EDELWEISS PUBLICATIONS
OPEN ACCESS

https://doi.org/10.33805/2572-6978.123
Volume 3 Issue 1 | PDF 123 | Page 6

Dental Research and Management

Review Article ISSN 2572-6978

The Prevention and Treatment of Neural Arterial Gingival Simplex

Cannon L Mark[1*] and Peldyak N John[2]

Affiliation

[1]Division of Dentistry, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

[2]Dentistry practitioner in Mt. Pleasant, Michigan, USA

[*]**Corresponding author:** Mark L Cannon, Professor, Division of Dentistry, Department of Otolaryngology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA, Tel: 847-899-6720, E-mail: drmarkcannon@outlook.com

Citation: Cannon ML and Peldyak JN. The prevention and treatment of neural arterial gingival simplex (2019) Dental Res Manag 3: 32-37

Received: Jun 04, 2019

Accepted: Jun 14, 2019

Published: Jun 21, 2019

Abstract

Neural Arterial Gingival Simplex is a common systemic disease linked to an invasive periodontal pathogen, Porphyromonas gingivalis as the key initiator. Instead of considering separate pathologic conditions as separate diseases, the health community should view this disease as a single entity, to diagnose and treat accordingly. We discuss the evidence for this hypothesis and the need for definitive research. A strategy to maintain a healthy, resilient microbiome with adjunctive support by probiotics and polyols is warranted. Newer diagnostic and monitoring technologies along with many possible therapeutic agents and protocols are readily available to prevent and treat Neural Arterial Gingival Simplex.

Keywords: Neural arterial gingival simplex, *Porphyromonas gingivalis*, Alzheimer's disease, Polyols.

Introduction

The importance of re-establishing a normal microbiome cannot be overemphasized [1,2]. Modern diet and the overuse of antimicrobials have resulted with a tremendous increase in autoimmune diseases that were virtually unheard of in the past [3-5]. This shift in diet occurred first in the Neolithic period, followed by another shift in the Industrial Era, and finally now with the combined effects of fast food and antimicrobials [6]. Even a number of common food preservatives and additives have been shown to exert negative health effects [7]. As a result, it is estimated that almost half of all middle-aged Americans have metabolic syndrome [8-10]. In short, the costs of western diet and life style have been significant, and unless a paradigm shift urgently occurs, we could be a society devoted only to extending the life span of the chronically ill, incapable of achieving the accomplishments of prior generations [11,12]. Fortunately, advances in scientific study of the microbiome provide hope that wellness can be restored and productive health span increased.

The connection of oral health to systemic health is now well established [13]. Indeed, there is no isolated disease such as periodontal disease; it is simply a symptom of a systemic disease that may best be described as Neural Arterial Gingival Simplex (NAGS). *Porphyromonas gingivalis*, has been found to be a causative agent of periodontal disease, arteriosclerosis and inflammatory Alzheimer's [14-16]. Because *P. gingivalis* can be considered the foremost or "keystone" initiator of periodontal disease, it is reasonable to describe *P. gingivalis* as a causal agent of NAGS, a single disease with all of its downstream comorbidities [17]. Such is the case for any other disease, for instance, viral acute gastroenteritis due to rotavirus may cause fever, chills, muscle aches, fatigue and nausea, and each component is not considered a separate disease [19,20].

Addressing the microbiome may very well become the preventive technique of choice. Oral and systemic preventive protocols would include probiotic supplementation, possibly with overlapping beneficial bacterial, archaeon, viral or yeast probiotics. For example, it may be stated that an historical precedent for use of a viral "probiotic" would be the cowpox inoculation by Jenner to prevent the mortality seen with the scourge of smallpox [21]. In this sense, cowpox may be considered a viral probiotic as it contributed to the health and even survivability of the individual.

Evolution Guerilla Tactics

P. gingivalis has been called a "guerilla" for its notable tactics of slowly subverting the host's defense mechanisms [22]. The host's immunity is bypassed by the ability of *P. gingivalis* fimbriae to attach to hosts cells, such as gingival epithelial cells or endothelial cells, and then to invade the cell itself [23]. The ability of *P. gingivalis* to shift genomes in different strains to specifically target different host cells makes it particularly virulent [24]. In addition, the epigenetic influence of *P. gingivalis* allows it to open the tight junctions between cells and to modulate the immune response [25]. All told, *P. gingivalis* subverts a massive host immune response, and does not normally overwhelm the host because that would effectively limit the spread of the pathogen. A dead host does not propagate a pathogen.

P. gingivalis is a perfect pathogen. It spreads from the older members of the host population to the younger members [26]. *P. gingivalis* is seen in children as young as 7-8 years of age, however, gingival pathology is not usually detected until age 17 [27,28]. The majority of young adults already have more than a millimeter of attachment loss [29]. It should be noted that in autopsy studies 20% of 2-15 year old children demonstrate atherosclerosis, and by age 21 50% will have

calcified aortic deposits [30-32]. This too perfectly coincides with the development of "periodontal disease". In addition, research at Northwestern University revealed that in their early 20's subjects were already developing beta amyloid plaque and tau protein deposits [33]. With recent publications demonstrating the correlation between gingipain from *P. gingivalis* and Alzheimer's disease, this should not be the least surprising [14].

With the new concept of *P. gingivalis* infection causing a single disease with multiple symptoms, it is now easy to understand the modes involved. The oral component is the initial infection where the immune system is alerted and subverted, creating an inflammatory environment. Circulating leukocytes carry *P. gingivalis* and associated Lipo Poly Saccharide (LPS), affecting the endothelial cells of arteries, and passing into the neural component, eventually reducing the cognitive ability of the host, which would reduce the oral hygiene of the host, further spreading the pathogen amongst all contacts [34].

Prevention

The key to prevention will always lie with having the healthiest microbiome [35]. A "healthy non- western microbiome" will trigger the more robust response to pathogens with the least autoimmune consequences. Unfortunately for the civilized world, we have brought upon ourselves the epidemic of autoimmune disease, while decreasing our innate response to common pathogens [36]. Much has been said of the hygiene hypothesis, and of us all being "too clean" [37]. But it is extremely doubtful that as a society, we will all return to our hunter-gatherer roots (barring some natural catastrophe). Probiotic supplementation appears to be the essential to re-establish a healthy resilient microbiome [38-42]. This option alone, without appropriate diet and lifestyle modification, is severely limited [43]. The appropriate diet is necessary to provide the required prebiotics that beneficial organisms need to thrive and to favorably influence the entire microbiome [44]. The microbiome metabolites then exert an epigenetic effect upon the host, either producing health, or illness [45]. Dysbiosis not only directly produces disease, but also the metabolites of the microbiome are messengers to the brain and the rest of the body [46]. The immune system responds, as does the behavior of the host [47]. Depression has been linked to the presence of a specific bacterial species, and also the lack of one species [48,49]. Schizophrenia is also an epigenetic disease and Autism Spectrum Disorder (ASD) has been linked to propionic acid producing bacterial species, such as, *Clostridia bolteae* and *Clostridia histolyticum* [50-54]. Conversely the presence of *Clostridia sporogenes* could help protect against ASD by combining propionic acid with indole to produce 3-Indole Propionate, a neural protective metabolite, thereby neutralizing the epigenetic effect of propionic acid [55,56]. It has been theorized that the absence of *C. sporogenes* is related to the use of glyphosate, known by the trade name Roundup [57]. Possibly the increase risk of non-Hodgkin's Lymphoma seen in chronic exposure to individuals exposed to Roundup is due to its effect on the host's microbiome, by removing or reducing the level of a protective bacterial species.

With dysbiosis, the existence of disease always means not just an increase in the presence of a pathogen, but normally always a decrease in the level of commensals, allowing the pathogen to generate the pathological response [58]. In a perfectly balanced system, the host should always survive, at least long enough for the pathogen to spread. The host should, by evolution, develop a robust response to the pathogen, increasing the chance of the host species survival [59]. If this does not happen, the host species will disappear and the pathogen can only survive by becoming a zoonotic disease pathogen, jumping species, such as, bird flu or swine flu [60]. There is a canine version of *P. gingivalis*, *Porphyromonas cangingivalis*, and periodontal pathogens typically seen in human hosts have been detected in canines [61-62]. Whether this is by co-evolution or zoonotic origin is of interest, as it should explain the disease process with greater clarity.

Gingipain-deficient mutant *P. gingivalis* may prove to be a precursor to an Alzheimer's preventive probiotic. After all, this mutant strain could and should compete with the "wild type" strains producing gingipain. A further example of this would be the strains of *Fusobacterium nucleatum* that do not have the FADA gene. These strains could occupy that ecological niche of *F. nucleatum* and possibly decrease miscarriages (spontaneous abortions) and colorectal cancer. Development of these less virulent strains is similar to Jeffrey Hillman's research into a low or non-lactic acid producing strain of *Streptococcus mutans* [63]. Colonization of the population with this safe probiotic could greatly decrease the most common disease of childhood, dental caries. It is estimated that over 98% of the human population suffers from dental caries, a totally preventable disease that is strictly due to dietary habits and dysbiosis [64]. Oddly enough, dentistry totally ignores this and concentrates only on fluoridation, limiting the effectiveness of prevention programs [65-72].

Treatment

Erythritol and xylitol are polyols that have been extensively researched and demonstrated to have notable anti-cariogenic and anti-periodontal disease properties [73]. Polyols (particularly the non-hexitol alditols or "sugar alcohols" erythritol and xylitol) have been found effective in inhibiting the transition to and maturation of biofilms from planktonic cells [74]. Xylitol clearly inhibited the formation of mixed species biofilms, which included *P. gingivalis in vitro* [75]. Erythritol suppressed the maturation of gingivitis biofilms, and contributed to a healthier oral ecosystem [76].

P. gingivalis takes advantage of early colonizers (Streptococci and Candida) to provide attachment and protection within the biofilm matrix. Polyols can reduce extracellular polysaccharide production and interfere with biofilm matrix elaboration, thereby reducing adherence and biofilm development [77-79].

Streptococci and Candida utilize common dietary sugars sucrose and D-glucose for preferred energy sources, as well as for polysaccharide production. Higher glucose concentrations stimulate Candida growth. Compared with common D-sugars, xylitol induced the lowest adhesion and biofilm formation on either *S. mutans or Candida albicans* [80].

Candida facilitates the colonization and proliferation of periopathic biofilm by co-aggregating with *P. gingivalis* and adhering to epithelial cells [81]. Patients with severe periodontitis have a higher rate of Candida colonization [82]. In diabetes, high levels of glucose in the gingival sulcus coupled with immunosuppression enhance Candida growth [83]. Glucose, fructose and mannose are the preferred sugars used for energy and biosynthesis by Candida, whereas polyols such as xylitol are poorly utilized. Sugar sensing drives virulence attributes, including adhesion, oxidative stress resistance, biofilm formation, morphogenesis, invasion, and antifungal drug tolerance in fungal pathogens [84,85]. In dual species biofilm Candida helps provide *P. gingivalis* adherence and protection against oxygen, allowing it to organize in shallower gingival pockets [86].

The hydroxyl groups of polyols may interfere with the hydrogen bonding between hydroxyl groups of polysaccharides and allow greater penetration of antimicrobials. Polyols, especially erythritol, enhanced the fungicidal effect of benzethonium chloride toward in vitro candidal biofilms [87]. Xylitol and sorbitol at the concentrations used in commercial oral health care products had some levels of candidacidal activities [88]. Polyols can penetrate biofilms to deliver probiotics [89]. Erythritol delivered zinc chloride deeper into the protective three-dimensional matrix of extracellular polymeric substances of mature biofilm [90].

Although *P. gingivalis* utilizes peptides for its main energy source, sugars are used by *P. gingivalis* for biosynthesis of macromolecules

[91]. Polyols can interfere with these processes. As a result, polyols reduce the growth and the virulence factors of *P. gingivalis*. Xylitol was found to inhibit the inflammatory cytokine expression provoked by LPS remnants of *P. gingivalis* [92]. Further, xylitol interferes with *P. gingivalis* phagocytosis by macrophages. In macrophages that are infected with live *P. gingivalis*, xylitol significantly decreased the production of cytokines, NO and chemokines such as TNF-α, IL-1β, IL-12p40, eotaxin, IP-10, MCP-1, and MIP-1α. Such potent anti-inflammatory activities recommend use of polyols for prevention and mitigation of periodontal conditions [93]. Plaque grown in the presence of polyols has consistently been shown to be less inflammatory and less irritating to tissues than sucrose-grown plaque [94-99].

Polyols can suppress the growth and virulence expression of mixed bacterial biofilms. Erythritol was the most effective polyol in suppressing the growth and organization of *P. gingivalis* grown on a Streptococcus gordonii biofilm. Erythritol exerted inhibitory effects on several pathways-reduced growths through DNA and RNA depletion, attenuated extracellular matrix production, and alterations of dipeptide acquisition and amino acid metabolism [100].

Recognition of NAGS corresponds with newer enhancements in the diagnosis, prevention and treatment of periodontal diseases. Periodontal diagnosis goes beyond gross visual, radiographic and mechanical probing to include Polymerase Chain Reaction (PCR), DNA determination of specific pathogenic entities and quantities-the overall pathogenic burden. Genetic and inflammatory markers are also included to help construct an overall assessment of individual patient risk and assign targeted treatment plans. Improved salivary and inflammatory diagnostics can help with monitoring treatment progress in achieving and maintaining therapeutic end points.

Awareness of NAGS likewise calls for prevention, treatment and maintenance that extend beyond localized mechanical strategies. Presence of *P. gingivalis* is not limited to those with bleeding gums and deep pockets [101]. *P. gingivalis* in dental biofilms is associated with expression of virulence factors leading to progression of periodontal disease [102]. *P. gingivalis* biofilms are not easily controlled by purely mechanical means and are more resistant to antimicrobials than planktonic cells [74]. Treatment of Periodontal disease and the prevention of dental caries should include a very strong polyol component [103- 108]. This therapy would not only prevent the oral disease, but should also help prevent the development of systemic disease, atherosclerosis and the scourge of the elderly, Alzheimer's disease [109,110]. Certainly, it would be advantageous to prevent NAGS, as the cost to society is enormous, and the cost to the individual can be devastating. Polyols are available in many forms such as tabletop sweeteners and as ingredients in commercial foods and beverages. More direct "polyol delivery systems" for oral care include toothpaste, lozenges, chewing gum, mouth rinses and oral sprays.

Further research is warranted and necessary to reduce the burden of this devastating disease on modern society. We should first perform a number of retrospective review of patients who have been diligent users of polyol products, especially the reviewing the children's health records of those that were subjects in the early Finnish studies of xylitol and erythritol supplements. Unfortunately, this may be difficult due to human subject privacy rules. On a positive note, there are apparently studies that have already been started that are long term in scope, such as the Pussinen et al study [111]. Prospective studies could take many decades to irrefutably prove the long term positive effects of polyol and probiotic supplementation. Due to the documented early onset of atherosclerosis in children, newer diagnostic technologies should be utilized to identify and monitor risk. With the now available non-invasive testing for the presence of *P. gingivalis* and use of ultrasound for atherosclerosis detection, the research may be accomplished sooner rather than later.

Conclusion

A disease of neural, arterial and gingival involvement resulting from an infection by *P. gingivalis* has since prehistoric times inflicted severe pathological effects on the homo genus. The disease is now of an epidemic nature and should be prevented by probiotic therapy, dietary changes, and life style adjustments. Treatment should include supplemental polyol support.

References

1. Sommer F and Bäckhed F. The gut microbiota-masters of host development and physiology (2013) Nat Rev Microbiol 11: 227-238. https://doi.org/10.1038/nrmicro2974
2. Rosenberg E and Zilber-Rosenberg I. Microbes Drive Evolution of Animals and Plants: the Hologenome Concept (2016) MBio 7: 2. https://doi.org/10.1128/mBio.01395-15
3. Szylit O and Andrieux C. Physiological and pathophysiological effects of carbohydrate fermentation (1993) World Rev Nutr Diet 74: 88-122.
4. Trasande J, Blustein M, Liu E, Corwin L, M Cox, et al. Infant antibiotic exposures and early-life body mass (2013) Int J Obes 37: 16-23. https://doi.org/10.1038/ijo.2012.132
5. Virta L, Auvinen A, Helenius H, Huovinen P and Kolho K. Association of repeated exposure to antibiotics with the development of pediatric Crohn's disease-a nationwide, register-based Finnish Case-Control Study (2012) Am J Epidemiol 175: 775-784. https://doi.org/10.1093/aje/kwr400
6. Honda K and Littman DR. The microbiota in adaptive immune homeostasis and disease (2016) Nature 535: 75-84. https://doi.org/10.1038/nature18848
7. Mummert A, Esche E, Robinson J and Armelagos GJ. Stature and robusticity during the agricultural transition: Evidence from the bioarchaeological record (2011) Eco Hum Biol 9: 284-301. https://doi.org/10.1016/j.ehb.2011.03.004
8. Dengate S and Ruben A. Controlled trial of cumulative behavioural effects of a common bread preservative (2002) J Paediatr Child Health 38: 373-376. https://doi.org/10.1046/j.1440-1754.2002.00009.x
9. Castro AV, Kolka CM, Kim SP and Bergman RN. Obesity, insulin resistance and comorbidities? Mechanisms of association (2014) Arq Bras Endocrinol Metabol 58: 600-609. http://dx.doi.org/10.1590/0004-2730000003223
10. Stears A, O'Rahilly S, Semple RK and Savage DB. Metabolic insights from extreme human insulin resistance phenotypes (2012) Best Pract Res Clin Endocrinol Metab 26:145-157. https://doi.org/10.1016/j.beem.2011.09.003
11. Mendrick DL, Diehl AM, Topor LS, Dietert RR, Will Y, et al. Metabolic Syndrome and Associated Diseases: From the Bench to the Clinic (2017) Toxicol Sci 162: 36-42.
12. Kanherkar RR, Bhatia-Dey N and Csoka AB. Epigenetics across the human lifespan (2014) Front Cell Dev Biol 2: 49. https://dx.doi.org/10.3389%2Ffcell.2014.00049
13. Li Y and Tollefsbol TO. Age-related epigenetic drift and phenotypic plasticity loss: implications in prevention of age-related human diseases (2018) Epigenomics 8:1637-1651. https://doi.org/10.2217/epi-2016-0078
14. Kim J and Amar S. Periodontal disease and systemic conditions: a bidirectional relationship (2006) Odontology 94: 10-21. https://dx.doi.org/10.1007%2Fs10266-006-0060-6
15. Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, et al. *Porphyromonas gingivalis* in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors (2019) Sci adv 5: eaau3333. https://doi.org/10.1126/sciadv.aau3333
16. Kim HJ, Cha GS, Kim HJ, Kwon EY, LeeJY, et al. *Porphyromonas gingivalis* accelerates atherosclerosis through oxidation of high-density lipoprotein (2018) J periodontal

implant sci 48: 60-68. https://doi.org/10.5051/jpis.2018.48.1.60

17. Bale BF, Doneen AD and Vigerust DJ. High-risk periodontal pathogens contribute to the pathogenesis of atherosclerosis (2016) Postgrad Med J 93: 215-220. https://doi.org/10.1136/postgradmedj-2016-134279
18. Hussain M, Stover CM and Dupont AP. Gingivalis in Periodontal Disease and Atherosclerosis - Scenes of Action for Antimicrobial Peptides and Complement (2015) Front Immunol 6: 45. https://doi.org/10.3389/fimmu.2015.00045
19. Hajishengallis G, Darveau RP and Curtis MA. The keystone-pathogen hypothesis (2012) Nat Rev Microbiol 10: 717-725. https://dx.doi.org/10.1038%2Fnrmicro2873
20. Rotavirus: vaccination. Centers for Disease Control and Prevention
21. Preventing norovirus infection. Centers for Disease Control and Prevention
22. Riedel S. Edward Jenner and the history of smallpox and vaccination (2005) Baylor University Medical Center Proceedings, USA, 18: 21-25. https://doi.org/10.1080/08998280.2005.11928028
23. Hajishengallis G. *Porphyromonas gingivalis*-host interactions: open war or intelligent guerilla tactics? (2009) Microbes infect 11: 637-645. https://doi.org/10.1016/j.micinf.2009.03.009
24. Moreno S and Contreras A. Functional differences of *Porphyromonas gingivalis* Fimbriae in determining periodontal disease pathogenesis: a literature review (2013) Colombia medica 44: 48-56.
25. Tribble GD, Kerr J E, and Wang BY. Genetic diversity in the oral pathogen *Porphyromonas gingivalis*: molecular mechanisms and biological consequences (2013) Future microbial 8: 607-620. https://doi.org/10.2217/fmb.13.30
26. Guo W, Wang P, Liu ZH, and Ye P. Analysis of differential expression of tight junction proteins in cultured oral epithelial cells altered by *Porphyromonas gingivalis*, *Porphyromonas gingivalis* lipopolysaccharide, and extracellular adenosine triphosphate (2018) Int J oral sci 10: e8. https://doi.org/10.1038/ijos.2017.51
27. Hajishengallis G and Lamont RJ. Breaking bad: manipulation of the host response by *Porphyromonas gingivalis* (2014) Eur J Immunol, 44: 328-338. https://doi.org/10.1002/eji.201344202
28. Lamell CW, Griffen AL, McClellan DL and Leys EJ. Acquisition and colonization stability of *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* in children (2000) J Clin Microbi0l 38: 1196-1199.
29. Liu Y, Zhang Y, Wang, L, Guo Y, and Xiao S. Prevalence of *Porphyromonas gingivalis* four rag locus genotypes in patients of orthodontic gingivitis and periodontitis (2013) PloS one 8: e61028. https://dx.doi.org/10.1371%2Fjournal.pone.0061028
30. Toledo BE, Barroso EM, Martins AT and Zuza, EP. Prevalence of Periodontal Bone Loss in Brazilian Adolescents through Interproximal Radiography (2012) Int J Dent 2012: 357056. https://doi.org/10.1155/2012/357056
31. Rao D, Sood D, Pathak P, and Dongre SD. A cause of Sudden Cardiac Deaths on Autopsy Findings; a Four-Year Report (2014) Emergency 2: 12-17.
32. Hong YM. Atherosclerotic cardiovascular disease beginning in childhood (2010) Korean Circ J 40: 1-9. https://doi.org/10.4070/kcj.2010.40.1.1
33. Berenson GS, Srinivasan SR, Bao W, Newman WP and Tracy RE. Association between Multiple Cardiovascular Risk Factors and Atherosclerosis in Children and Young Adults (1998) Engl J Med 338: 1650-1656 https://doi.org/10.1056/NEJM199806043382302
34. Baker-Nigh A, Vahedi S, Davis EG, Weintraub S, Bigio EH, et al. Neuronal amyloid-β accumulation within cholinergic basal forebrain in ageing and Alzheimer's disease (2015) Brain 138: 1722-1737. https://doi.org/10.1093/brain/awv024
35. Hajishengallis G. Periodontitis: from microbial immune subversion to systemic inflammation (2015) Nat Rev Immunol 15: 30-44. https://doi.org/10.1038/nri3785
36. Marques TM, Cryan JF, Shanahan F, Fitzgerald GF, Ross RP, et al. Gut microbiota modulation and implications for host health: dietary strategies to influence the gut-brain axis (2014) Innov Food Sci Emerg Technol 22: 239-47. https://doi.org/10.1016/j.ifset.2013.10.016
37. Walsh CJ, Guinane CM, O'Toole PW and Cotter PD. Beneficial modulation of the gut microbiota (2014) FEBS Lett 588: 4120-4130. https://doi.org/10.1016/j.febslet.2014.03.035
38. Okada H, Kuhn C, Feillet H and Bach JF. The hygiene hypothesis for autoimmune and allergic diseases: an update (2010) Clin Exp Immunol 160: 1-9. https://doi.org/10.1111/j.1365-2249.2010.04139.x
39. Thomas S, Izard J, Walsh E, Batich K, Chongsathidkiet P, et al. The Host Microbiome Regulates and Maintains Human Health: A Primer and Perspective for Non-Microbiologists (2017) Cancer Res 77: 1783-1812. https://doi.org/10.1158/0008-5472.CAN-16-2929
40. Barengolts E. Gut Microbiota, Prebiotics, Probiotics, And Synbiotics In Management Of Obesity And Prediabetes: Review Of Randomized Controlled Trials (2016) Endoc Prac 22: 1224-1234. https://doi.org/10.4158/EP151157.RA
41. Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, et al. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study (2017) Microbiome 5: 10. https://doi.org/10.1186/s40168-016-0225-7
42. Swartwout B and Luo XM. Implications of Probiotics on the Maternal-Neonatal Interface: Gut Microbiota, Immunomodulation, and Autoimmunity (2018) Front Immunol 9: 2840. https://doi.org/10.3389/fimmu.2018.02840
43. Tsai YL, Lin TL, Chang CJ, Wu TR, Lai WF, et al. Probiotics, prebiotics and amelioration of diseases (2019) J biomed sci 26: 3. https://doi.org/10.1186/s12929-018-0493-6
44. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, et al. Influence of diet on the gut microbiome and implications for human health (2017) J Transl Med 15: 73 https://doi.org/10.1186/s12967-017-1175-y
45. Mach N and Fuster-Botella D. Endurance exercise and gut microbiota: A review (2016) J Sport Health Sci 6: 179-197. https://doi.org/10.1016/j.jshs.2016.05.001
46. Qi Y and Wade PA. Crosstalk between the microbiome and epigenome: messages from bugs (2017) J Biochem1 63: 105-112. https://doi.org/10.1093/jb/mvx080
47. Kelly JR, Minuto C, Cryan JF, Clarke G and Dinan, TG. Cross Talk: The Microbiota and Neurodevelopmental Disorders (2017) Front Neurosci 11: 490. https://doi.org/10.3389/fnins.2017.00490
48. Lach G, Schellekens H, Dinan TG and Cryan JF. Anxiety, Depression, and the Microbiome: A Role for Gut Peptides (2017) Neurotherapeutics 15: 36-59. https://doi.org/10.1007/s13311-017-0585-0
49. Strandwitz P, Kim KH, Terekhova D, Liu JK, Anukriti Sharmaet, et al. GABA-modulating bacteria of the human gut microbiota (2019) Nature Microbiol 4: 396-403. https://www.nature.com/articles/s41564-018-0307-3
50. Föcking M, Doyle B, Munawar N, Dillon ET, Cotter D, et al. Epigenetic Factors in Schizophrenia: Mechanisms and Experimental Approaches (2019) Mol Neuropsychiatry. 5:6-12. https://doi.org/10.1159/000495063
51. MacFabe DF, Cain DP, Rodriguez-Capote K, Franklin AE, Hoffman JE, et al. Neurobiological effects of intraventricular propionic acid in rats: possible role of short chain fatty acids on the pathogenesis and characteristics of autism spectrum disorders (2007) Behav Brain Res 176: 149-69. https://doi.org/10.1016/j.bbr.2006.07.025

52. Shultz SR, MacFabe DF, Ossenkopp KP, Scratch S, Whelan J, et al. Intracerebroventricular injection of propionic acid, an enteric bacterial metabolic end-product, impairs social behavior in the rat: implications for an animal model of autism (2008) Neuropharmacology 54: 901-911. https://doi.org/10.1016/j.neuropharm.2008.01.013
53. Shultz SR, Macfabe DF, Martin S, Jackson J, Taylor R, et al. Intracerebroventricular injections of the enteric bacterial metabolic product propionic acid impairs cognition and sensorimotor ability in the Long-Evans rat: further development of a rodent model of autism (2009) Behav Brain Res 200: 33-34. https://doi.org/10.1016/j.bbr.2008.12.023
54. MacFabe DF, Cain NE, Boon F, Ossenkopp KP and Cain DP. Effects of the enteric bacterial metabolic product propionic acid on object-directed behavior, social behavior, cognition, and neuroinflammation in adolescent rats: Relevance to autism spectrum disorder (2011) Behav Brain Res 217: 47-54. https://doi.org/10.1016/j.bbr.2010.10.005
55. Rose S, Bennuri SC, Davis JE, Wynne R, Slattery JC, et al. Butyrate enhances mitochondrial function during oxidative stress in cell lines from boys with autism (2018) Translational Psychiatry 8: 42. https://doi.org/10.1038/s41398-017-0089-z
56. Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites (2009) Proceedings of the National Academy of Sciences of the United States of America, USA 106: 3698-3703. https://doi.org/10.1073/pnas.0812874106
57. Parthasarathy A, Cross PJ, Dobson R, Adams LE, Savka MA, et al. A Three-Ring Circus: Metabolism of the Three Proteogenic Aromatic Amino Acids and Their Role in the Health of Plants and Animals (2018) Front Mol Biosci 5: 29. https://doi.org/10.3389/fmolb.2018.00029
58. Argou-Cardozo I and Zeidán-Chuliá F. Clostridium Bacteria and Autism Spectrum Conditions: A Systematic Review and Hypothetical Contribution of Environmental Glyphosate Levels (2018) Med Sci (Basel) 6: 29. https://doi.org/10.3390/medsci6020029
59. Hooks KB and O'Malley MA. Dysbiosis and Its Discontents (2017) mBio 8: e01492-1517. https://doi.org/10.1128/mbio.01492-17
60. Park M, Loverdo C, Schreiber SJ and Lloyd-Smith JO. Multiple scales of selection influence the evolutionary emergence of novel pathogens (2013) Philo Transac Roy Soc London Series B Biol Sci 368: 20120333. https://doi.org/10.1098/rstb.2012.0333
61. Han BA, Kramer AM and Drake JM. Global Patterns of Zoonotic Disease in Mammals (2016) Trends Parasitol 32:565-577. https://doi.org/10.1016/j.pt.2016.04.007
62. Davis IJ, Wallis C, Deusch O, Colyer A, Milella L, et al. A cross-sectional survey of bacterial species in plaque from client owned dogs with healthy gingiva, gingivitis or mild periodontitis (2013) PloS one 8: e83158. https://doi.org/10.1371/journal.pone.0083158
63. Yamasaki Y, Nomura R, Nakano K, Naka S, Matsumoto-Nakano M, et al. Distribution of periodontopathic bacterial species in dogs and their owners (2012) Arch Oral Biol 57: 1183-1188. https://doi.org/10.1016/j.archoralbio.2012.02.015
64. Hillman JD, McDonell E, Hillman CH, Zahradnik RT and Soni MG. Safety assessment of probiora3, a probiotic mouthwash: subchronic toxicity study in rats (2009) Int J Toxicol 28: 357-367. https://doi.org/10.1177/1091581809340705
65. Dye BA, Thornton-Evans G, Xianfen L and Iafolla TJ. Dental caries and tooth loss in adults in the United States, 2011-2012 (2015) NCHS Data Brief 197.
66. Islam B, Khan SN and Khan AU. Dental caries: from infection to prevention (2007) Med Sci Monit 13: RA196-203.
67. Meurman JH and Stamatova I. Probiotics: contributions to oral health (2007) Oral Diseases 13: 443-451. https://doi.org/10.1111/j.1601-0825.2007.01386.x
68. Meurman JH, Antila H and Salminen S. Recovery of Lactobacillus strain GG (ATCC 53103) from saliva of healthy volunteers after consumption of yoghurt prepared with the bacterium (1994) Microb Ecol Health Dis 7: 295-298. https://doi.org/10.3109/08910609409141368
69. Nase L, Hatakka K, Savilahti E, Saxelin M, Ponka A, et al. Effect of long-term consumption of a probiotic bacterium, Lactobacillus rhamnosus GG, in milk on dental caries and caries risk in children (2001) Caries Res35: 412-420. https://doi.org/10.1159/000047484
70. Ahola AJ, Yli-Knuuttila H, Suomalainen T, Poussa T, Ahlström A, et al. Short-term consumption of probiotic-containing cheese and its effect on dental caries risk factors (2002)Arch Oral Biol 47: 799-804.
71. Nikawa H, Makihira S, Fukushima H, Nishimura H, Ozaki Y, et al. Lactobacillus reuteri in bovine milk fermented decreases the oral carriage of mutans streptococci (2004)Int J Food Microbiol 95: 219-223. https://doi.org/10.1016/j.ijfoodmicro.2004.03.006
72. Cildir SK, Germec D, Sandalli N, Ozdemir FI, Arun T, et al. Reduction of salivary mutans streptococci in orthodontic patients during daily consumption of yoghurt containing probiotic bacteria (2009) Eur J Orthod 31: 407-411. https://doi.org/10.1093/ejo/cjn108
73. Hedayati-Hajikand T, Lundberg U, Eldh C and Twetman. Effect of probiotic chewing tablets on early childhood caries-a randomized controlled trial (2015) BMC oral health 15: 112. https://doi.org/10.1186/s12903-015-0096-5
74. Janakiram C, Deepan Kumar CV and Joseph J. Xylitol in preventing dental caries: a systematic review and meta-analyses (2017) J Nat Sci Biol Med 8: 16-21. https://doi.org/10.4103/0976-9668.198344
75. Sánchez MC, Romero-Lastra P, Ribeiro-Vidal H, Llama-Palacios A and Figuero E. Comparative gene expression analysis of planktonic *Porphyromonas gingivalis* ATCC 33277 in the presence of a growing biofilm versus planktonic cells (2019) BMC Microbiol 19: 58. https://doi.org/10.1186/s12866-019-1423-9
76. Badet C, Furiga A and Thébaud N.Effect of xylitol on an in vitro model of oral biofilm (2008) Oral Health Prev Dent 6: 337-341.
77. Janus MM, Volgenant CMC, Brandt BW, Buijs MJ, Keijser BJF, et al. Effect of erythritol on microbial ecology of in vitro gingivitis biofilms (2017)J Oral Microbiol 9: 1. https://doi.org/10.1080/20002297.2017.1337477
78. Söderling E, Hietala and Lenkkeri AM. Xylitol and erythritol decrease adherence of polysaccharide-producing oral streptococci (2010) Curr Microbiol 60: 22-29. https://doi.org/10.1007/s00284-009-9496-6
79. Ferreira AS, Silva-Paes-Leme AF, Raposo NR and da Silva SS.By passing microbial resistance: xylitol controls microorganisms growth by means of its anti-adherence property (2015) Curr Pharm Biotechnol 16: 35-42.
80. Ghezelbash GR, Nahvi I and Rabbani M. Comparative inhibitory effect of xylitol and erythritol on the growth and biofilm formation of oral Streptococci (2012) AJMR 6: 4404-4408.
81. Brambilla E, Ionescu AC, Cazzaniga G, Ottobelli M and Samaranayake LP. Levorotatory carbohydrates and xylitol subdue *Streptococcus mutans* and *Candida albicans* adhesion and biofilm formation (2015) J Basic Microbiol 56: 480-492. https://doi.org/10.1002/jobm.201500329
82. Sardi JC, Duque C, Mariano FS, Peixoto IT, Höfling JF, et al. Candida spp. in periodontal disease: a brief review (2010) J Oral Sci 52: 177-185.https://doi.org/10.2334/josnusd.52.177

83. De-La-Torre J, Quindós G, Marcos-Arias C, Marichalar-Mendia X, Gainza ML, et al. Oral candida colonization in patients with chronic periodontitis. Is there any relationship (2018) Rev Iberoam Micol 35: 134-139. https://doi.org/10.1016/j.riam.2018.03.005
84. Rodrigues CF, Rodrigues ME and Henriques M. Candida sp. infections in patients with diabetes mellitus (2019) J Clin Med 8: 76. https://doi.org/10.3390/jcm8010076
85. Vargas SL, Patrick CC, Ayers GD and Hughes WT. Modulating effect of dietary carbohydrate supplementation on *Candida albicans* colonization and invasion in a neutropenic mouse model (1993) Infect Immun 61: 619-626.
86. Van Ende M, Wijnants S and Van Dijck P. Sugar sensing and signaling in *Candida albicans* and *Candida glabrata* (2019) Front Microbiol 10: 99. https://doi.org/10.3389/fmicb.2019.00099
87. Bartnicka D, Karkowska-Kuleta J, Zawrotniak M, Satała D, Michalik K, et al. Adhesive protein-mediated cross-talk between *Candida albicans* and *Porphyromonas gingivalis* in dual species biofilm protects the anaerobic bacterium in unfavorable oxic environment (2019) Sci Rep 9: 4376. https://doi.org/10.1038/s41598-019-40771-8
88. Ichikawa T, Yano Y, Fujita Y, Kashiwabara T and Nagao K. The enhancement effect of three sugar alcohols on the fungicidal effect of benzethonium chloride toward Candida albicans (2008) J Dent 36: 965-968. https://doi.org/10.1016/j.jdent.2008.07.013
89. Kim J, Yoon-Young Kim, Ji-Youn Chang and Hong-Seop Kho. Candidacidal activity of xylitol and sorbitol (2016) J Oral Med Pain 41: 155-160 https://doi.org/10.14476/jomp.2016.41.4.155
90. Lipińska L, Klewicki R, Sójka M, Bonikowski R, Żyżelewicz D, et al. Antifungal activity of lactobacillus pentosus ŁOCK 0979 in the presence of polyols and galactosyl-polyols (2017) Probiotics Antimicrob Proteins 10: 186-200. https://doi.org/10.1007/s12602-017-9344-0
91. Lim JH, Jeong Y, Song SH, Ahn JH, Lee JR, et al. Penetration of an antimicrobial zinc-sugar alcohol complex into *Streptococcus mutans* biofilms (2018) Scientific Reports 8: 16154. https://doi.org/10.1038/s41598-018-34366-y
92. Arimoto T, Ansai T, Yu W, Turner AJ and Takehara T. Kinetic analysis of PPi-dependent phosphofructokinase from *Porphyromonas gingivalis* (2002) FEMS Microbiology Letters 207:35-38.https://doi.org/10.1111/j.1574-6968.2002.tb11024.x
93. Han SJ, Jeong SY, Nam YJ, Yang KH, Lim HS, et al. Xylitol inhibits inflammatory cytokine expression induced by lipopolysaccharide from *Porphyromonas gingivalis* (2005) Clin Diagn Lab Immunol 12: 1285-1291. https://doi.org/10.1128/CDLI.12.11.1285-1291.2005
94. Park E, Na HS, Kim SM, Wallet S, Cha S, et al. Xylitol, an anticaries agent, exhibits potent inhibition of inflammatory responses in human THP-1-derived macrophages infected with *Porphyromonas gingivalis* (2014) J Periodontol 85: e212-e223. https://doi.org/10.1902/jop.2014.130455
95. Luostarinen V, Paunio J, Varrela M, Rekola M, Luoma S, et al. Turku sugar studies, XV. Vascular reactions in the hamster cheek pouch to human gingival exudate (1975) Acta Odontologica Scandinavica 33: 287-291.
96. Harjola U and Liesmaa H. Effects of polyol and sucrose candies on plaque, gingivitis and lactobacillus index scores (1978) Acta Odontologica Scandinavica 36: 237-242.
97. Tenovuo J, Mielityinen H and Paunio K.Effect of dental plaque grown in the presence of xylitol or sucrose on bone resorption in vitro (1981) Pharmacol Ther Dent 6: 35-43.
98. Mielityinen H, Tenovuo J, Söderling E and Paunio K. Effect of xylitol and sucrose plaque on release of lysosomal enzymes from bones and macrophages in vitro (1983) Acta Odontol Scand 41: 173-180.
99. Mäkinen KK, Pemberton D, Cole J, Mäkinen PL, Chen CY, et al. Saliva stimulants and the oral health of geriatric patients (1995) Adv Dental Research 9: 125-126. https://doi.org/10.1177/08959374950090020901
100. Shyama M, Honkala E, Honkala S and Al-Mutawa SA.Effect of xylitol candies on plaque and gingival indices in physically disabled school pupils (2006) Clin Dent 17: 17-21.
101. Hashino E, Kuboniwa M, Alghamdi SA, Yamaguchi M, Yamamoto R, et al. Erythritol alters microstructure and metabolomic profiles of biofilm composed of *Streptococcus gordonii* and *Porphyromonas gingivalis* (2013) Mol Oral Microbiol 28: 435-451. https://doi.org/10.1111/omi.12037
102. How KY, Song KP and Chan KG. *Porphyromonas gingivalis*: An Overview of Periodontopathic Pathogen below the Gum Line (2016) Frontiers in microbiology 7: 53. https://doi.org/10.3389/fmicb.2016.00053
103. Zenobia C and Hajishengallis G. *Porphyromonas gingivalis* virulence factors involved in subversion of leukocytes and microbial dysbiosis (2015) Virulence 6: 236-243. https://doi.org/10.1080/21505594.2014.999567
104. Boesten DM, Berger A, De Cock P, Dong H, Hammock BD, et al. Multi-targeted mechanisms underlying the endothelial protective effects of the diabetic-safe sweetener erythritol (2013) PLoS One 8: e65741. https://doi.org/10.1371/journal.pone.0065741
105. Park E, Sam Na H, Min Kim S, Wallet S, Cha S, et al. Xylitol, an anticaries agent, exhibits potent inhibition of inflammatory responses in human thp-1-derived macrophages infected with *porphyromonas gingivalis* (2014) J Periodontol 85: e212–e223. https://doi.org/10.1902/jop.2014.130455
106. Nayak PA, Nayak UA and Khandelwal V. The effect of xylitol on dental caries and oral flora (2014) Clin Cosmet Investig Dent 6: 89-94. https://doi.org/10.2147/CCIDE.S55761
107. Söderling E, Isokangas P, Pienihäkkinen K and Tenovuo J. Influence of maternal xylitol consumption on acquisition of mutans streptococci by infants (2000) J Dent Res 79: 882-887. https://doi.org/10.1177/00220345000790031601
108. Falony G, Honkala S, Runnel R, Olak J, Nõmmela R, et al. Long-term effect of erythritol on dental caries development during childhood: a post-treatment survival analysis (2016) Caries Res 50: 579-588. https://doi.org/10.1159/000450762
109. Ur-Rehman S, Mushtaq Z, Zahoor T, Jamil A and Murtaza MA. Xylitol: a review on bioproduction, application, health benefits, and related safety issues (2015) Crit Rev Food Sci Nutr 55: 1514-1528. https://doi.org/10.1080/10408398.2012.702288
110. Cock PD. Erythritol functional roles in oral-systemic health (2018) Advances in Dental Research 29: 104-109. https://doi.org/10.1177/0022034517736499
111. Pussinen PJ, Paju S, Koponen J, Viikari JSA, Taittonen L, et al. Association of Childhood Oral Infections With Cardiovascular Risk Factors and Subclinical Atherosclerosis in Adulthood (2019) JAMA Netw Open 2: e192523. https://doi.org/10.1001/jamanetworkopen.2019.2523