobial combinations unless there is a clear indication outlined in the guidelines.
- Select an antimicrobial in accordance with relevant guidelines, at an appropriate dose, for the shortest effective duration and with appropriate route of administration (preferably oral if possible).
- Select an antimicrobial with a spectrum of activity as narrow as possible."

Although, to date, there is no compelling evidence to support the need for microbiological diagnosis testing to prescribe systemic adjunctive antibiotics in periodontal treatment, more research in this area should be conducted. Similarly, other systemic drugs should be

investigated as alternatives to the combination of metronidazole and the broad-spectrum amoxicillin.

5.2 | The need for systemic antimicrobials in the treatment of periodontitis

As explained in the Section 1, systemic antimicrobials may help overcome mechanical instrumentation therapy's limitations (deep pockets, furcation lesions, vertical defects, inexperienced operators) and drawbacks (dentin hypersensitivity, gingival recession).[218,219] These may explain why some sites or patients do not respond well to mechanical periodontal treatment.[17] In addition, the 2018 classification characterized grade C periodontitis patients with a "lack of expected response to standard bacterial control therapies."[1,20]

Thus, it is obvious that something extra may be needed in some patients/sites, guiding research on alternative or adjuvant therapeutic procedures,[21-23] such as different treatment strategies (full-mouth disinfection), debridement approaches (lasers, antimicrobial photodynamic therapy), or adjunctive therapies (antimicrobials, probiotics, anti-inflammatory drugs, antioxidant micronutrients).[24]

The critical evaluation of the available research on new treatment strategies,[16] alternative debridement approaches,[220] adjunctive nonantimicrobial,[221] and antimicrobial therapies[28,160] yields few clinically useful recommendations, as only instrumentation within 24 h and antimicrobials were not discarded (either not recommended or not suggested) by the European Federation of Periodontology clinical practice guideline.[14] Therefore, local and systemic antimicrobials are the only options (qualified with *may be considered*) in cases where something other than the *standard* approach is needed (eg, grade C periodontitis, which has a characteristic of "lack of expected response to standard bacterial control therapies").[14]

But Section 4.1 also suggests that we should stop using systemic antimicrobials once we have alternatives. In the meantime, these drugs should be used only when necessary for treatment success. For that, advances in etiology, pathogenicity, and technology give hope to finding the right patient, drug, and timing.

The advances in our knowledge of etiology and pathogenicity may change our microbiological targets. As reviewed, those targets were the whole subgingival microbiota (when using antimicrobials empirically and following the "nonspecific plaque hypothesis") or specific periodontal pathogens like spirochetes, *A. actinomycetemcomitans*, or *P. gingivalis* (when using microbiological sampling and following the "specific plaque hypothesis" or "true infection" concept). Today, the focus is on subgingival biofilm dysbiosis, but some targets in the subgingival microbiome, such as "keystone" pathogens, have been clearly identified.[222,223]

Advanced technologies can improve knowledge and understanding and help develop personalized medicine approaches, which are essential for identifying patients who will benefit most from an adjunctive systemic antimicrobial and which one to use. Although unsupported by literature,[184] microbiological sampling, culture, polymerase chain reaction, and deoxyribonucleic acid-deoxyribonucleic acid checkerboard hybridization were used to guide treatment decisions in the past, omic technologies, including microbiome analyses, will guide individual periodontal therapy in the future.

6 | SUMMARY AND CONCLUSIONS

Antimicrobials were first suggested for periodontal diseases treatment over 100 years ago.[39,40] However, a proper scientific evaluation could only begin when it was convincingly shown that systemic antimicrobial intake provided acceptable drug levels in crevicular fluid[41] or in saliva.[42] In the late 1980s, it was suggested that their use could be justified for three reasons: (a) controlling difficult bacterial targets, such as those that invade periodontal tissues or hard-to-reach areas; (b) reducing the need for periodontal surgery; and (c) improving treatment results in terms of new attachment and/or periodontal regeneration.[46]

In this narrative review, European contributions to the evaluation of the use of systemic periodontal antimicrobial therapy are discussed. The first clinically significant European studies were published in the 1970s and 1980s, following US pioneering research in the 1960s and 1970s. In the 1990s, Europe led the field with many important studies, including the evaluation of the combination of metronidazole and amoxicillin. Europe is not leading the performance of clinical trials in the 21st century, but its workshops and clinical practice guidelines are highly relevant.

Historically, periodontitis was considered an infection, and specific pathogens were essential, so treatment approaches were developed and tested based on this view, and patients were selected based on microbiological information. Europe reported the first dual antibiotic therapy (suppression of *A. actinomycetemcomitans* using amoxicillin and metronidazole), as in other fields of medicine (suppression of *Helicobacter pylori*, treatment of tuberculosis, treatment of sepsis due to brain or abdominal abscesses). *A. actinomycetemcomitans* suppression was associated with significantly improved clinical outcomes.

Thus, systemic antimicrobials used in periodontal therapy are typically antibiotics that specifically (or also nonspecifically) target bacteria in subgingival biofilms. Among those, some antibiotics have garnered more attention:

- Historically, tetracyclines were one of the first antibiotics to show acceptable levels in crevicular fluid and were used to treat periodontitis. However, controlled studies failed to demonstrate significant and relevant advantages when used as a supplement to periodontal therapy. A search for substitute agents was required.
- Metronidazole was created to treat protozoal infections (trichomoniasis and amebiasis). With knowledge of the specific plaque hypothesis in mind, its effect on spirochetes and gram-negative, stringent anaerobes sparked curiosity. In the 1980s, this antibiotic

was studied because these bacteria were found in the microbiological profiles of several periodontal conditions, including necrotizing forms. Walter Loesche and colleagues conducted experiments to evaluate systemic metronidazole as an adjuvant to subgingival instrumentation and address clinical issues like dosage, timing, and compliance.

- Owing to their relevance in the management of serious, life-threatening illnesses, penicillins were deemed inappropriate for the treatment of periodontitis. Macrolides, which target mostly gram-positive bacteria, were also deemed inappropriate for the treatment of periodontitis. Azithromycin was an exception owing to its suggested specific action against *P. gingivalis* and *A. actinomycetemcomitans*, as well as its higher concentrations in inflammatory tissues.
- Several other drugs, like kanamycin, vancomycin, and clindamycin, have also been evaluated.

Although the initial developments in this field were undertaken in the United States, in the 1990s, Europe started to be the most important region for the study of systemic antimicrobials, for at least two decades, with numerous publications reporting randomized controlled trials and systematic reviews. Among the most important contributions, Van Winkelhoff and coworkers evaluated the use of amoxicillin and metronidazole to specifically target *A. actinomycetemcomitans* and supported this with in vitro and in vivo studies.

Another contribution to European periodontology was the European workshops on periodontology, organized and held on the basis of a collection of meticulously written position papers. With the turn of the century, however, the workshops of the 21st century underwent a significant transformation, since systematic reviews of periodontal practice gained popularity. The European Federation of Periodontology initiated the foundation-building process for periodontal practice. The systematic reviews prepared for the workshops attempted to include the strongest data, which was often drawn from randomized controlled trials. At the fourth, fifth, and sixth workshops, the adjunctive use of systemic antimicrobials was considered. These workshops concluded that:

- Dental plaque is a microbial biofilm with increased resistance and tolerance to antimicrobials. Not only the biofilm itself but also the microbial interactions between different bacteria contribute to the increased resistance and tolerance in biofilms.
- Transmission of periodontal infections between family members has been demonstrated; however, the clinical ramifications are not well understood.
- It is difficult to offer broad therapeutic recommendations on the adjunctive use of systemic antimicrobials with scaling and root planing in the treatment of periodontitis.
- Owing to their adverse effects and the rise in antimicrobial resistance, systemic antimicrobials should not be utilized routinely.
- In patients with *active* sites, *aggressive* forms of periodontitis, severe and progressive forms of periodontitis, or with certain microbiological profiles, systemic antimicrobials application may sometimes be justified.
- Systemic antimicrobials must be delivered under conditions believed to be safest and most effective in order to achieve the most desirable results. They should be used as adjuncts to mechanical instrumentation, usually nonsurgically, intake should begin on the day that debridement is completed, and debridement should be performed in a short period of time (preferably less than a week) and with an adequate level of quality.

In 2019, the 16th European Workshop on Periodontology planned to develop a clinical practice guideline for the treatment of stages I-III periodontitis at the S3 level. The clinical advice stated that "because of concerns regarding patient health and the effect of systemic antibiotic use on public health, its routine use as an adjuvant to subgingival debridement in patients with periodontitis is not indicated."[14] Despite the therapeutic benefits reported in the systematic review,[160] a strong recommendation against the use of these drugs was provided. This is due to growing concerns regarding antibiotic abuse and the development of antibiotic resistance. In benefit-to-harm evaluations, the overall use of antimicrobials for the patient and for public health should be taken into account. The second portion of the advice was open-ended: "The supplementary use of particular systemic antibiotics may be considered for certain patient categories (such as stage III periodontitis in young people)."[14]

It should be highlighted that the antimicrobial resistance profiles of periodontal bacteria are greater in populations with higher frequencies of exposure to systemic antimicrobials.[214-216] The significance of this fact is that it is prompting calls for measures to control systemic antibiotic prescriptions and, when prescriptions are necessary, to use them under optimal settings.

As of now, local and systemic antimicrobials are the only available alternatives (qualified with a "may be considered" in the clinical practice guideline) in the specific cases where something other than the "standard" approach is required (for instance, in grade C periodontitis, a characteristic is "lack of expected response to standard bacterial control therapies"). However, whenever alternatives are available, it would be prudent to discontinue the use of antimicrobials, particularly those administered systemically. In the interim, efforts should be made to limit the use of these medications to situations in which their usage is crucial to the effectiveness of the treatment. For this reason, breakthroughs in the understanding of etiology and pathogenicity, as well as the development of new technologies, provide extra promise for identifying the optimum patient, medicine, and timing.

In conclusion, Europe and its researchers have significantly contributed to the use of systemic antimicrobials in the treatment of periodontitis. This was done not only by investigating different types of systemic antimicrobials but also by seeking the most optimal settings for their use. On the other hand, European researchers are taking the lead in limiting the use of systemic antimicrobials by exploring alternatives and guiding clinical practice by providing guidelines.

CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest with respect to this study.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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