The use of chemical and pharmaceutical adjunctive therapies in the treatment of peri-implant mucositis (PiM): a narrative review

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Objectives: Peri-implant mucositis is a reversible inflammatory condition that may progress to peri-implantitis if untreated. Professional mechanical plaque removal (PMPR) is the standard therapy, although complete resolution is not always achieved. This review aimed to evaluate the effectiveness of chemical and pharmacologic adjunctive therapies to PMPR in peri-implant mucositis management. **Method and materials:** A literature search was conducted in PubMed and Scopus up to March 2025. Randomized controlled trials including adult patients with peri-implant mucositis, reporting bleeding on probing changes, and with a minimum follow-up of 3 months were included. Nine randomized controlled trials (414 patients) were qualitatively analyzed. **Results:** PMPR alone resulted in significant reductions in bleeding on probing and probing depth, but complete disease resolution was inconsistent. Adjunctive therapies, including chlorhexidine, local antibiotics, sodium hypochlorite, probiotics, and bioactive agents, showed intra-group improvements. However, additional benefits over PMPR alone were limited and often not statistically significant. Study heterogeneity in diagnostic criteria, outcome definitions, and treatment protocols limited comparability. **Conclusions:** PMPR remains the gold standard for peri-implant mucositis treatment. Adjunctive therapies may provide additional clinical benefits in selected cases, but their routine use is not supported by consistent evidence. Standardized randomized controlled trials with long-term follow-up are needed.
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Keywords: adjunctive therapy, adjuvant therapy, bleeding on probing, PiM

Peri-implant mucositis (PiM) is a reversible biofilm-related inflammatory lesion of the soft tissues around implants without bone loss beyond the crestal bone level changes resulting from initial remodeling.[1,2] Clinical signs include the presence of bleeding (ie, more than one spot at a location around the implant or the presence of a line of bleeding or profuse bleeding at any location), erythema, swelling, and/or suppuration without increase in probing depth (PD).[2]

The disruption of host-microbial homeostasis at the implant–mucosa interface is considered the primary factor contributing to PiM development, while biofilm accumulation, smoking, and radiation therapy are related to the onset and progression of the disease.[2]

Conversely, peri-implantitis is defined as an inflammation of the peri-implant mucosa with concomitant and progressive loss of supporting bone, based on the radiographic bone level assessment at 1 year following the delivery of the prosthetic crown. Peri-implantitis is clinically characterized by bleeding on probing (BoP) and/or suppuration, increased PD, and/or recession of the mucosal margin, in addition to radiographic bone loss compared with previous examinations.[3-5] In the absence of previous clinical and/or radiographic data, implants with bone loss ≥ 3 mm and/or PD ≥ 6 mm in conjunction with profuse bleeding are considered affected by peri-implantitis.[6]

The primary etiologic factor for peri-implantitis onset is represented by the accumulation of biofilm, while a history of

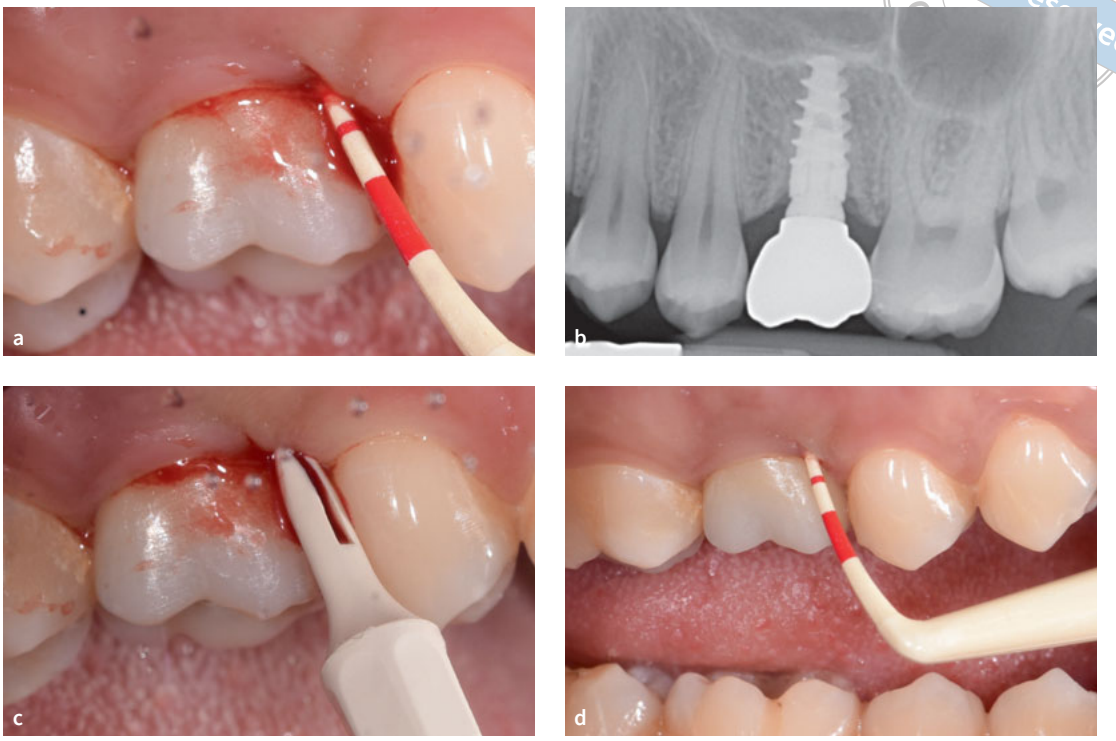

Fig 1a to d PMPR for the treatment of PiM. Implant showing BoP *(a)*. Radiographic exam showing no bone loss around the implant *(b)*. Removal of subgingival biofilm by means of a sonic scaler with plastic tip *(c)*. Disease resolution (ie, absence of BoP) *(d)*.

severe periodontitis, poor plaque control, no regular supportive peri-implant care (SPC),[7] and absence of peri-implant keratinized mucosa[8] may be considered as risk factors. The European Federation of Periodontology (EFP) S3 level clinical practice guidelines highlighted how less conclusive evidence was found for smoking, diabetes, and local factors.[2]

The influence of implant morphology and surface characteristics remains unclear, as well as prosthetic design. Nevertheless, a certain importance seems to be played by the presence of long transmucosal,[9] convex prosthetic designs with high emergence angles[10] and lack of adequate contact between implant restorations and natural teeth.[11]

If not adequately and preventively treated, PiM could evolve into peri-implantitis, with a high probability of implant loss.[2,6] The incidence of peri-implantitis in patients with PiM who are not enrolled in SPC programs is estimated at 43.9%, compared with 18% in patients receiving SPC.[12] Therefore, PiM can be considered the precursor of peri-implantitis; in this perspective, an effective treatment of PiM resulting in resolution of inflammation represents the prerequisite for the prevention of peri-implantitis[13] and for the establishment of long-lasting implant health, as defined by the 2017 classification of periodontal and peri-implant diseases and conditions.[14,15]

The EFP S3 level clinical practice guidelines recommend professional mechanical plaque removal (PMPR) for the treatment of PiM. The term "PMPR" encompasses a heterogenous group of procedures such as scaling or polishing (or both) at supragingival/supramucosal locations, subgingival/submucosal sites, or a combination of each. Evidence from periodontal literature shows that PMPR, if combined with oral hygiene instructions (OHI), may lead to increased reductions in both plaque score and gingival inflammation (Fig 1). Therefore, patient plaque control is indispensable for preventing and managing peri-implant mucositis.[2,16] Nevertheless, complete resolution is not always achieved using nonsurgical mechanical debridement alone.[2]

The multifactorial nature of PiM together with the limitations observed with the use of mechanical debridement alone has drawn attention to the use of adjunctive therapies, either physical, mechanical, chemical, or pharmacologic, which have been proposed to enhance treatment efficacy. Adjunctive therapy aims to target microbial biofilm more effectively, modulate the host immune response, and support tissue healing and regeneration.[17] Among chemical and pharmaceutical adjuncts, antiseptics such as chlorhexidine (CHX), locally delivered antibiotics, anti-inflammatory agents like hyaluronic acid, and probiotics have been evaluated as an addition to standard peri-implant care.

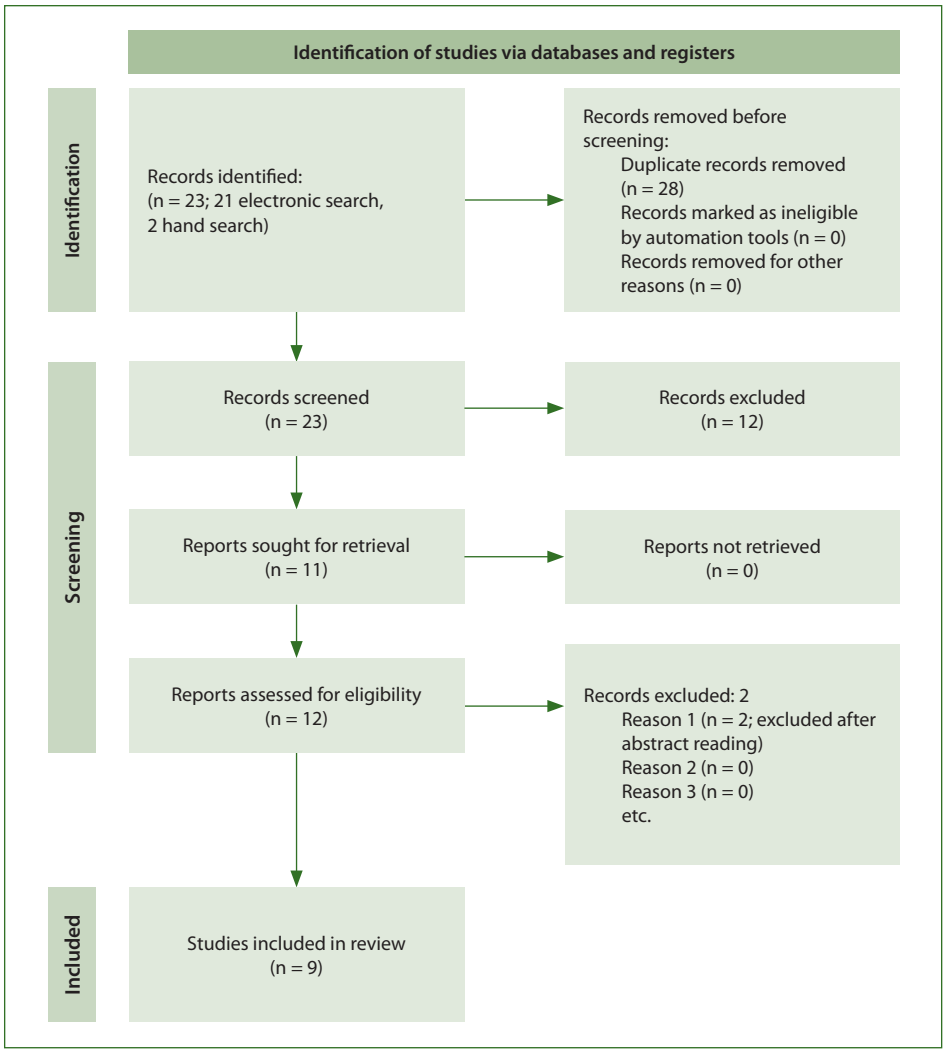

Fig 2 PRISMA flowchart.

The heterogeneity in diagnostic criteria for PiM and its clinical resolution complicates the assessment of treatment success, while variations in study design, sample size, follow-up duration, outcome definitions, and patient-related factors contribute to the difficulty in comparing results and formulation of definitive clinical recommendations.

In this context, despite multiple studies exploring adjunctive therapies to PMPR, the clinical benefit of these agents compared to mechanical debridement alone remains unclear. Therefore, the present review aims to synthesize the most recent (up to March 2025) randomized clinical trials evaluating the effectiveness of different adjunctive approaches in the management of PiM to provide a comprehensive overview of chemical and pharmacologic adjuncts to PMPR.

Method and materials

Comprehensive hand and electronic searches were conducted in PubMed and Scopus databases during the period from January to March 2025. No time restrictions were applied to the publication dates of the studies retrieved. In addition, the methodologic quality and design limitations of the included trials were qualitatively evaluated and discussed. The inclusion and exclusion criteria were as follows.

Inclusion criteria:

- age ≥ 18 years
- English studies
- randomized-controlled trials (RCTs)

- studies reporting implants affected by PiM
- studies evaluating BoP changes
- implant-supported fixed dental prostheses (cemented or screwed)
- length of follow-up clearly stated (at least 3 months)
- "treatment success" clearly defined
- healthy patients and controlled-diabetes patients.

Exclusion criteria:

- studies reporting implants affected by peri-implantitis
- studies with unclear definition of PiM and/or mixed population
- studies including patients with relevant systemic disease or uncontrolled diabetes
- removable implant-supported dental prostheses
- studies with patients' follow-up not specified
- radiographic studies
- studies with only histologic data
- animal studies.

The electronic search was conducted on PubMed and Scopus using the following search string: ((((("dental implants"[Supplementary Concept] OR "dental implants"[All Fields] OR "dental implant"[All Fields] OR "dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR ("dental"[All Fields] AND "implant"[All Fields])) AND ("mucosalization"[All Fields] OR "mucosalized"[All Fields] OR "muco-sally"[All Fields] OR "mucose"[All Fields] OR "mucoses"[All Fields] OR "mucositis"[MeSH Terms] OR "mucositis"[All Fields] OR "mucositides"[All Fields] OR "mucous membrane"[MeSH Terms] OR ("mucous"[All Fields] AND "membrane"[All Fields]) OR "mucous membrane"[All Fields] OR "mucosal"[All Fields]) AND (("periodontal"[All Fields] OR "periodontally"[All Fields] OR "periodontically"[All Fields] OR "periodontics"[MeSH Terms] OR "periodontics"[All Fields] OR "periodontic"[All Fields] OR "periodontitis"[MeSH Terms] OR "periodontitis"[All Fields] OR "periodontitides"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])) AND (("adjunct"[All Fields] OR "adjunction"[All Fields] OR "adjunctions"[All Fields] OR "adjunctive"[All Fields] OR "adjunctively"[All Fields] OR "adjunctives"[All Fields] OR "adjuncts"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields]))) NOT ("laser s"[All Fields] OR "lasers"[MeSH Terms] OR "lasers"[All Fields] OR "laser"[All Fields] OR "lasered"[All Fields] OR "lasering"[All Fields]) NOT ("powder s"[All Fields] OR "powdered"[All Fields] OR "powdering"[All Fields] OR "powders"[Supplementary Concept] OR "powders"[All Fields] OR "powder"[All Fields] OR "powders"[MeSH Terms])) AND ((randomizedcontrolledtrial[Filter]) AND (humans[Filter]) AND (english[Filter])).

The literature search yielded 21 (electronic search) and two (hand search) studies. The selection process involved an initial screening of titles and abstracts (author AC) to identify studies relevant to the topic. Upon screening, author AC identified seven articles by electronic search and two by manual search as relevant, respectively, and then conducted a full text review of the selected studies. Finally, nine articles were included (Fig 2). Data were extracted from the selected studies, and a narrative synthesis was performed to summarize and interpret the findings. Characteristics of the selected studies with the clinical procedures, variables analyzed, and outcomes (including whether selected by manual or electronic search) are summarized in Table 1.

Given the narrative design of the present review, the methodologic quality of each included study was evaluated based on study design, blinding, and follow-up duration. Although a structured literature search and selection process were performed to ensure transparency, a quantitative synthesis or meta-analysis was not performed because of the high heterogeneity of the retrieved studies in term of design, interventions, and outcome definitions. Furthermore, the present review focused solely on chemical and pharmacologic adjunctive therapies to PMPR. Physical or mechanical interventions were intentionally excluded, as these represent distinct treatment modalities with different mechanisms of action.

Relevant sections

CHX-based formulations

The use of a CHX gel as adjunct in PiM therapy was proposed by Heitz-Mayfield et al.[22] In this study a total of 29 patients were enrolled, randomly divided between test (15 patients) and control (14 patients) group. Following the recording of the clinical parameters (PD, BoP), implants diagnosed with PiM were mechanically debrided with titanium-coated or carbon fiber curettes, followed by prophylaxis with rubber cup and polishing paste. While the test group was instructed to brush around the implant twice daily using 0.5% CHX gel for 4 weeks, the control group received a placebo gel to be applied to the peri-implant area. No further instrumentation was planned for subsequent follow-up at 1 and 3 months. The results of this multicentric RCT study showed how BoP change and PD reduction were statisti-

Table 1 Characteristics of the included studies

Study	PiM reported definition	Patients (N)	Treatment	Clinical outcomes	Follow-up	Results	Complete resolution definition
Heitz-Mayfield et al[22]	Inflammation of the peri-implant soft tissues without loss of supporting bone (Zitzmann and Berglundh[18])	29; T: 15; C: 14	T: titanium-coated/carbon fiber curettes (for implants) + rubber cup and polishing paste + 0.5% CHX gel 2/day (4 wks). C: titanium-coated/carbon fiber curettes (for implants) + rubber cup and polishing paste + placebo gel 2/day (4 wks)	PD, BoP	1, 3 mos	BoP and PD significant improvement at 1 mo (both T and C); No differences between T and C for BoP and PD; No added benefit for T compared to C; Less PD reduction for implants with submucosal restoration margins	BoP = 0; 1 mo, T: 28%, C: 28%; 3 mos, T: 38%, C: 38%
Ilyes et al[25]	Implants showing presence of bleeding (more than one spot at a location around the implant) and/or suppuration on gentle probing in the absence of bone loss (Tonetti et al[29])	31; T: 16; C: 15	PMPR with sonic scaler with plastic tip (for implants) + air polishing. T: Piperacillin + tazobactam gel + rinsing with 0.20% CHX solution twice a day for 2 wks. C: placebo gel + rinsing with 0.20% CHX solution twice a day for 2 wks.	PD, BoP, SoP, mPII, mBI, FMPS, FMBS	3, 6 mos	BoP, mBI: significant intra-group (3, 6 mos) and inter-group (6 mos for T) differences; PD, mPII: no statistical differences; FMPS: Significant intra-group.	BoP ≤ 1 site; 6 mos, T: 56%, C: 40%
Iorio-Siciliano et al[26]	Inflammation of the peri-implant soft tissues without loss of supporting bone (Zitzmann and Berglundh[18])	46; T: 23; C: 23	Full-mouth supragingival scaling with ultrasonic device with metal tip. T: (Amino acid buffered sodium hypochlorite gel delivered for 30s + ultrasonic scaling with plastic tip); repeated 5 times. C: (placebo + ultrasonic scaling with plastic tip); repeated 5 times	PII, mPI, BoP, PD, FMPS, FMBS	1 ,3, 6 mos	Significant reduction of FMPS and FMBS at 6 mos (both T and C); Significant differences between T and C at 1 mo; Significant PD reduction at 6 mos (both T and C); No statistically significant differences between groups in terms of implants with plaque or with BoP+	BoP = 0; 6 mos, T: 45%; C: 32%
Iorio-Siciliano et al[28]	Inflammatory lesion in the soft tissues around dental implant without peri-implant bone loss caused by biofilm accumulation in peri-implant sulcus (Meyer et al[19])	40; T: 20; C: 20	Full-mouth supragingival scaling with ultrasonic device with metal tip. T: Sonic scaling with plastic tip (for implants) + spermidine and hyaluronic acid gel + calcium chloride gel. C: Sonic scaling with plastic tip (for implants)	PD, BoP, mPII, FMPS, FMBS	1, 3 mos	Significant reduction of FMPS and FMBS at 3 mos (both T and C); Significant PD reduction at 3 mos (both T and C); Significant BoP change at 1, 3 mos (both T and C); No statistically significant differences between groups for FMPS, FMBS, PD, BoP change	BoP ≤ 1 site; 1 mo, T: 70%; C: 65%; 3 mos, T: 85%; C: 70%
Isola et al[23]	Inflammatory lesion in the soft tissue around dental implants without peri-implant bone (Berglundh et al[3])	56; T: 28; C: 28	PMPR with ultrasonic device with metal tip + sonic scaling with plastic tip (for implants) + rubber cup and a polishing paste. T: Tongue brushing with CHX 1% gel + subgingival irrigation of implant affected by PiM 3 times with CHX 0.12% + CHX 0.12% mouth-wash (twice daily for 2 wks). C: Tongue brushing with placebo gel + placebo solution mouthwash + subgingival irrigation with placebo	BoP, mPII, mGI, FMPS, FMBS, PD	1 ,3, 6 mos	Significant reduction at 6 mos of BoP, PD, FMPS, FMBS, mPII, mGI (both T and C); Significant BoP reduction, mPII in T compared to C at 6 mos	BoP ≤ 1 site; 1 mo, T: 62.9%, C: 40%; 3 mos, T: 48.6%, C: 37.5%; 6 mos, T: 42.9%, C: 25%
Kashefimehr et al[31]	Presence of BoP, PD ≥ 4 mm, no recession of soft tissue, and bone loss not exceeding than the first-year annual amount (≤ 2 mm) (Sanz et al[20])	41; T: 20; C: 21	T: Subgingival debridement using an ultrasonic device with plastic tip and glycine-based powder air polishing + subgingival EMD after 2 wks. C: Subgingival debridement using an ultrasonic device with plastic tip and glycine-based powder air polishing	BoP, PD, LPI, WMPI, PoP	3 mos	Statistically significative difference for the intergroup analysis for BoP and PD ($P < .0001$); No statistical difference between T and C for LPI, WMPI	BoP = 0
Philip et al[30]	Inflammatory lesion of the mucosa surrounding an endosseous implant without loss of supporting peri-implant bone (Heitz-Mayfield and Salvi[1])	89; T1 (Delmopinol): 31, T2 (CHX): 30; C: (Placebo): 28	PMPR for all groups; Mouth rinsing twice a day	BoP, mBI, mPI, IPPD	1, 3 mos	No statistically significant differences between T1, T2, and C at 3 mos	BoP = 0; 1 mo, T1: 77%, T2: 73%, C: 75%; 3 mos, T1: 87%, T2: 60%, C: 71%.

Table 1 Characteristics of the included studies (contd.)

Study	PiM reported definition	Patients (N)	Treatment	Clinical outcomes	Follow-up	Results	Complete resolution definition
Pulcini et al[24]	Presence of inflammation in the peri-implant mucosa with or without increased PD and without loss of supporting bone (Lang and Berglundh[21])	46; T: 24; C: 22	PMPR with ultrasonic devices using a plastic tip and powered air polishing. T: mouth rinse (0.03% CHX and 0.05% CPC). C: placebo gel + ultrasonic scaler with plastic tip + rubber cup and a polishing paste	PD, BoP, mPlI	3, 6, 9, 12 mos	Statistically significative difference only at buccal site at 12 mos for BoP between T and C group; No statistically significative difference for PD between T and C	BoP = 0; 12 mos, T: 58.3%, C: 50%
Santana et al[32]	Mucosal inflammation around implants, with BoP and/or SoP (Berglundh et al[3])	36; T: 18; C: 18	Mechanical debridement with Teflon-coated scaler, rubber cup, and polishing paste. T: topical application of carboxymethyl cellulose gel containing 10^9 CFUs of *Bifidobacterium lactis* HN019™, *Lacticaseibacillus rhamnosus* HN001™, and *Lacticaseibacillus paracasei* Lpc-37®, around the implants. C: placebo	BoP, mPI, PD, mSBI	3, 6 mos	Statistically significative improvements at 3 and 6 mos of mPI and BoP (both T and C); Statistically significant differences between T and C for BoP at 3 and 6 mos; No statistical difference for mPI, PD, and mSBI	BoP = 0; 6 mos, T: 72.2%, C: 33.3%

BoP, bleeding on probing; C, control group; CHX, chlorhexidine; CPC, cetylpyridinium chloride; EMD, enamel matrix derivative; FMBS, full-mouth bleeding score; FMPS, full-mouth plaque score; IPPD, implant pocket probing depth; LPI, Local Plaque Index; mBI, modified Bleeding index; mGI, modified Gingival Index; mPlI, modified Plaque Index; mSBI, modified Sulcus Bleeding Index; NaOCl, sodium hypochlorite; PD, probing depth; PiM, peri-implant mucositis; PMPR, professional mechanical plaque removal; PoP, pain on probing; SoP, suppuration on probing; T, test group; WMPI, whole-mouth Plaque Index.

cally significant at 1-month follow-up in both groups, although no significant inter-group differences were reported. When considering the absence of bleeding in all four implant sites, the authors reported a percentage of success of 28% at 1 month and 38% at 3 months (both test and control groups). Therefore, clinical outcomes suggested that nonsurgical debridement and self-performed plaque control with and without adjunctive application of CHX gel were effective for the treatment of PiM, although the use of CHX did not provide an additional benefit.

A CHX-based protocol for the treatment of PiM was recently proposed in the study of Isola et al.[23] Full-mouth supragingival debridement with ultrasonic device with metal tips was provided for 56 patients, while the implants (n = 85) were treated with sonic scaler with a plastic tip followed by polishing with a plastic cup and polishing paste. Subsequently, the test group (28 patients, 40 implants) was treated by brushing the dorsum of the tongue for 1 minute using CHX 1% gel, CHX 0.12% mouthwash (1 minute), and subgingival irrigation of implants affected by PiM three times within 10 minutes each using a solution with CHX 0.12%. In the control group (28 patients, 35 implants), all the procedures (tongue brushing, mouth rising, subgingival irrigation) were performed using placebo devices which had the same flavor and color as CHX-based adjuncts used in the test group. Clinical examination (six sites for implant) at the 6-month follow-up reported a higher number of implants with a maximum of one BoP-positive site in the test group, which also showed a significant BoP reduction and modified Plaque Index (mPlI). Treatment success (implants with all negative BoP or a maximum of one bleeding spot) was reached in 42.9% of test implants compared to 25% of the control group at 6 months after treatment, although a complete resolution was not achieved in either group.

The randomized clinical study by Pulcini et al[24] evaluated the efficacy of a mouthwash containing CHX (0.03%) and cetylpyridinium chloride (CPC) (0.05%) in the treatment of PiM in 46 patients (24 in the test group and 22 in the control group) with a 1-year follow-up. Although a statistically significant reduction in vestibular BoP of 24.49% was observed in the test group compared to the control group ($P = .022$), at baseline implants in the test group had a significantly greater BoP than implants in the control group ($P = .006$), and there were no significant differences at 12 months for BoP between the test and control groups. Disease resolution was 58.3% of implants in the test group and 50% in the control group.

Local antibiotics

Local antibiotics as additional treatments to PMPR were recently proposed in PiM therapy to improve the effectiveness of nonsurgical debridement. In the placebo-controlled RCT study

by Ilyes et al,[25] a local drug delivery based on slow release of piperacillin and tazobactam was evaluated. PMPR with plastic tip and air polishing was performed for all implants. After the randomization process, piperacillin plus tazobactam gel and placebo gel were applied in the test (16 implants) and control (15 implants) groups, respectively, followed by rinsing with 0.20% CHX solution twice a day for 2 weeks after treatment. The results at the 3- and 6-month follow-ups showed an intra-group significance for BoP and modified Bleeding Index (mBI) and an inter-group statistically significant difference at 6 months for BoP in favor of the test group. No statistical differences were found for PD and mPII. Treatment success (implant with BoP ≤ 1 implant spot) was reached in 56% of cases in the test group and in 40% of implants in the control group. Therefore, the authors concluded that the use of local antibiotic resulted in a higher BoP reduction when compared to the control, but no significant differences were observed regarding the changes in other clinical and microbiologic parameters.

Sodium hypochlorite gel

In the multicenter double-arm RCT proposed by Iorio-Siciliano et al,[26] a formulation of sodium hypochlorite (NaOCl) gel was tested as adjunct to mechanical therapy of PiM, considering its bactericidal and emollient properties on the microbial biofilm. All patients (46 participants) were subjected to full-mouth supragingival scaling followed by prophylaxis with rubber cup and polishing paste. After recording clinical parameters (PD, BoP, mPII) at baseline on four implant sites, patients were randomly assigned to test (22 subjects and 33 implants) and control (23 subjects and 34 implants) groups. In the test group the protocol included the application of 0.95% amino acid-buffered NaOCl gel into the implant sulcus five times for 30 seconds, followed each time by ultrasonic scaling with a plastic tip (Fig 3). Subsequently, polishing was performed with rubber cup and polishing paste. The control group was treated with the same protocol but with a placebo gel. A formulation of 0.12% CHX gel was prescribed for both groups twice daily for 2 weeks following treatment. Clinical parameters were recorded at 1, 3, and 6 months following treatment, with professional prophylaxis and air polishing at each reevaluation time. While PD and mPII were statistically significant in the intra-group comparison for each follow-up period, BoP change resulted significant only at intra-group level but not between groups at 6 months. Furthermore, the percentage of absence of BoP at all four implant sites (treatment success) was 45% in the test and 32% in the control group at 6 months following therapy, suggesting incomplete resolution of PiM. Therefore, no further clinical benefits were found with the adjunctive use of NaOCl gel.

Spermidine + hyaluronic acid and calcium chloride

The role of spermidine and hyaluronic acid in periodontal healing was reported by several studies.[27] The RCT study proposed by Iorio-Siciliano et al[28] tested the use of a gel containing these two additional agents for PiM therapy of implants diagnosed with PiM associated with a sealant gel (eg, calcium chloride), with a 3-month follow-up. All examined implants diagnosed with PiM (n = 40) were treated by sonic scaler with a plastic tip and rubber cup with polishing paste. After PMPR, the gel A (spermidine and hyaluronic acid) was applied in the peri-implant sulcus of test implants (n = 20) followed by the gel B (calcium chloride), whereas mechanical debridement alone was performed for the control group (n = 20). Finally, a 0.12% CHX solution was prescribed for 1 week to support local plaque control. The results of the study showed at 1-month follow-up complete disease resolution, defined by Tonetti et al[29] as one implant spot with positive BoP, was reached in 85% of the test implants and in 70% of control implants, respectively. However, implants in the test group showed no statistically significant differences when compared with those of the control group. Therefore, complete disease resolution was not achieved in both experimental groups, although the control group with incomplete disease resolution showed a greater number of BoP-positive sites.

Results

A total of nine RCTs were included, with a total of 414 patients diagnosed with PiM. The follow-up periods of the analyzed studies ranged from 1 to 12 months. Characteristics of the selected studies with the clinical procedures, variables analyzed, and outcomes are summarized in Table 1.

All studies required a submarginal instrumentation phase, either with hand or sonic/ultrasonic instruments, or both. For the powered instrumentation, the use of both metal and plastic inserts was reported.

Among the included studies, the majority considered different formulations of CHX as adjunct in therapy of PiM. While Isola et al[23] tested for CHX used both supramarginally (ie, 0.12% mouthwash and 1% gel) and submarginally (ie, 0.12% irrigations), Heitz-Mayfield et al[22] only prescribed supramarginal 0.5% CHX gel. One of the two test groups of Philip et al[30] was 0.2% CHX mouthwash, and the other was 0.2% delmopinol chloride (DEL) mouthwash, whereas a 0.03% CHX with 0.05% CPC mouthwash was used in the research of Pulcini et al.[24] Finally, Ilyes et al[25] prescribed 0.2% CHX mouthwash to both test and control groups, and the test group also received a topical antibiotic (piperacillin + tazobactam) gel.

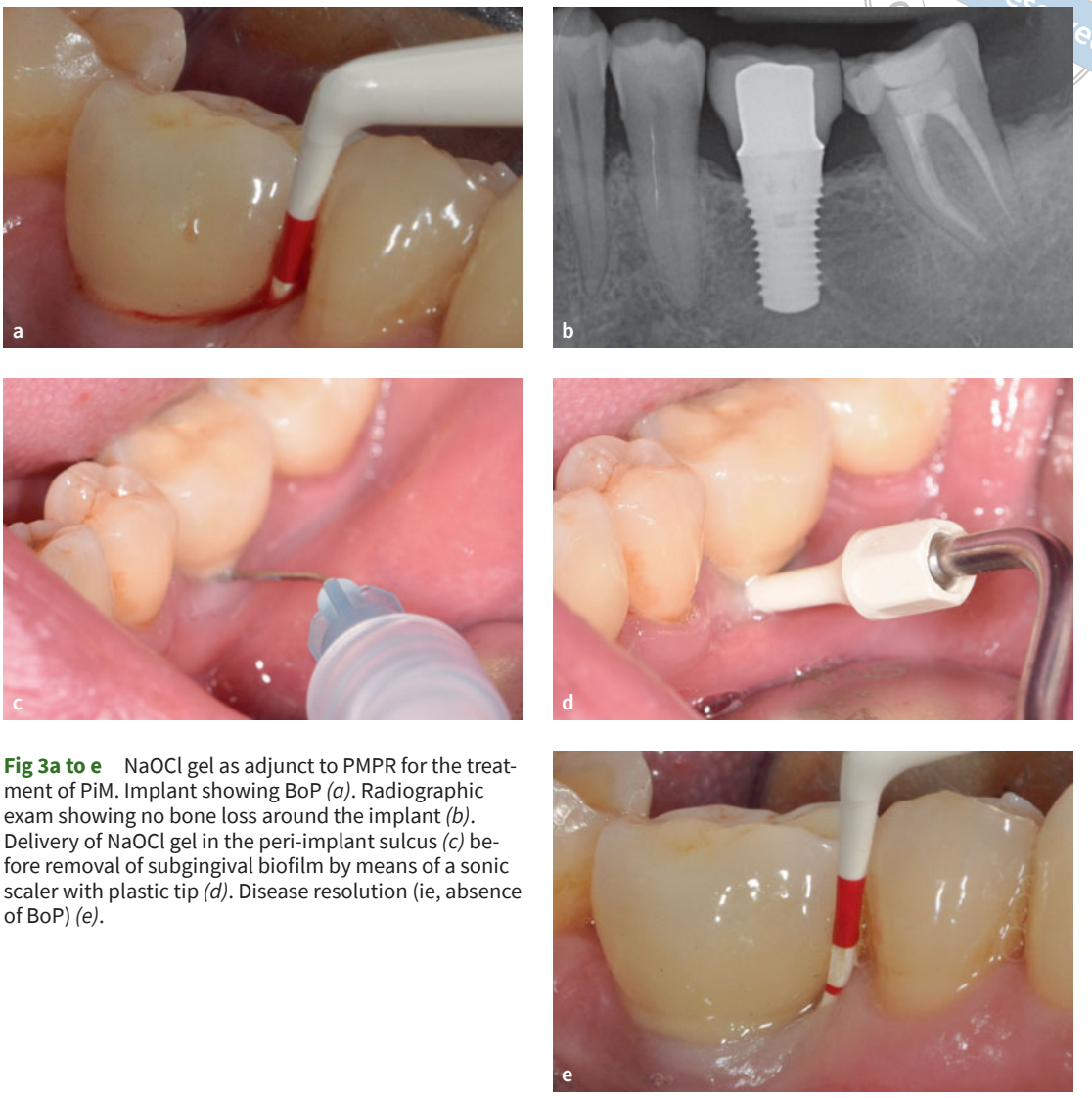

Fig 3a to e NaOCl gel as adjunct to PMPR for the treatment of PiM. Implant showing BoP *(a)*. Radiographic exam showing no bone loss around the implant *(b)*. Delivery of NaOCl gel in the peri-implant sulcus *(c)* before removal of subgingival biofilm by means of a sonic scaler with plastic tip *(d)*. Disease resolution (ie, absence of BoP) *(e)*.

Other studies evaluated different adjunctive therapies: Santana et al[32] evaluated the effects of topical application of probiotics (ie, carboxymethyl cellulose gel containing 10^9 CFUs of *Bifidobacterium lactis* HN019, *Lacticaseibacillus rhamnosus* HN001, and *Lacticaseibacillus paracasei* Lpc-37), Kashefimehr et al[31] delivered amelogenin (an enamel matrix derivative [EMD]) submarginally, and Iorio-Siciliano et al[28] applied a spermidine and hyaluronic acid gel submarginally with a calcium chloride sealant gel. Finally, Iorio-Siciliano et al[26] repeatedly applied an amino acid buffered sodium hypochlorite gel during submarginal instrumentation.

The most frequently evaluated clinical parameters were BoP, PD, mPII, full-mouth plaque score (FMPS), and full-mouth bleeding score (FMBS). All studies considered BoP as the primary variable and used it to determine disease resolution, although with different parameters. In fact, some considered PiM resolved when no implant site showed BoP, while others considered it resolved when implants showed BoP at no more than one spot, without the presence of a line of bleeding or profuse bleeding.

Significant reductions in BoP over time were recorded both in test (T) and control (C) groups in all the included studies.

A statistically significant difference between groups was reported by Ilyes et al[25] that showed a greater BoP reduction in the test group at 6 months (56%) compared to the control group (40%). Similarly, Isola et al[23] reported a significant difference in terms of BoP reductions at 6 months: 48.7% and 39.0% for test and control group, respectively. Significant differences between test and control groups in terms of BoP reduction were also ob-

served by Santana et al[32] (33.3% and 44.4% in test group and 25.7% and 32.3% in control group at 3 and 6 months, respectively), and by Kashefimehr et al[31] (median reduction 50% in test group compared to no reduction in control group). Finally, Pulcini et al[24] recorded a significant difference in BoP reduction between the test and control group only at the buccal site at 12 months.

Conversely, Heitz-Mayfield et al[22] and Iorio-Siciliano et al[26,28] observed no statistically significant intergroup differences in BoP reduction. Philip et al[30] also showed comparable BoP levels across DEL, CHX, and placebo groups, with mean BoP values at 3 months of 3.22%, 8.88%, and 7.73% respectively, indicating no added benefit of active rinsing agents.

PD or implant pocket probing depth (IPPD) was an outcome measure in all the included studies. Nevertheless, studies failed to demonstrate a significant influence of the adjuncts on PD reduction, apart from Kashefimehr et al,[31] who reported significant differences in PD between test and control at 3 months ($P < .0001$).

Ilyes et al,[33] Iorio-Siciliano et al,[28] and Isola et al[23] considered treatment successful when there was no more than one spot at a location around the implant or presence of a line of bleeding or profuse bleeding at any location, as defined by Tonetti et al,[29] while the other studies required no BoP around the implants. Among the former studies, treatment resolution rates varied between 40% and 80%, while for the latter studies the rates ranged between 33% and 87%.

The efficacy of adjunctive therapies, in particular antimicrobial gels (eg, piperacillin/tazobactam, spermidine-hyaluronic acid), probiotics, and CHX-based protocols, were variable. Santana et al[32] observed a mucositis resolution rate of 72.2% at 3 months in the probiotic test group, compared to 33.3% in the control group while Pulcini et al[24] recorded a significant difference in BoP only at the buccal site at 12 months, and no difference in PD.

Most studies did not report details of implant or prosthetic design, including whether restorations were cemented or screw-retained, which may influence plaque control and peri-implant tissue response.

Discussion

The present narrative review aimed to critically evaluate the clinical benefits of adjunctive therapies used in combination with PMPR for the management of PiM, a reversible inflammatory condition that, if not properly treated, may evolve into peri-implantitis.[1]

Adjunctive approaches investigated in the literature include antiseptic agents (eg, CHX-based formulations), antimicrobial compounds (eg, local antibiotics and sodium hypochlorite), and biologically active agents (eg, spermidine, hyaluronic acid, EMD, and probiotics).[23,25,26]

The available evidence from the nine included RCTs consistently indicates that PMPR alone is effective in reducing key clinical parameters, particularly BoP and PD. However, complete resolution of inflammation is not consistently achieved,[1] which has led to the introduction of adjunctive therapies intended to enhance treatment outcomes. Although some of these strategies demonstrated improvements in clinical parameters within test groups, their additional benefit over PMPR alone remains limited and often not statistically significant.

Among antiseptics, CHX-based protocols were the most frequently evaluated. While slight improvements in treatment success were reported in some studies,[23] the overall evidence suggests no consistent advantage compared with mechanical debridement alone.[22,24]

Similarly, local antibiotic (ie, piperacillin and tazobactam gel) delivery systems showed a greater reduction in BoP in isolated cases, but without significant effects on other clinical parameters such as PD or plaque indices.[25]

Sodium hypochlorite gel[26] and biologically active compounds (ie, spermidine and hyaluronic acid) also demonstrated favorable intra-group outcomes yet failed to provide clear inter-group differences.[28,34] Probiotics, although promising in a single study, require further investigation due to limited sample size and lack of reproducibility.[32]

A major factor limiting the interpretation of these findings is the substantial heterogeneity across studies. Differences in outcome definitions, particularly regarding the criteria for disease resolution, significantly affect the comparability of results. While earlier studies required complete absence of BoP, more recent[29] definitions allow for minimal bleeding, leading to variability in reported success rates. Clinical interpretation of data, therefore, could be affected by the lack of common standardized success criteria. Among the included studies, three[23,25,28] that adopted the success criterion described by Tonetti et al[29] reported a disease resolution rate for the adjunctive therapies ranging from 56% to 85%, while for the others disease resolution ranged from 0% to 87%.

Additional sources of heterogeneity include variations in adjunctive protocols (eg, concentration, mode of delivery, and duration), follow-up periods, and inconsistencies in OHI. In many cases, OHI protocols were insufficiently described, despite their well-known impact on treatment outcomes. Patient-related factors such as smoking status, systemic conditions, and baseline oral hygiene were also inconsistently

reported or controlled, further complicating data interpretation. For example, some studies excluded all smokers or only heavy smokers, other studies included all types of smokers, but without any stratification, and others estimated the negative effect of smoking on BoP reduction.[23]

Furthermore, implant characteristics and prosthetic configurations were not reported in any of the studies, despite their potential influence on plaque retention. Whether the prosthetic crown was cemented or screw-retained, and whether it was removed during debridement was not specified, representing a significant gap in understanding the clinical context of each case.

Similarly, variations in PMPR protocols and home care instructions may have contributed to differences in clinical outcomes. While most studies employed ultrasonic scaling followed by polishing, the use of plastic versus metal tips, as well as the frequency of professional maintenance visits was variable across studies. Without proper and well-documented patient education, the influence of adjunctive therapy may be reduced.

Despite these limitations, the present review highlights that adjunctive therapies seem to offer intra-group clinical improvements, particularly in BoP reduction. Although in most studies no statistically significant differences were found in favor of additional therapies compared to PMPR alone, a positive clinical effect was nevertheless observed for almost all the examined adjuncts. In facts, certain agents such as probiotics, spermidine, piperacillin/tazobactam, hyaluronic acid gels, and sodium hypochlorite seem to guarantee interesting results due to their demonstrated potential in isolated studies both in teeth and implants.[35-37] Therefore, while the adjuncts may be used selectively, especially in patients with persistent inflammation or compromised response to standard therapy, their use in clinical practice should be carefully evaluated. Clinicians should still rely on evidence-based approaches focusing on identifying individual patient risk profiles including systemic health, smoking status, oral hygiene habits, and prosthetic design. The careful integration of adjunctive therapy into a comprehensive maintenance program may offer enhanced outcomes when traditional mechanical debridement does not reach the endpoints result.

Future research should focus on RCT studies with more standardized outcomes and mucositis definitions, together with clear documentation of prosthetic and implant characteristics, a specific patient selection, and long-term follow-up to assess whether these adjuncts can offer benefits in clinical practice.

Finally, in addition to the chemical and pharmacologic adjuncts, technologies such as photodynamic therapy, probiotics, and host-modulation therapies have been evaluated. These therapies seem to show promising results both in improving microbial profile and promoting tissue regeneration. However, long-term data and larger patients' samples are needed for application in everyday clinical practice.

Conclusions

While adjunctive therapies such as CHX, sodium hypochlorite, antibiotics, and probiotics showed some localized improvements, a complete resolution of peri-implant mucositis was not achieved. Therefore, PMPR still remains the gold standard while adjunctive therapies should be evaluated case by case, providing a personalized therapy program for each patient.

Future directions

Treatment of PiM represents a crucial step in the prevention of peri-implantitis, and the need for additional measures to enhance the efficacy of PMPR is crucial.

The introduction of new adjunctive measures, as well as the rational use of existing ones, can represent a significant development in the management of PiM. However, it is essential that the new RCTs use a univocal definition of disease resolution, include larger sample sizes, have a long-term follow-up, and provide a more detailed analysis of patient-related and implant-related factors.

Disclosure

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Author contributions

Conceptualization and design of the study, supervision: VIS; Methodology: LM; Acquisition of data, software, and validation, writing-original draft preparation: AC and AA; Formal synthesis, resources, search strategy, evaluation, and interpretation of data, data curation: AB; Writing-review and editing: VP; Writing-review and editing, supervision, agreement, final approval of the version to be submitted: GI and LR. All authors conceptualized the research and have read and agreed to the published version of the manuscript.

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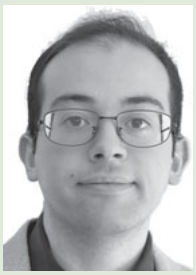

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