Host modulators

A possible adjunctive to NSPT?

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Periodontology 2000

REVIEW ARTICLE

Current understanding of periodontal disease pathogenesis and targets for host-modulation therapy

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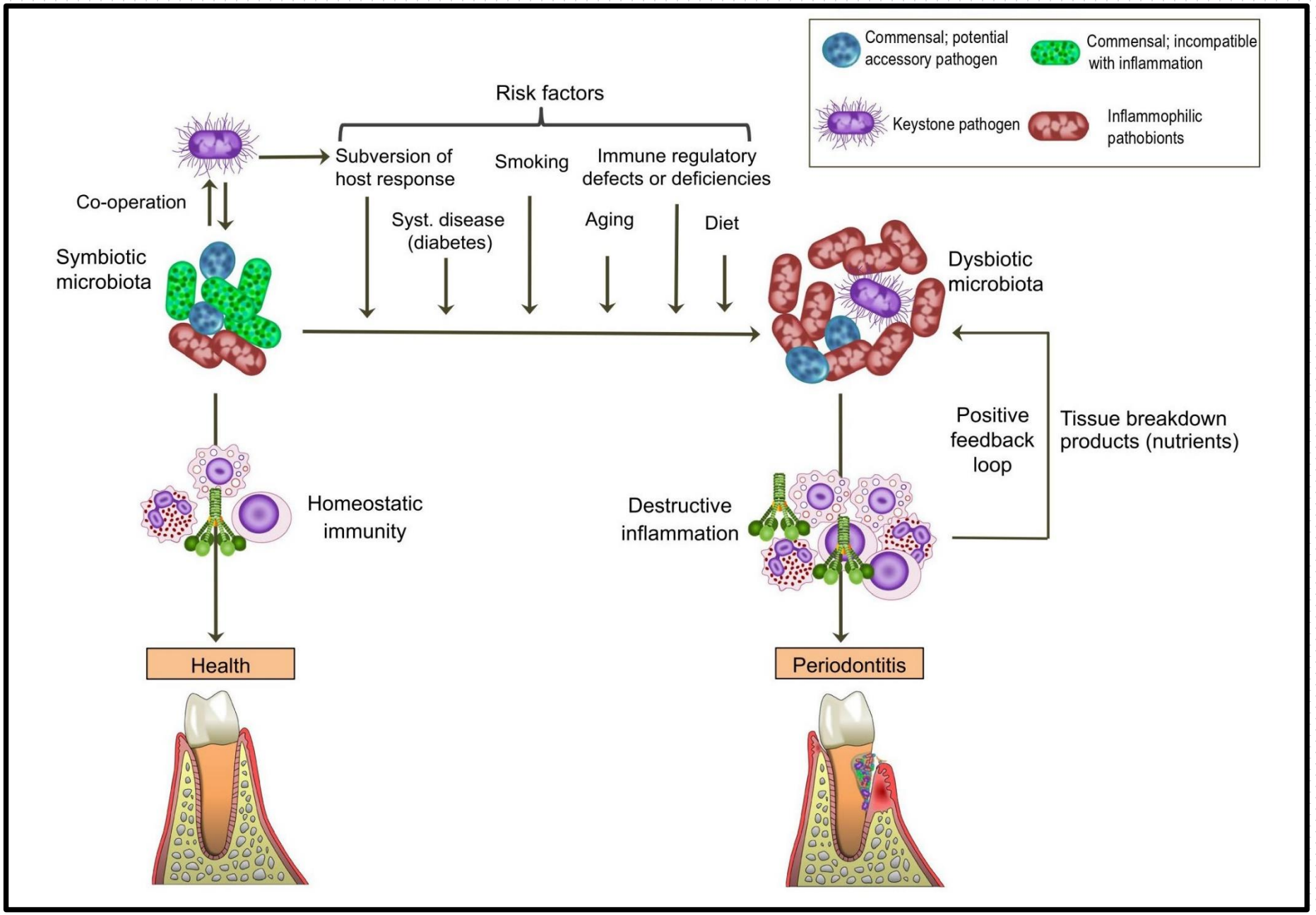
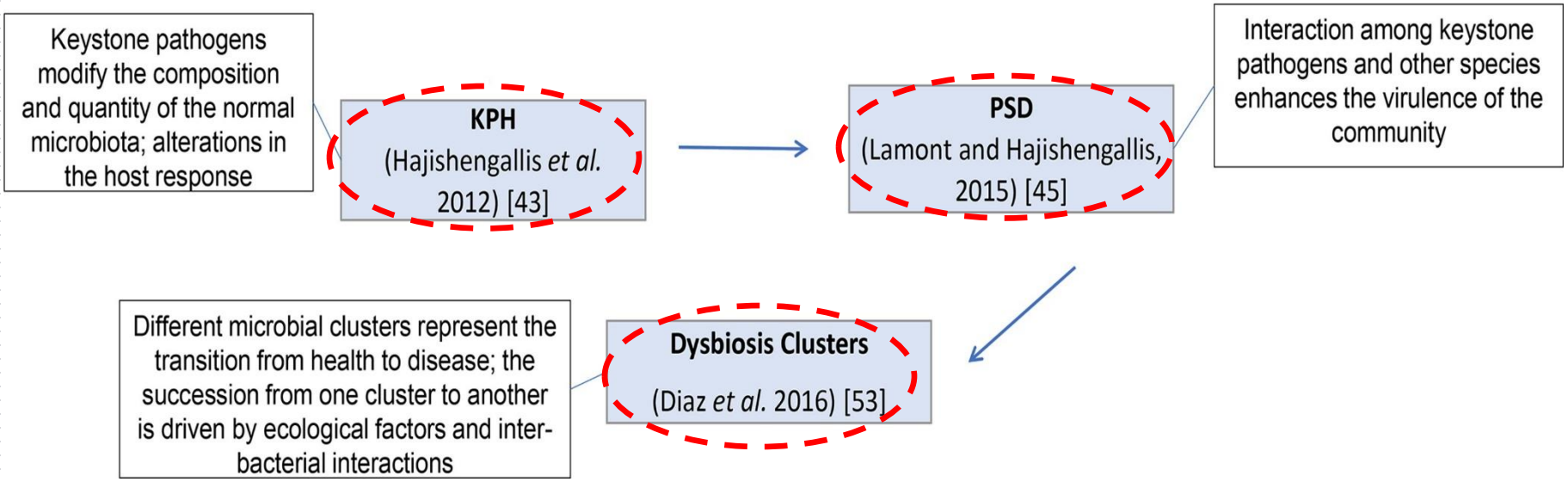
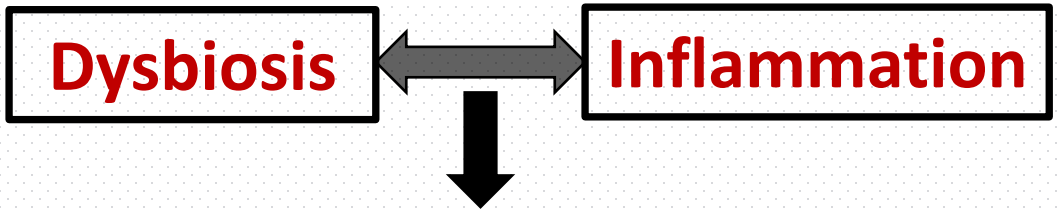


Adapted by **Hajishengallis *et al* 2020**





"Inflammophilic" pathobiotic bacteria

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CLINICAL PRACTICE GUIDELINE

Journal of Clinical Periodontology WILEY

Treatment of stage I–III periodontitis—The EFP S3 level clinical practice guideline

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DOI: 10.1111/jcpe.13232

SYSTEMATIC REVIEW

Journal of Clinical Periodontology WILEY

The adjunctive use of host modulators in non-surgical periodontal therapy. A systematic review of randomized, placebo-controlled clinical studies

Nikolaos Donos[1] | Elena Calciolari[1] | Nele Brusselaers[2] | Matteo Goldoni[3] | Nagihan Bostanci[4] | Georgios N. Belibasakis[4]

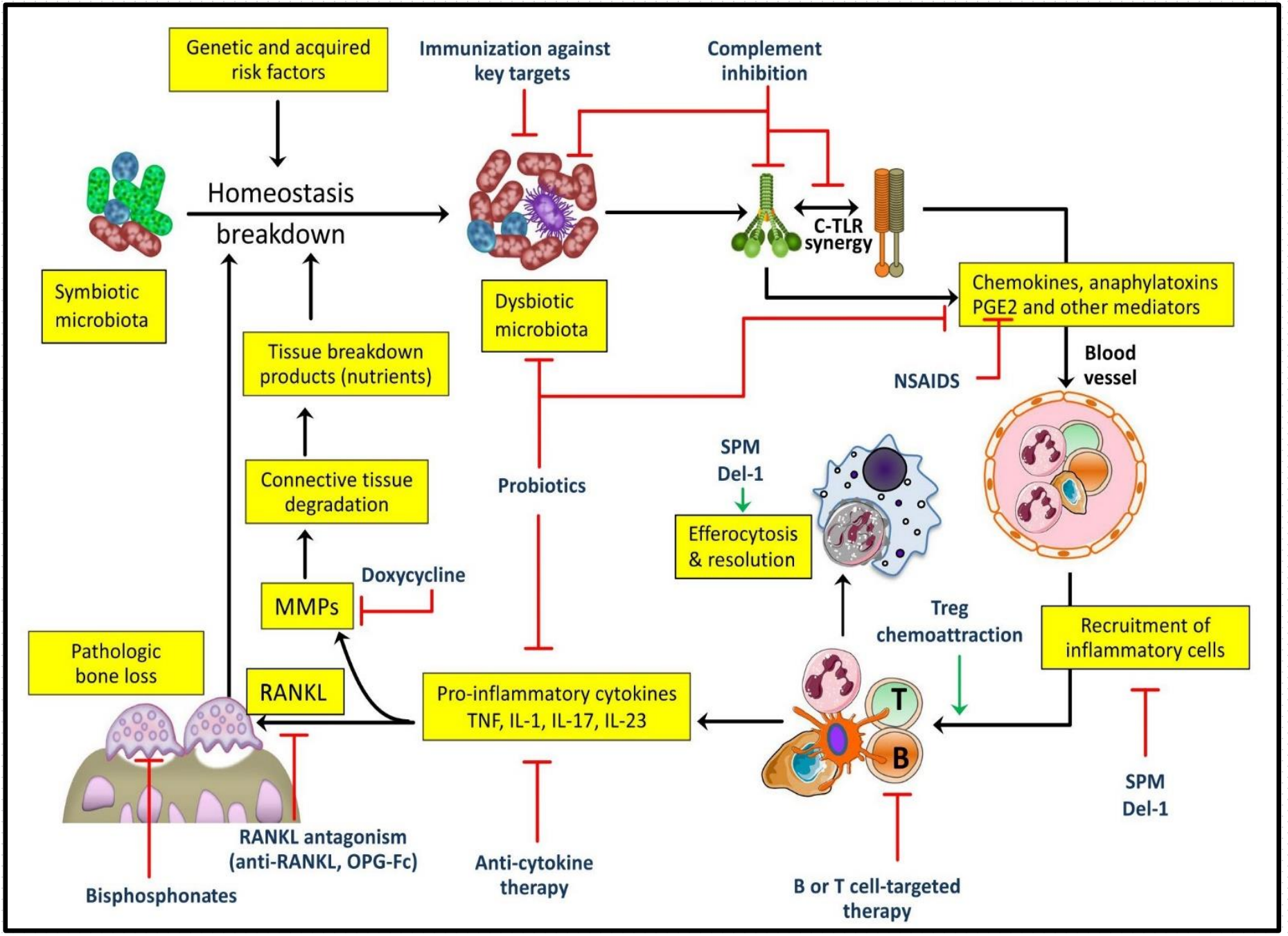
Host-response modulation approaches

Came from

Tissue damage in periodontitis:

1- Is mediated primarily by the host inflammatory response.

2- Exploited by the dysbiotic microbial community for growth and persistence


Genetic and acquired risk factors
Immunization against key targets
Complement inhibition
Homeostasis breakdown
Symbiotic microbiota
Dysbiotic microbiota
C-TLR synergy
Chemokines, anaphylatoxins PGE2 and other mediators
Blood vessel
NSAIDS
Tissue breakdown products (nutrients)
Connective tissue degradation
Probiotics
SPM Del-1
Efferocytosis & resolution
Doxycycline
MMPs
Pathologic bone loss
RANKL
Pro-inflammatory cytokines TNF, IL-1, IL-17, IL-23
Treg chemoattraction
Recruitment of inflammatory cells
T
B
SPM Del-1
RANKL antagonism (anti-RANKL, OPG-Fc)
Bisphosphonates
Anti-cytokine therapy
B or T cell-targeted therapy

Grade of recommendation grade[a]	Description	Syntax
A	Strong recommendation	We recommend (↑↑)/ We recommend not to (↓↓)
B	Recommendation	We suggest to (↑)/ We suggest not to (↓)
0	Open recommendation	May be considered (↔)

[a]If the group felt that evidence was not clear enough to support a recommendation, Statements were formulated, including the need (or not) of additional research.

INFLAMMATION AND ITS RESOLUTION

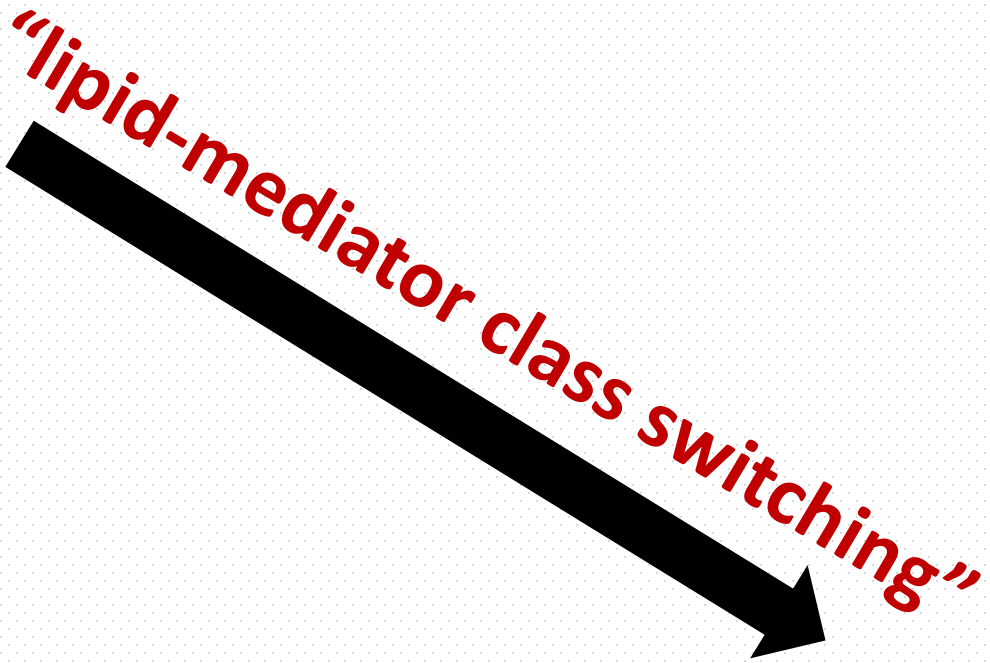
R2.6 | Does the adjunctive use of local statins improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.6)
We **recommend not to use** local administration of statin gels (atorvastatin, simvastatin, rosuvastatin) as adjuncts to subgingival instrumentation.
Supporting literature Donos et al. (2019)
Quality of evidence Twelve placebo-controlled RCTs (n = 753), for 1.2% atorvastatin (six RCTs, n = 180), 1.2% simvastatin gel (5 RCTs, n = 118) and 1.2% rosuvastatin gel (four RCTs, n = 122)
Grade of recommendation Grade A—↓↓
Strength of consensus Strong consensus (0% of the group abstained due to potential CoI)

R2.11 | Does the adjunctive use of omega-3 polyunsaturated fatty acids (PUFA) improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.11)
We **recommend not to** use omega−3 PUFAs as an adjunct to subgingival instrumentation.
Supporting literature Donos et al. (2019)
Quality of evidence Three placebo-controlled RCTs (*n* = 160) with 6-month administration of omega-3 PUFAs.
Grade of recommendation Grade A−↓↓
Strength of consensus Consensus (0% of the group abstained due to potential CoI)

Environment rich in proinflammatory prostaglandins and leukotrienes



Environment rich in proresolving mediators:

- Arachidonic acid-derived **lipoxins**
- **Omega-3** polyunsaturated fatty acid-derived **resolvins**
- **Protectins**

The successful resolution of inflammation is an active and well-coordinated process, including:

- ↓ Proinflammatory mediators and ↑ regulatory or pro-resolution mediators.
- Termination of neutrophil recruitment.
- Clearance of apoptotic neutrophils by tissue phagocytes (Efferocytosis).

↓

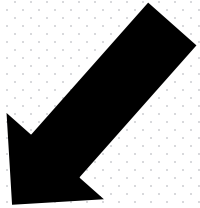
- Initiation of tissue repair.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

R2.10 | Does adjunctive use of systemic/local non-steroidal anti-inflammatory drugs to subgingival instrumentation improve the clinical outcomes?

Evidence-based recommendation (2.10)
We **recommend not to use** systemic or local non-steroidal anti-inflammatory drugs (NSAIDs) as an adjunct to subgingival instrumentation
Supporting literature Donos et al. (2019)
Quality of evidence Two placebo-controlled RCTs (*n* = 88) on local application (1% flurbiprofen toothpaste; irrigation with 200 ml buffered 0.3% acetylsalicylic acid); two placebo-controlled RCTs (*n* = 133) on systemic applications (celecoxib, diclofenac potassium)
Grade of recommendation Grade A—↓↓
Strength of consensus Strong consensus (1.3% of the group abstained due to potential CoI)

- Block the cyclooxygenase pathway of arachidonic acid metabolism.



Prostaglandin E2

(Vasodilator, promote vascular permeability, and bone resorption

Challenges:

1- Decline rapidly after drug withdrawal.

2- Have serious adverse effects for long term use.

3- Nonselective NSAIDs are associated with GI mucosal damage and renal toxicity.

4- Induce prothrombotic side-effects (cyclooxygenase-2 inhibitors).

ANTI- CYTOKINE THERAPY

- Use of neutralizing monoclonal antibodies or receptor antagonists to block the action of proinflammatory cytokines (antagonists).

TNF, IL-1, or IL-17

(**Treatment of periodontitis in preclinical models**)

Using anti-rheumatic drugs in rheumatoid patients with periodontitis.

Infliximab (monoclonal antibody to TNF).

Etanercept (a soluble form of TNF receptor).

Anakinra (IL-1 receptor antagonist).

Reducing periodontal inflammation??

Challenges:

1- Small number of studies performed.

2- Has potentially adverse effects on immunity.
(Preferred to be administered locally than systemically).

3- Blockade of a single cytokine may not be very effective in cytokine network-induced inflammation.

However,

Anti-interleukin-23 therapy (**ustekinumab**, a monoclonal antibody).

↓

Blocks IL-12/IL-23 p40 in **LAD-1**

↓

Inhibited gingival expression of interleukin-17

Resolve inflammation

PROBIOTICS

R2.7 | Does the adjunctive use of probiotics improve the clinical outcome of subgingival instrumentation?

Evidence-based recommendation (2.7)
We **suggest not to use** probiotics as an adjunct to subgingival instrumentation
Supporting literature Donos et al. (2019)
Quality of evidence Five placebo controlled RCTs (*n* = 176) testing preparations containing *L. ramnosus* SP1, *L. reuteri* or the combination of *S. oralis* KJ3, *S. uberis* KJ2 and *S. rattus* JH145.
Grade of recommendation Grade B—↓
Strength of consensus Consensus (0% of the group abstained due to potential CoI)

- Modulate both the microbiota and the host response

  Transient treatment till the end of treatment

- Gastric intubation of *L. gasseri* SBT2055 in mice inhibited *P. gingivalis*-induced gingival inflammation and alveolar bone loss

- In mice, topical application of *L. brevis* CD2 was shown to:

  - Inhibit ligature-induced gingival inflammation and bone loss.
  - Reduce the counts of gram-negative bacteria (**3 times daily for 14 days**)

Problems:

- Small sample sizes.
- Studies are quite heterogeneous.
  - Use of different probiotic strains.
  - Different doses.
  - Different modes of administration.

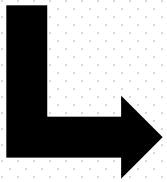
COMPLEMENT

- A cause-and-effect relationship between complement and periodontitis was established in preclinical mouse models.

Mice deficient in **C3** or **C5aR1** were found to be protected against experimental periodontitis compared with wild-type controls

- C3 inhibitor (Cp40) (analog of the compstatin family of C3 inhibitors).

AMY-101



Suppression of IL-17, TNF-11, MMP

Safe (up to 3 months) in hematological, biochemical, or immunological parameters

SCIENCE ADVANCES | RESEARCH ARTICLE

CORONAVIRUS

Complement C3 inhibition in severe COVID-19 using compstatin AMY-101

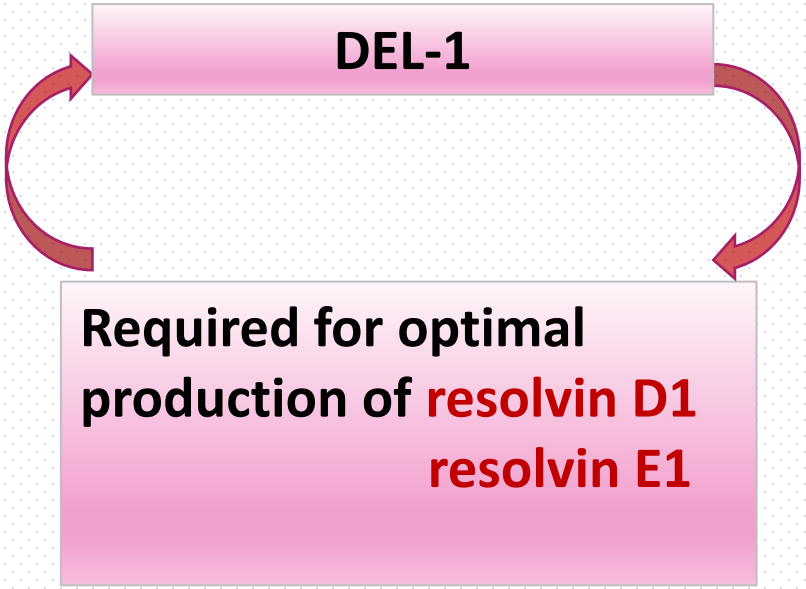
Panagiotis Skendros[1], Georgios Germanidis[2], Dimitrios C. Mastellos[3], Christina Antoniadou[1], Efstratios Gavriilidis[1], Georgios Kalopitas[2], Anna Samakidou[4], Angelos Liontos[5], Akrivi Chrysanthopoulou[1], Maria Ntinopoulou[1], Dionysios Kogias[1], Ioanna Karanika[2], Andreas Smyrlis[1], Dainora Cepaityte[2], Iliana Fotiadou[1], Nikoleta Zioga[1], Ioannis Mitroulis[1], Nikolaos K. Gatselis[4], Charalampos Papagoras[1], Simeon Metallidis[2], Haralampos Milionis[5], George N. Dalekos[4], Loek Willems[6], Barbro Persson[7], Vivek Anand Manivel[7], Bo Nilsson[7], E. Sander Connolly[8], Simona Iacobelli[9], Vasileios Papadopoulos[1], Rodrigo T. Calado[10], Markus Huber-Lang[11], Antonio M. Risitano[12], Despina Yancopoulou[13], Konstantinos Ritis[1], John D. Lambris[14]*

HOMEOSTATIC PROTEINS

EPIDERMAL GROWTH FACTOR-LIKE and DISCOIDIN-LIKE DOMAINS

- **Developmental endothelial locus-1 (DEL-1)**
- **Milk fat globule-epidermal growth factor-8 (MFG-E8)**

Have important homeostatic functions in non-human primate models



Inhibit periodontitis in mouse and

Inhibited
IL-17 production
Neutrophil accumulation
Bone loss

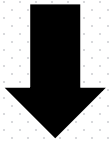
TARGETING ADAPTIVE IMMUNE CELL S

- Antibody-mediated neutralization of **tumor necrosis factor ligand superfamily member 13** or **B-lymphocyte stimulator** in mice

Diminish the B-cell numbers in the gingival tissue and inhibit periodontal bone loss **(Belimumab, Rituximab)**

SLE **PD**

- **T-helper 17 inhibitor (Inhibitor GSK805)**



Blocked inflammatory bone loss in a murine model

DIRECT INHIBITION OF PERIODONTAL TISSUE DESTRUCTION

(MMPs, TNF ligand superfamily member 11)

R2.8 | Does the adjunctive use of systemic sub-antimicrobial dose doxycycline (SDD) to subgingival instrumentation improve clinical outcomes?

Evidence-based recommendation (2.8)
We **suggest not to use** systemic sub-antimicrobial dose doxycycline (SDD) as an adjunct to subgingival instrumentation.
Supporting literature Donos et al. (2019)
Quality of evidence Eight placebo-controlled RCTs (14 publications, *n* = 610). Meta-analysis on PPD reduction was performed in five RCTs (*n* = 484)
Grade of recommendation Grade B—↓
Strength of consensus Consensus (1.3% of the group abstained due to potential CoI)

- Sub-antimicrobial doses of tetracycline could block the activity of MMPs.

- Systemically delivered doxycycline as an adjunct to scaling and root planning (20 mg, taken twice daily). (Approved by Us FDA as **Periostat**)

R2.9 | Does the adjunctive use of systemic/local bisphosphonates to subgingival instrumentation improve clinical outcomes?

Evidence-based recommendation (2.9)

We **recommend not to use** locally delivered bisphosphonate (BP) gels or systemic BPs as an adjunct to subgingival instrumentation.

Supporting literature Donos et al. (2019)

Quality of evidence Seven placebo-controlled RCTs (*n* = 348), on local delivery of 1% alendronate gel (six studies) and 0.5% zolendronate gel (one study); two placebo-controlled RCTs (*n* = 90) on systemic administration of BPs (alendronic acid and risedronate).

Grade of recommendation Grade A—↓↓

Strength of consensus Strong consensus (0% of the group abstained due to potential CoI)

- **Bisphosphonates** promotes osteoclast apoptosis (treatment of osteoporosis).

Decreased alveolar bone loss and improved mineral density in periodontitis patients **(Risedronate or Alendronate)**

- Blocks the interaction of tumor necrosis factor ligand superfamily member 11 with its receptor on the surface of osteoclast precursors **(Denosumab)**

Prevent the differentiation of osteoclasts

Osteoclasts regulators (frizzled-related proteins) **(protein 5)**

Bind TNF ligand superfamily member 11 → preventing its interaction with TNF receptor superfamily member 11A

Inhibiting osteoclastogenesis

Has anti-inflammatory properties

VACCINATION

- Emerged according to specific microorganisms (*P. gingivalis*, *T. forsythia*, *T. denticola*, and *A. actinomyctemcomitans*).

- Challenging as:

1. The disease results **from collateral tissue damage of the host immune response** rather than from direct bacterial action .

Therefore,

Vaccine-induced antimicrobial response should not activate a destructive inflammatory response

2. P**eriodontitis is initiated by synergistic and dysbiotic microbial** communities rather than by a few select "periodontopathogens."

- *P. gingivalis* vaccine: -Cysteine proteinases (RgpA, RgpB, and Kgp)

  -Hemagglutinin B.
  -Fimbriae.

  Chimera vaccine

  ↓

  IgG1, 2 and T-helper

- Subcutaneous immunization of rats with the **hemoglobin-binding domain of *P. gingivalis* gingipain**.

  ↘

  Induce specific IgG
  Protection against bone loss

- Subcutaneous immunization of monkeys using purified *P. gingivalis* cysteine proteinase elicited specific antibody responses.
  Did not suppress *P. gingivalis* (?????)

- Using ***S. gordonii*** vector that express *FimA* of *P. gingivalis* elicited salivary IgA and serum IgG and decreasing periodontal bone loss.

- More has to be done to: Define the most favorable **adjuvant** formulations and **immunization routes**

Conclusion

- Most of the host-modulation approaches would not be relevant only in a therapeutic setting; but implemented for **preventive** basis.
  (prior to the onset of periodontitis, to high-risk individuals, such as cigarette smokers and patients with diabetes)

- Despite the demonstrated potential to inhibit periodontitis, a clinical evaluation for the drug's risks and benefits raised the question to use them as treatment agents? (more towards adjunctive)

- The great complexity of pathogenic mechanisms in periodontitis appear to complicate the development of a periodontitis vaccine

Thank you