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MICROBIOME MODULATION THERAPY IN ORAL DISEASES: A NARRATIVE REVIEW

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ABSTRACT:

Background: The major oral diseases are no longer understood as infections by single pathogens but as ecological disorders, in which a resident microbial community shifts from a symbiotic to a dysbiotic state under environmental pressure. This reframing implies that therapy might restore the community rather than eliminate it, and has produced a large literature on probiotics, prebiotics, postbiotics, targeted antimicrobials and microbiota transplantation.

Objective: To evaluate microbiome modulation therapy across the spectrum of oral disease according to the level of evidence each strategy has attained, and to identify why a field with abundant randomised trials has produced so little that has changed practice.

Methods: A narrative review was conducted. PubMed, Embase, the Cochrane Library and ClinicalTrials.gov were searched on microbiota-modulating interventions in dental caries, periodontitis, peri-implant disease, oral candidiasis, halitosis and cancer therapy-induced oral mucositis. Randomised trials, meta-analyses, observational studies, preclinical work and trial registrations were eligible.

Findings: Evidence is extensive but varies in quality and strength. Probiotics reduce caries in children, but not adults; improve periodontitis short-term when added to mechanical debridement; reduce bleeding, but not probing depth, in peri-implant mucositis; and lessen severe mucositis during cancer therapy. An 8% arginine dentifrice reduced caries increment versus fluoride in a 6,000-child phase 3 trial, making substrate modification the strongest-supported ecological strategy. Postbiotics, synbiotics, and nitrate approaches remain largely limited to surrogate microbiological outcomes, while C16G2 completed phase 2 without published efficacy data. Replacement therapy, phage therapy, and oral microbiota transplantation remain preclinical or early-stage.

Conclusions: The obstacle in this field is not a shortage of trials but a shortage of trials that measure disease. Reliance on microbiological surrogates, the transience of exogenous colonisation, and the regulation of most products as foods rather than medicines have together produced a literature that is large, positive and largely unable to support clinical recommendation.

KEYWORDS: oral microbiome; dysbiosis; probiotics; prebiotics; dental caries; periodontitis.

INTRODUCTION

The oral cavity supports one of the most diverse microbial communities in the human body, comprising several hundred commonly detected bacterial taxa together with fungi, viruses and archaea, organised into structurally distinct biofilms on teeth, mucosa and tongue.[1] For most of the twentieth century these communities were approached through an infectious disease model: identify the causative organism, and eliminate it. Dental caries was attributed to Streptococcus mutans, periodontitis to the red complex, and treatment was correspondingly antimicrobial and non-specific.

That model has been substantially revised. The ecological plaque hypothesis proposed that disease arises not from acquisition of an exogenous pathogen but from environmental pressure that selects for organisms already resident in the community.[2] Frequent sugar exposure lowers plaque pH and selects for acidogenic and aciduric species; gingival inflammation supplies proteinaceous substrate and selects for proteolytic anaerobes. The keystone pathogen hypothesis and the polymicrobial synergy and dysbiosis model extended this by showing that low-abundance organisms such as Porphyromonas gingivalis can subvert host immunity and remodel an entire community without themselves being numerically dominant.[3,4,5]

The therapeutic implication is substantial. If disease reflects an ecological shift rather than an infection, then restoring the community becomes a legitimate treatment goal, and interventions that add beneficial organisms, supply substrates favouring them, deliver their metabolic products, or remove pathogens selectively all become plausible. Probiotics alone have been tested in dozens of randomised trials across caries, periodontitis, peri-implant disease, candidiasis, halitosis and mucositis.[6,7]

Yet, despite this growing body of research, probiotics have had little impact on clinical practice. No professional guideline currently recommends a probiotic as standard care for any oral condition. This review therefore asks why promising findings have not translated into routine clinical practice. Rather than examining probiotic agents individually according to their proposed mechanisms, we classify interventions according to their ecological mode of action and evaluate each in relation to the level of evidence it has actually achieved. Throughout, we distinguish between studies

that demonstrate changes in microbial counts or composition and those that demonstrate meaningful effects on clinical disease outcomes.

METHODS

PubMed, Embase, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov were searched from inception to the date of writing. Search terms combined “oral microbiome”, “dysbiosis”, “dental plaque” and “biofilm” with “probiotic”, “prebiotic”, “synbiotic”, “postbiotic”, “arginine”, “nitrate”, “bacteriophage”, “antimicrobial peptide”, “replacement therapy” and “microbiota transplantation”, and were cross-referenced against dental caries, periodontitis, peri-implantitis, oral candidiasis, halitosis and oral mucositis.

English-language randomised controlled trials, systematic reviews, meta-analyses, observational studies, preclinical work and trial registrations were eligible. Reference lists of retrieved articles were hand-searched. Throughout, a distinction is maintained between microbiological surrogate endpoints, such as salivary Streptococcus mutans counts or plaque pH, and clinical disease endpoints, such as caries increment, probing depth or mucositis grade; where a body of evidence rests only on surrogates this is stated explicitly. Selection of studies was purposive rather than exhaustive, prioritising the highest available level of evidence for each strategy and condition.

The ecological basis for modulation

Three features of the oral ecosystem determine what modulation can and cannot achieve, and they recur in every section that follows.

The first is that the community is resilient. Oral biofilms are spatially organised, metabolically integrated and colonisation-resistant, which is precisely why they are stable in health and why they resist correction in disease.1 An exogenous organism introduced into an established biofilm faces the same barriers that protect a healthy community from pathogens. The second is that dysbiosis is driven by environmental conditions rather than by community composition alone.[2] Removing a pathogen without removing the selective pressure that favoured it invites recolonisation by the same or an equivalent organism, which is the ecological explanation for the long-term failure of broad-spectrum antimicrobial approaches. The third is that inflammation is both consequence and cause: proteolytic taxa in the periodontal pocket feed on inflammatory exudate, so the dysbiotic community actively sustains the conditions that favour it.[4,5]

These features generate the four strategies illustrated in Figure 1. Organisms may be added, as probiotics or as a transplanted community. Substrate may be added to favour health-associated metabolism, the prebiotic approach exemplified by arginine and nitrate. Microbial products may be delivered without live organisms, the postbiotic approach. Or specific organisms may be removed while the remainder of the community is preserved, through targeted antimicrobial peptides or bacteriophages. The strategies differ in how directly they address the underlying selective pressure, and, as the evidence shows, this turns out to matter.

Figure 1 sets out the ecological axis along which oral disease develops and the four points at which modulation therapy is proposed to intervene.

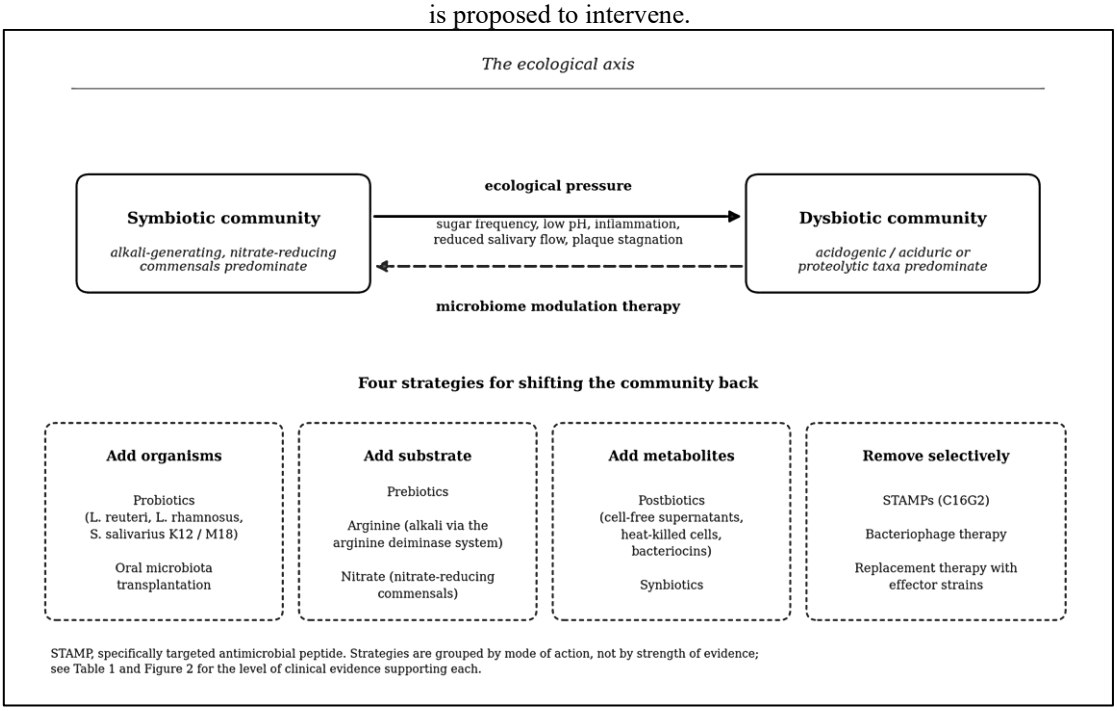

Figure 1: The ecological axis in oral disease and the four strategies of microbiome modulation.
Environmental pressure drives the resident community from a symbiotic to a dysbiotic state; modulation therapy aims to reverse that shift. Strategies are grouped by mode of action rather than by strength of evidence, which is summarised separately in Table 1 and Figure 2.

Adding Organisms: Probiotics

Probiotics dominate this literature and are the only strategy tested at scale across every condition considered here. They are treated first and at length because the pattern of their results, positive on surrogates, inconsistent on disease, is the pattern the whole field must contend with.

Dental caries

The microbiological case is settled. A systematic review and meta-analysis of 50 trials in 3,247 participants found that probiotics significantly increased the likelihood of reducing salivary Streptococcus mutans below 10^4 colony-forming units per millilitre, with an odds ratio of 2.20 (95% CI 1.23 to 3.92), and confirmed the reduction on a continuous scale with a standardised mean difference of -1.18 (95% CI -1.64 to -0.72).7 The same review found the evidence for caries incidence itself far weaker, and noted that lactobacilli are themselves acidogenic and aciduric, so that reducing one cariogenic organism by introducing another is not self-evidently beneficial.

More recent pooling has begun to separate populations. A meta-analysis of 18 randomised trials found that in children, across 12 trials and approximately 2,300 participants, probiotics significantly reduced new or progressive caries with a risk ratio of 0.80 (95% CI 0.68 to 0.95), graded as moderate certainty; in adults, across 6 trials and approximately 1,100 participants, there was no significant benefit, with a risk ratio of 0.95 (95% CI 0.80 to 1.12).[8] Lactobacillus rhamnosus and L. reuteri delivered in lozenges or dairy products accounted for most of the paediatric signal.

This age discrepancy deserves more attention than it usually receives. It is consistent with the ecological framework: the developing biofilm of a young child is less established and more susceptible to displacement than the mature, colonisation-resistant community of an adult. If that interpretation is correct, the therapeutic window for adding organisms is narrow and early, and the routine marketing of oral probiotics to adults is not supported by the evidence.

Periodontitis

Probiotics in periodontitis are used as an adjunct to scaling and root planing rather than as monotherapy, which is appropriate given that mechanical disruption of the biofilm removes the substrate and creates the ecological opening an exogenous organism would need. A systematic review and meta-analysis of probiotics as an adjunct to non-surgical periodontal treatment found improvement in probing pocket depth and clinical attachment level.[9] Benefit is consistently greatest in deep pockets, smallest or absent in shallow ones, and short-lived, typically no longer demonstrable beyond three months.

The short duration is the central problem, and it is not a trial design artefact. It reflects the fact that Lactobacillus reuteri and similar strains do not establish durably in the periodontal pocket. When administration stops, the strain disappears and the pocket environment, which was never altered, reselects the original community. Probiotics in periodontitis are therefore better understood as a temporary pharmacological effect than as ecological restoration.

Peri-implant disease

Peri-implant disease provides the clearest demonstration of endpoint dependence in this literature. A systematic review and meta-analysis of probiotics adjunctive to mechanical debridement in peri-implant mucositis found no benefit on the primary outcome: the weighted mean difference in probing depth reduction was -0.12 mm (95% CI -0.38 to 0.14, p=0.38).[10] A later meta-analysis of 10 randomised trials in 391 participants found that probiotics reduced bleeding on probing at three and six months and improved plaque index at three months, but again found no effect on probing depth, and no effect at all in established peri-implantitis.

Bleeding on probing is an inflammatory sign; probing depth reflects tissue destruction. A therapy that improves the former without the latter may be modulating host response rather than reversing disease. Reporting such a result as evidence that probiotics work in peri-implant disease, as several secondary sources do, overstates what was shown.

Oral candidiasis, halitosis and oral mucositis

Beyond the plaque-related diseases, three further indications have accumulated randomised evidence. In oral candidiasis, a meta-analysis of four randomised trials in 480 elderly denture wearers found a combined odds ratio of 0.24 (95% CI 0.09 to 0.63) favouring probiotics over placebo or no treatment, with reductions in Candida counts and clinical signs.[11] The important qualification is that probiotics were not compared with conventional antifungal therapy, so the result establishes superiority to nothing rather than a place in management.

In halitosis, Streptococcus salivarius K12 has been the most studied agent, acting through bacteriocin-mediated suppression of halitogenic proteolytic anaerobes. A double-blind randomised placebo-controlled trial found that organoleptic scores and volatile sulphur compound levels fell significantly in the test group immediately after a 30-day course, but the investigators concluded that K12 had no significant effect when tongue coating had not first been physically or chemically removed.[12] This is an ecological finding in miniature: the probiotic worked only when the niche had been cleared for it.

Cancer therapy-induced oral mucositis is the outlier. A systematic review and meta-analysis of seven randomised trials found a significantly lower incidence of severe mucositis with probiotics, with a risk ratio of 0.65 (95% CI 0.53 to 0.81), and a reduced requirement for enteral nutrition with an odds ratio of 0.34 (95% CI 0.13 to 0.92).[13] These are patient-relevant endpoints and the effect size is meaningful. It is worth noting, however, that the mechanism here is probably immunomodulatory and partly systemic rather than a local correction of oral dysbiosis, which makes mucositis the condition in which probiotics perform best and the one in which the ecological rationale applies least.

Adding Substrate: Prebiotic Approaches

Arginine

Arginine is metabolised by the arginine deiminase system of commensal streptococci, principally Streptococcus sanguinis and S. gordonii, generating ammonia and raising plaque pH. Arginine deiminase activity is consistently lower in caries-active than caries-free individuals, so supplying exogenous arginine amounts to feeding the alkali-generating fraction of a community in which it has been outcompeted.

The ecological effect has been demonstrated directly. An arginine-containing dentifrice normalised the oral microbiota of caries-active individuals towards that of caries-free controls in microbial structure, species abundance and the expression of glycolytic and alkali-generating enzymes; combining arginine with fluoride enriched S. sanguinis and suppressed S. mutans more effectively than either alone.[14] A randomised double-blind in situ study confirmed that arginine dentifrice substantially reduced lactic acid production from plaque without reducing total biofilm biomass or the live-to-dead ratio, which is the signature of ecological modulation rather than antimicrobial action.[15]

Crucially, this strategy has been carried through to a disease endpoint. A two-year, three-arm, double-blind phase 3 randomised trial across three centres enrolled 6,000 children aged 10 to 14 with active caries lesions, comparing 8.0% arginine, 1.5% arginine and 0.32% sodium fluoride dentifrices. The 8.0% arginine dentifrice produced a 26.0% greater reduction in incremental DMFS and a 25.3% greater reduction in incremental DMFT than the fluoride control, while 1.5% arginine was equivalent to fluoride.[16]

This is by a wide margin the strongest evidence in the field: a hard clinical endpoint, a large sample, an active rather than placebo comparator, and a demonstrated dose response. It is also the strategy that most directly addresses the selective pressure itself rather than the community composition, and the contrast with the probiotic literature on this point is instructive.

Nitrate

Dietary nitrate is reduced to nitrite by commensal genera including Rothia, Neisseria, Actinomyces and Veillonella, generating nitric oxide with local antimicrobial and vasoregulatory effects. Nitrate-reducing capacity is diminished in periodontitis and recovers after periodontal treatment, and nitrate-reducing isolates have been characterised specifically as candidate oral probiotics.[17] Nitrate supplementation shifts community composition towards nitrate-reducing taxa and away from Prevotella and Porphyromonas.

The approach is attractive because it is dietary, inexpensive and targets abundant commensals rather than requiring a foreign organism to establish. Clinical evidence, however, remains limited to small short-duration studies reporting gingival inflammation indices, with no adequately powered trial against periodontal disease progression. Nitrate is best described as mechanistically well founded and clinically unproven.

Postbiotics and Synbiotics

Postbiotics, comprising cell-free supernatants, heat-killed cells, bacteriocins and other microbial products, avoid the central difficulty of live organisms: they need not colonise, and they carry no risk of acidogenic strains persisting in a caries-prone mouth. A systematic review identified 21 studies, of which 18 were in vitro and only three were randomised trials; postbiotics inhibited S. mutans growth, biofilm formation and virulence gene expression, and human trials reported reduced salivary S. mutans counts and raised salivary pH.[18] No trial has reported a caries increment.

Synbiotic combinations of prebiotic and probiotic remain similarly confined to surrogate endpoints.[6,8] For both classes the honest description is that they are formulation advances awaiting clinical evaluation, not therapies with demonstrated benefit.

Selective Removal and Community Engineering

Specifically targeted antimicrobial peptides

C16G2 is the most fully developed attempt at precision antimicrobial therapy in dentistry. It joins a targeting domain derived from the S. mutans competence stimulating peptide to a broad-spectrum killing domain, producing selective killing of S. mutans within seconds while sparing S. sanguinis and S. gordonii.[19] In an intra-oral remineralisation and demineralisation model, a 0.04% rinse reduced plaque and salivary S. mutans, lactic acid production and enamel demineralisation with minimal impact on total plaque bacteria.[20] A single treatment produced a community shift that resisted S. mutans regrowth through repeated sucrose challenge.[21]

The concept is therefore validated: selective removal can produce durable ecological change in humans, which is more than can be said for most strategies here. C16G2 progressed through rinse, varnish and strip formulations into phase 2 trials.[22] No peer-reviewed efficacy publication from those trials has appeared, and the programme has not advanced. Whether this reflects efficacy, cost, formulation or commercial factors is not established in the public record, and reviews that list C16G2 among promising future therapies without noting that its development stalled give a misleading impression.

Replacement therapy

Replacement therapy proposes to install a permanent effector strain that occupies the cariogenic niche without causing disease. The most developed example, a genetically modified S. mutans deficient in lactate dehydrogenase and producing a bacteriocin allowing it to displace wild-type strains, was designed to colonise once and persist indefinitely.[23]

The strategy is ecologically coherent, since permanent colonisation is exactly what transient probiotics fail to achieve. It has not progressed. Deliberate permanent establishment of a genetically modified organism in a human, irreversibly and for a non-fatal condition, presents a risk-benefit and regulatory problem that has not been solved. Replacement therapy is best regarded as a demonstration of what the field would need rather than a therapy in development.

Bacteriophage therapy

Phages offer species-level or strain-level specificity, self-amplification at the site of infection, and activity against biofilms through depolymerases. Phages targeting Porphyromonas gingivalis, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, S. mutans and the endodontic pathogen Enterococcus faecalis have been predicted or isolated.[24] Evidence is entirely in vitro and in animal models; no oral clinical trial has been reported. Narrow host range, which is the source of the specificity, also means that a single phage may fail against the strain diversity present in any individual mouth.

Oral microbiota transplantation

Transplantation of a whole healthy community, by analogy with faecal microbiota transplantation in Clostridioides difficile infection, is the most ambitious form of modulation. In vitro and animal work has shown that transplanted supragingival communities can reduce periodontitis-associated taxa and increase health-associated ones, and protocols for donor identification and niche clearance have been published.[25]

No controlled human trial has demonstrated clinical benefit. The obstacles are specific to the oral cavity: unlike the colon, the mouth cannot be emptied before inoculation, so the resident community must be cleared without destroying the surfaces to which a new one must attach; donor screening is complicated by the fact that periodontal pathogens are present in health; and transmissibility to household contacts raises questions with no counterpart in gut transplantation.

Three Problems Common to the Field

Reading these literatures together, the same three difficulties recur regardless of strategy, and they explain the gap between the volume of positive trials and the absence of clinical recommendations.

The first is colonisation persistence. Conventional probiotic strains are transient in the mouth, and detection typically ceases within weeks of stopping administration. Most strains in use were isolated from the gastrointestinal tract and are not adapted to salivary flow, a biofilm lifestyle or oral surface receptors. A transient organism cannot restore an ecosystem; at best it produces a pharmacological effect for as long as it is being administered, which is what the short duration of benefit in periodontitis and halitosis reflects.

The second is endpoint validity. A very large proportion of trials in this field report salivary or plaque counts, plaque pH, or community composition by sequencing, rather than caries increment, attachment loss or mucositis grade. Surrogates are cheaper and faster, and they respond readily. But the surrogate and the disease can diverge, as the peri-implant literature shows directly, where bleeding improved and probing depth did not.10 The recurring claim that an intervention favourably modulates the oral microbiota is frequently true and frequently uninformative about whether it prevents disease.

The third is regulatory status. Most oral probiotics are marketed as food supplements rather than licensed as medicines. This lowers the evidentiary threshold for market entry and removes the commercial incentive to run the large, long, disease-endpoint trials that would be required for a licensed indication. The consequence is visible in the literature: many small short trials on surrogate endpoints, few definitive ones. The single exception, the 6,000-child arginine dentifrice trial, was conducted by a manufacturer seeking to position a product against fluoride in a regulated dentifrice market, which is precisely the commercial structure that generates definitive evidence.[16]

Synthesis

Table 1 summarises each strategy by agent, condition, highest evidence attained and principal limitation.

Table 1: Microbiome modulation strategies in oral disease by agent, condition, evidence level and principal limitation.

STRATEGY	AGENT	CONDITION	HIGHEST EVIDENCE	PRINCIPAL LIMITATION
Add substrate	Arginine dentifrice (8%)	Caries	Phase 3 RCT, 6,000 children, caries increment16	Dose-dependent; 1.5% no better than fluoride
Add organisms	Probiotics (lactobacilli, bifidobacteria)	Caries, children	Meta-analysed RCTs, caries increment8	Moderate certainty; strain and vehicle heterogeneity

STRATEGY	AGENT	CONDITION	HIGHEST EVIDENCE	PRINCIPAL LIMITATION
Add organisms	Probiotics	Caries, adults	Meta-analysed RCTs, no benefit7,8	Effect confined to children; acidogenic strains a theoretical risk
Add organisms	Probiotics adjunct to SRP	Periodontitis	Meta-analysed RCTs, pocket depth and attachment9	Short-term only; benefit largest in deep pockets
Add organisms	Probiotics adjunct to debridement	Peri-implant mucositis	Meta-analysed RCTs, bleeding only10	No effect on probing depth or peri-implantitis
Add organisms	Probiotics	Oral candidiasis	Meta-analysed RCTs, denture wearers11	Four small trials; not compared with antifungals
Add organisms	Probiotics (lactobacilli)	Oral mucositis	Meta-analysed RCTs, severe mucositis13	Heterogeneous regimens; systemic not local mechanism
Add organisms	S. salivarius K12	Halitosis	RCTs, volatile sulphur compounds12	Requires tongue debridement first; effect not durable
Add substrate	Nitrate / nitrate-reducing commensals	Periodontitis, gingivitis	Mechanistic and early clinical work17	No adequately powered clinical endpoint trial
Add metabolites	Postbiotics	Caries	Three RCTs, surrogate endpoints18	Predominantly in vitro; no caries increment data
Remove selectively	C16G2 (STAMP)	Caries	Phase 2 completed; no efficacy publication19-22	Development not carried forward
Remove selectively	Replacement therapy (effector strains)	Caries	Early human safety work only23	Deliberate permanent colonisation; regulatory barrier
Remove selectively	Bacteriophage therapy	Caries, periodontitis, endodontic	In vitro and animal only24	Narrow host range; no oral clinical trial
Add organisms	Oral microbiota transplantation	Periodontitis	In vitro, animal, protocols25	Donor screening and niche clearance unresolved

DMFS, decayed missing and filled surfaces; DMFT, decayed missing and filled teeth; RCT, randomised controlled trial; SRP, scaling and root planing; STAMP, specifically targeted antimicrobial peptide.

Figure 2 presents the same information as a readiness map, plotting each strategy against the highest level of evidence it has reached and distinguishing trials that measured microbiological surrogates from those that measured disease.

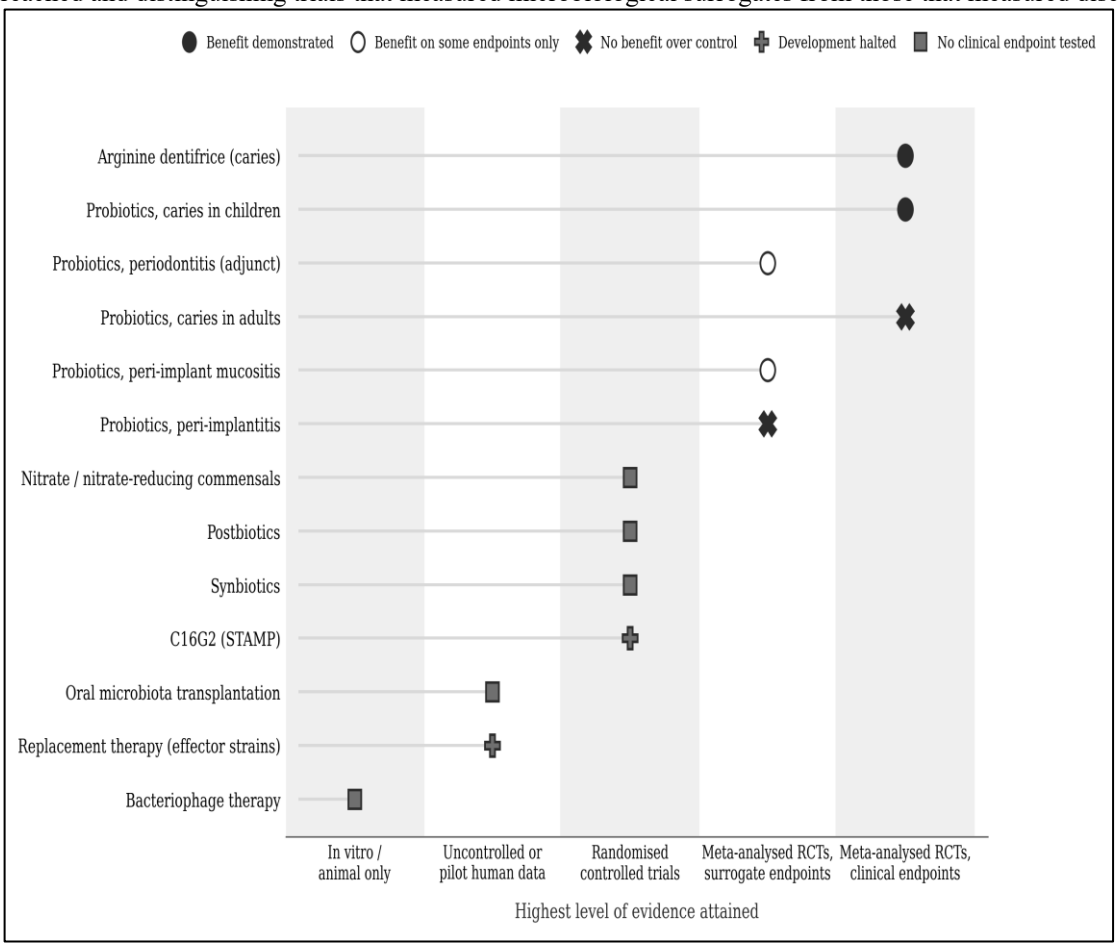

Figure 2: Evidence attained by microbiome modulation strategies in oral disease. The two rightmost categories separate meta-analysed randomised evidence on microbiological surrogate endpoints from meta-analysed randomised evidence on clinical disease endpoints, a distinction that is central to interpreting this literature. Marker position reflects evidential level, not relative clinical value; entries marked as development halted have not progressed despite favourable early results.

Three observations follow: First, the only strategy supported by a large trial against a hard clinical endpoint and an active comparator is substrate modification with arginine, and it is also the strategy that acts on the selective pressure rather than on community membership. Second, probiotic benefit tracks two conditions: a cleared or immature niche, as in children, in debrided pockets and after tongue debridement; and an indication where the mechanism is host-directed rather than ecological, as in mucositis. Third, the approaches that address ecological restoration most directly, replacement therapy, targeted peptides and transplantation, are the least advanced, and two of them have stalled for reasons that are regulatory and commercial rather than scientific.

CONCLUSION

The reconceptualisation of caries and periodontitis as ecological disorders is sound and has been productive. It has not yet produced a microbiome-based therapy that has entered routine care, and the reason is not that the trials are absent. They are numerous, mostly positive, and mostly uninformative about disease.

Where the evidence is strongest, it points in a consistent direction. Arginine, which changes the metabolic conditions of the biofilm rather than its membership, has reduced caries increment against fluoride in a large phase 3 trial. Probiotics, which add organisms without altering conditions, help in children whose communities are not yet fixed, in pockets and tongues that have just been cleared, and in mucositis where the mechanism is probably not ecological at all. Strategies that would achieve genuine ecological restoration, permanent effector strains, targeted antimicrobials and community transplantation, remain unrealised.

Progress will require trials that measure disease rather than microbes, strains that persist rather than pass through, interventions paired with removal of the pressure that caused the dysbiosis, and a regulatory route that rewards definitive evidence. Until then, microbiome modulation in oral disease remains a well-founded idea with one convincing clinical success and a great deal of supporting data that does not answer the question clinicians need answered.

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