Supplementary information

Efficacy of adjunctive systemic or local antibiotic therapy in peri-implantitis: a systematic review and meta-analysis of randomized controlled clinical trials

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Table S1 Basic information of the included studies

Reference	Study design	Smoker	Diagnostic criteria	Group evaluated	Intervention	Intervention frequency	Number of patients/implants	Follow-up periods	Outcomes	Success criteria
Nonsurgical+systemic antibiotics										
Blanco et al., 2022	RCT	Smokers and nonsmokers	PPD≥6 mm, BOP/SOP^{+} and MBL≥3 mm	Test group	NST+250 mg MTZ	2 capsules TID, last for 7 days	16 patients/28 implants	3, 6, 12 months	Both two groups showed improvement in PPD, CAL, and BL. Antibiotics significantly reduced PPD, CAL, BL, Pg, Tf, and Cr for intergroup comparison.	PPD was reduced to 5 mm with no BOP or to <5 mm irrespective of BOP, and no further bone loss was detected between baseline and 1 year.
				Control group	NST+placebo	2 capsules TID, last for 7 days	16 patients/34 implants			
Polymeri et al., 2022	RCT	Smokers and nonsmokers	PPD≥5 mm, BOP/SOP^{+} and MBL≥3 mm	Test group	NST+375 mg AMX and 250 mg MTZ	1 tablet TID, last for 7 days	18 patients/18 implants	3 months	Both two groups showed improvement in PPD, BOP, and SOP. Between-group comparisons were non-significant.	PPD<5 mm, and no BOP.
				Control group	NST	NR	19 patients/19 implants			
Shibli et al., 2019	RCT	Nonsmokers	PPD> 5 mm, BOP/SOP^{+} and MBL> 4 mm	Test group	NST+400 mg MTZ and 500 mg AMX	TID, last for 14 days	20 patients/20 implants	3, 6, 12 months	Both two groups showed improvement in PPD, CAL, and BL, but no significant differences were found between two groups at 1 year.	PPD<5 mm, no BOP, and no bone loss
				Control group	NST+placebo	NST+placebo	20 patients/20 implants			
Nonsurgical+local antibiotics										
Park et al., 2021	RCT	Smoke with <10 cigarette a day	PPD≥5 mm, BOP/SOP^{+}, and the presence of peri-implant bone loss in a peri-apical radiograph	Test group	NST+201 mg MTZ and 10 mg MH ointment	Administered at 1, 2, and 3 weeks	38 patients/39 implants	3 months	Both two groups showed improvement in PPD and BOP. Antibiotics significantly reduced mean PPD, BOP, and red complex counts for intergroup comparison.	The absence of BOP, SOP, and sites showing deep PPD (PPD≥5 mm)
				Control group	NST	One application	37 patients/39 implants			
Surgical+systemic antibiotics										
Carcuac et al., 2016	RCT	Smokers and nonsmokers	PPD≥6 mm in at least 1 aspect of the implant, BOP/SOP^{+} and MBL>3 mm	Test group	ST+750 mg AMX	BID, commenced at 3 days before surgery and last for 10 days	25 patients/46 implants	6, 12 months	Both two groups showed improvement in PPD and BOP. Antibiotics contributed to extra bone gain and significantly reduced PPD for intergroup comparison.	PPD≤5 mm, no BOP/SOP, and no additional bone loss
				contRol group	ST	NR	24patients/49 implants (1 lost to FU)			

Surgical+local antibiotics										
Cha et al., 2019	RCT	Nonsmokers	PPD>5 mm, BOP^{+} and MBL>2 mm	Test group	ST+1 mg MH ointment	Administered at 1 and 3 M	24 patients/24 implants (1 lost to FU)	3, 6 months	Both two groups showed improvement in PPD, BOP, and MBL. Antibiotics significantly reduced PPD and BL for intergroup comparison.	PPD<5 mm, no BOP/SOP, and no further bone loss
				Control group	ST+placebo	Administered at 1, 3 M	22 patients/22 implants (3 lost to FU)			
Emanuel et al., 2020	RCT	Nonsmokers	PPD 6 to 10 mm, BOP/SOP^{+}, and radiographic evidence for bone loss > 2 mm	Test group	ST + D-PLEX500(0.65% docycycline hyclate)	one application	14 patients/18 implants	6, 12 months	Both two groups showed improvement in PPD, BOP, and CAL. Antibiotics significantly reduced PPD, CAL, and BL at 12 months for intergroup comparison.	NR
				Control group	ST	NR	13 patients/14 implants			

RCT, randomized clinical trial; PPD, pocket probing depth; BOP, bleeding on probing; SOP, suppuration on probing; MBL, marginal bone loss; CAL, clinical attachment level; NST, nonsurgical treatment; ST, surgical treatment; SRP, scaling and root planning; MTZ, metronidazole; AMX, amoxicillin; MH, minocycline; BID, twice a day; TID, three times a day; NR, Not reported; Pg, Porphyromonas gingivalis; Cr, Campylobacter rectus; Tf, Tannerella forsythia; $^{+}$, positive; FU, follow-up

Table 2 Statistical data of the included studies

Reference	Group evaluated	[Δ]PPD (mm)			[Δ]CAL (mm)			[Δ]BOP (%)			[Δ]BL (mm)			Success rate (%)	Microbiology results
		3 M	6 M	12 M	3 M	6 M	12 M	3 M	6 M	12 M	3 M	6 M	12 M		
Nonsurgical+systemic antibiotics															
Blanco et al., 2022	Antibiotics	2.13[‡]	2.24[‡]	2.42[‡]	1.69[‡]	1.76[‡]	1.73[‡]	NR	NR	NR	0.40	1.32	2.15[‡]	57.1 (16/28)	Quantitative reduction: *Porphyromonas gingivalis* (antibiotics group, 6 M), *Porphyromonas gingivalis* and *Tannerella forsythia* (antibiotics group, 12 M)
	Control	0.59	0.76[‡]	0.89[‡]	0.11[‡]	0.40[‡]	0.50[‡]	NR	NR	NR	0.24	0.81	0.95[‡]	23.5 (8/34)	
Polymeri et al., 2022	Antibiotics	2.28[†]	NR	NR	NR	NR	NR	16	NR	NR	MR	NR	NR	5 (1/18)	NR
	Control	1.47[†]	NR	NR	NR	NR	NR	11	NR	NR	NR	NR	NR	5 (1/19)	
Shibli et al., 2019	Antibiotics	NR	NR	3.1	NR	NR	2.6	NR	NR	NR	NR	NR	0.41	65 (13/50)	Quantitative reduction: red complex species (both groups, 14 d and 3 M); Quantitative regrowth: red complex pathogens (both groups, 3 M to 1 year)
	Control	NR	NR	1.8	NR	NR	1.4	NR	NR	NR	NR	NR	0.47	55 (11/50)	
Nonsurgical+local antibiotics															
Park et al., 2021	Antibiotics	1.95[‡]	NR	NR	NR	NR	NR	51[‡]	NR	NR	NR	NR	NR	31.6 (12/39)	Quantitative reduction: *P. gingivalis*, *T. forsythia*, *T. denticola*, *P. intermedia*, *C. rectus*, and *F. nucleatum* (antibiotics group, 12 W)
	Control	1.28[‡]	NR	NR	NR	NR	NR	33[‡]	NR	NR	NR	NR	NR	20.5 (8/39)	
Surgical+systemic antibiotics															
Carcuac et al., 2016	Antibiotics	NR	3.49[‡]	3.44[‡]	NR	NR	NR	NR	NR	34.8	NR	NR	0.51[‡]	65.2 (30/46)	Quantitative reduction: total DNA probe counts (both groups, during 12 M); Quantitative regrowth: *Fusobacterium nucleatum* and *Prevotella intermedia*/*Prevotella nigrescens* (both groups, 12 M after)
	Control	NR	2.18[‡]	2.16[‡]	NR	NR	NR	NR	NR	44.4	NR	NR	-0.69[‡]	37.5 (18/48)	
Surgical+local antibiotics															
Cha et al., 2019	Antibiotics	NR	2.68[‡]	NR	NR	NR	NR	NR	49	NR	NR	0.72[‡]	NR	66.7 (16/24)	Quantitative reduction: red complex bacteria (both groups, 6 M)
	Control	NR	1.55[‡]	NR	NR	NR	NR	NR	31	NR	NR	0.31[‡]	NR	35.3 (8/22)	
Emanuel et al., 2020	Antibiotics	NR	1.59	2.40	NR	1.59	2.21[‡]	NR	19.6	36.3[‡]	NR	1.08[‡]	0.88	NR	NR
	Control	NR	1.33	0.96	NR	0.89	0.42[‡]	NR	13.0	15.2	NR	-0.24[‡]	–0.33	NR	

PPD, pocket probing depth; BOP, bleeding on probing; SOP, suppuration on probing; BL, bone level; CAL, clinical attachment level; NST, nonsurgical treatment; ST, surgical treatment; SRP, scaling and root planning; MTZ, metronidazole; AMX, amoxicillin; MH, minocycline; BID, twice a day; TID, three times a day; W, week; M, month; NR: not reported. [Δ] Mean change from baseline to last follow-up; [†] Statistically significant compared with baseline; [‡] Statistically significant between groups (on superior group).

Table 3 Detailed information about treatment of the included studies

Reference	Group evaluated	Before treatment	Surgical/nonsurgical treatment	Instrument	Implant supported restorations	After treatment	Follow-up periods	Analyzed time point
Nonsurgical+systemic antibiotics								
Blanco et al., 2022	Antibiotics	Rinsed with 0.12% CHX digluconate	Supra- and submucosal mechanical debridement+ removing granulation tissue and minor mucosal curettage+being irrigated with 0.12% CHX digluconate	Ultrasonic stainless steel scaling inserts (EMS®, Electro Medical Systems), stainless steel Columbia 4R/4L curette (LM Instruments Oy)	Removed if possible	MTZ 250 mg (2 tablets TID,7D)	3, 6, 12 months	6 months
	Control					placebo pills (2 tablets TID,7D)		
Polymeri et al., 2022	Antibiotics	NR	Nonsurgical debridement	Ultrasonic devices (EMS, Electro Medical Systems, Nyon, Switzerland) with the Polyether Ether Ketone (PEEK) fiber tip (PI instrument®, EMS, Nyon, Switzerland), and carbon fiber reinforced plastic hand instruments (Universal Implant Deplaquer®; Kerr Dental, Bioggio, Switzerland)	Not removed	AMX 375 mg, MTZ 250 mg (1 tablet TID, 7 d) +0.12% CHX (BID, 4 weeks)	3 months	3 months
	Control					0.12% CHX (BID, 4 weeks)		
Shibli et al., 2019	Antibiotics	NR	Nonsurgical debridement	Teflon curettes	NR	MTZ 400 mg, AMX 500 mg (TID, 14 d)	3, 6, 12 months	12 months
	Control					placebo pills (TID, 14 d)		
Nonsurgical+local antibiotics								
Park et al., 2021	Antibiotics	Oral hygiene	Nonsurgical debridement	Ultrasonic scaler (EMS, Nyon, Switzerland)	NR	MTZ 201mg+MH 10 mg ointment	1, 2, 3 months	3 months
	Control					NR		
Surgical+systemic antibiotics								
Carcuac et al., 2016	Antibiotics	Oral hygiene+ 750 mg AMX BID 3 d	Pocket elimination+implant, decontamination with saline	Titanium-coated curettes (Hu-Friedy)	Removed	AMX 750 mg (BID, 7 d)+CHX 0.2% (BID, 14 d)	6, 12 months	6,12 months
	Control	oral hygiene	pocket elimination+implant decontamination with 0.2%CHX			CHX0.2% (BID,14D)		
Surgical+local antibiotics								
Cha et al., 2019	Antibiotics	NR	pocket elimination+implant surface clean	titanium-coated curettes (Gracey; Hu-Friedy), a metallic copper-alloy ultrasonic scaler tip (B&L Biotech), a titanium brush (Dentium), an air-powder abrasive device (Air-Flow Master; Electronic Medical Systems)	NR	MH 10mg ointment+ AMX 500mg、ibuprofen (TID,3D)	1, 3, 6 months	6 months
	Control					placebo ointment+ AMX500mg、ibuprofen (TID, 3D)		
Emanuel et al., 2020	Antibiotics	NR	Pocket elimination	NR	NR	D-PLEX500 (0.65% docycycline hyclate)	6, 12 months	6 months
	Control					NR		

PPD, pocket probing depth; BOP, bleeding on probing; SOP, suppuration on probing; BL, bone level; CAL, clinical attachment level; NST, nonsurgical treatment; ST, surgical treatment; SRP, scaling and root planning; MTZ, metronidazole; AMX, amoxicillin; MH, minocycline; BID, twice a day; TID, three times a day; NR: not reported.

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