OHSU School of Dentistry
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Welcome to the inaugural issue of the Oregon Health & Science University School of Dentistry Anthology.

This publication follows years of planning by leaders from the School of Dentistry Student Research Group, faculty and the OHSU Library. Contributors include Conor Scanlon, Siva Prakasam, Samyia Chaudhry, Christina Truong, Pam Pierce, Robin Champieux and me. The publication is for students, residents, staff members and junior faculty to share their scholarly activity, while learning about the publication process. The short submission-to-publication cycle is intended to be inclusive of a variety of formats and content areas. There are no fees when submitting to the anthology. The publication is peer-reviewed, fully citable and searchable through the OHSU Library Digital Collections.

Purpose and objectives of the School of Dentistry Anthology:

- **Educational and professional development:** By involving various members of the school, the anthology will become a learning tool for understanding the publication process, including writing, peer review and editorial work.
- **Showcasing expertise and contributions:** The anthology will highlight the diverse range of expertise and contributions made by our school in the field of oral health. This includes original research, case studies, reviews and insightful commentaries or editorials.
- **Promotion and visibility:** Through the anthology, the school will enhance its visibility in the academic and dental communities. It can serve as an example of the school's expertise and advances in oral health.
- **Networking and collaboration:** The anthology will foster collaboration among faculty, students and staff of the school, university and community, leading to a more integrated and interdisciplinary approach to education and research.
- **Encouraging scholarly activity:** By reducing the barriers for publication, we are encouraging more members of the school to engage in scholarly activities, which is crucial for academic development.

The School of Dentistry Anthology, or SoDA, is a significant milestone for our school, further enhancing its academic reputation and dedication to research and scholarly activity. Thank you for being a part of this momentous effort.

Ron Sakaguchi, D.D.S., M.S., Ph.D., M.B.A., School of Dentistry dean and senior editor

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The Baker Lab at the OHSU School of Dentistry: leveraging bioinformatics and molecular biology to discover how the bacteria that live in our mouth impact human health and disease

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Abstract

The microorganisms living in the human oral cavity, collectively known as the oral microbiota, play a critical role in not only oral health, but systemic and overall health. The Baker Lab leverages emerging technologies in bioinformatics and molecular biology to answer fundamental questions regarding the ecology, physiology, and pathogenesis of the oral microbiota. We use a microbial 'omics approach, which has included pioneering the use of nanopore sequencing on saliva and oral bacterial RNA. The resulting work discovered novel bacterial species and biosynthetic pathways which impact the ecology of the oral microbiota and its relationship to human disease. This article will briefly define the oral microbiota. It will also summarize how bioinformatics and 'omics-based research have revolutionized oral health research. The article will then provide a broad summary of our past, present and future research and educational programs.

What is the oral microbiota/microbiome, how is it studied, and why does it matter?

The oral microbiota is the collection of microorganisms that live in the human oral cavity, and includes bacteria, viruses, archaea, and microeukaryotes such as fungi (Baker *et al.*, 2023). These microbes have a major impact on human health, with extremely prevalent and costly oral diseases such as dental caries, periodontal disease, and oral cancers having mainly microbial etiologies (Baker *et al.*, 2023). Prior to the mid-2000s, microbiological research at large, including that of the oral microbiota, was limited to the species of microorganisms that could be physically isolated, cultured (i.e., grown), and studied in a laboratory (Baker, 2023). Much of the study of microbial pathogens employed Koch's Postulates, in which causative microbial agents of disease were identified by isolation from diseased sites, grown in pure culture, and subsequently able to cause disease when introduced into healthy model organisms (Falkow, 2004). In the context of oral microbiology, these classical approaches enabled the discovery of several oral pathogens associated with oral diseases. Two prominent examples were the association of *Streptococcus mutans* with dental caries and the association of *Porphyromonas gingivalis* with periodontal disease (Edwardsson, 1968, Kagan, 1980). Organisms associated generally with good oral health, such as *Streptococcus gordonii*, were also identified and studied during this period (Nyvad & Kilian, 1990). Since one does not know *a priori* what organisms are present in an environment, or how to isolate and cultivate them, only a minority of the microorganisms residing in the oral cavity were identified and studied in-depth using traditional microbiological techniques.

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The development of culture-independent analysis methods, such as high throughput sequencing and modern mass spectrometry, allowed detection and analysis of all microorganisms present in a sample, not just the ones that could be isolated and grown in a lab. This revealed that the species isolated and cultured to that point in time, using classic microbiological methods, represented a small percentage of the diversity present in most environments, including the oral microbiota (Venter *et al.*, 2004, Ley *et al.*, 2005, Gill *et al.*, 2006). In the approximately 20 years since the emergence of this technology, there has been an explosive growth of microbiome research, which has provided an ever more complete picture of which microorganisms are present or abundant in human oral microbiotas associated with good oral health, or with microbiotas associated with oral diseases such as caries, periodontal disease, and oral cancer (Baker *et al.*, 2023). In addition to its relationship with oral diseases, a growing body of evidence is also linking the oral microbiota to a myriad of systemic diseases. These include cardiovascular disease, diabetes, colorectal cancer, obesity, Rheumatoid arthritis, Alzheimer's disease and others (Hajishengallis & Chavakis, 2021, Baker *et al.*, 2023). The oral microbiota is now known to contain over 700 species, and the health-associated microbiota defends the mouth against pathogenic organisms (Chen *et al.*, 2010, He *et al.*, 2010, Baker *et al.*, 2023). As an increasing amount is known about which species are present in various environments and conditions, there is a growing need to move past this type of research and understand the mechanisms underpinning how the microbiome is affecting the health of the human host (Nascimento *et al.*, 2017, Burne, 2018).

What is 'omics research?

'Omics research is the informal term for the collective research approaches that end in the suffix, 'omics,' and each aim to characterize and quantify entire pools of molecules or interactions in a given setting. Examples that are particularly relevant to oral microbiome research are: genomics, analysis of genomes; metagenomics, simultaneous analysis of multiple genomes in a community; transcriptomics, analysis of RNA of a given species; metatranscriptomics, analysis of the RNA of a community of organisms: metabolomics, analysis of metabolites (i.e., small molecules); proteomics, analysis of proteins; lipidomics, analysis of lipids; pangenomics, analysis of gene families across multiple organisms; and phylogenomics, analysis of the evolutionary relationship between organisms. The Baker Lab has experience leveraging diverse 'omics methods across several research projects and collaborations. Examples include: (1) genomics to assemble complete genomes of novel species and strains from the oral microbiome (Baker & Edlund, 2020, Baker, 2021, Baker, 2022), (2) metagenomics to discover new species and observe disparities in the oral microbiome, and the biosynthetic pathways it encodes, associated with dental caries and periodontal disease (Aleti *et al.*, 2019, Baker & Edlund, 2021, Baker *et al.*, 2021, Baker, 2022), (3) proteomics to map the *S. mutans* acid and oxidative stress responses and discover new functions of a transcriptional regulator (Tinder *et al.*, 2022), (4) pangenomics to explore gene families across various bacterial species and strains to predict metabolic repertoires and ecological roles (Baker, 2021, Baker *et al.*, 2021, Baker, 2022), (5) phylogenomics to determine the evolutionary lineage of novel bacteria (Baker, 2021, Baker *et al.*, 2021, Baker, 2022), and (6) lipidomics to discover how bacteria modify their cell membranes in response to stress, in an effort persist and cause disease (project in progress).

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Nanopore sequencing: leveraging an emerging technology

As stated above, the development of culture-independent analysis of microbiomes was enabled by so-called next-generation sequencing (Bennett, 2004, Margulies *et al.*, 2005, Bentley *et al.*, 2008, McKernan *et al.*, 2009). Illumina was the most broadly used sequencing platform of the 2010s, and revolutionized the life sciences by reducing the cost of sequencing by orders of magnitude, providing exceptionally accurate sequencing data, and increasing throughput. However, the latest generation of emerging sequencing technologies (i.e., "third generation sequencing") is in the process of disrupting biomedical research once more (Athanasopoulou *et al.*, 2021). One technology that has gained considerable traction in the last several years is nanopore sequencing (Oxford Nanopore Technologies Inc. (ONT)) (Jain *et al.*, 2015). While Illumina sequencing-by-synthesis technology generates sequences that are generally 150 or 300 base pairs of DNA in length, ONT sequencing theoretically has no upper limit on the length of output sequence, with single reads of more than 1 million base pairs of DNA routinely reported (Jain *et al.*, 2015). Because most genomes contain repeat regions spanning much longer than 300 base pairs, the puzzle that is a given genome cannot typically be completed with Illumina short-read sequencing alone (i.e., because all these short reads match up nonspecifically to all their cognate sequences in the repeat regions of the chromosome). The long reads produced by ONT sequencing much more easily span the repeat regions of genomes enabling significantly easier assembly of complete chromosomes. However, until recently ONT technology was plagued with a considerably higher error rate than competing technologies, limiting its applicability (Amarasinghe *et al.*, 2020). This error rate decreased in recent years, with a crucial inflection point being reached in 2022, when studies illustrated that the contemporary ONT instrumentation and software could produce genome assemblies with an error rate on par with those produced by Illumina sequencing (Sereika *et al.*, 2022).

The Baker Lab was an early adapter of ONT technology, and in 2022 published the first protocols to obtain multiple complete bacterial genomes simultaneously directly from saliva using ONT sequencing (Baker, 2022). Several of the genomes completed using these methods were the first complete genome for their given species (*Candidatus* Saccharibacteria HMT-870, *Candidatus* Saccharibacteria HMT-348, *Actinomyces graevenitzii*) (Baker, 2021, Baker, 2022, Baker, 2022). Particularly intriguing were the genomes from the enigmatic Saccharibacteria family, which are essentially tiny (even by bacterial standards) parasitic bacteria that depend on larger host bacteria to survive (He *et al.*, 2015). The novel complete genomes from our study illustrated that the G6 group of Saccharibacteria likely has a different lifestyle, and possibly host and host dependencies than the more well-understood G1 group of Saccharibacteria (Baker, 2021). These differences likely extend to ecological and pathogenic roles as well, as Saccharibacteria appear to have a relationship to inflammation and periodontal disease (albeit poorly understood at this stage) (Chipashvili *et al.*, 2021). The ability to obtain complete genomes directly from complex samples, such as saliva, will revolutionize microbiology research, as it was previously only possible to obtain complete genomes of species that were isolated and cultivated in the lab in a pure culture (i.e., only incomplete, draft genomes could be obtained from metagenomes using earlier sequencing technologies) (Athanasopoulou *et al.*, 2021). Obtaining genomes that are

both complete and accurate is of importance because they then allow accurate identification and quantification of the species of interest in microbiome samples, and enable accurate prediction of the metabolic capabilities (and therefore ecological and pathogenic roles) of the species (Venter *et al.*, 2004, Naito *et al.*, 2016). This data can further guide wet-lab research and help scientists design experiments, isolate, cultivate and study species that were previously intractable (Cross *et al.*, 2019). In addition to genomics and metagenomics using ONT, The Baker Lab pioneered use of the ONT sequencing platform for RNA sequencing of oral bacteria (Baker *et al.*, 2022). RNA sequencing via ONT has several advantages as well. Because ONT can sequence native DNA and RNA molecules (unlike most sequencing methods, which must first reverse transcribe the RNA to cDNA, and/or amplify the DNA or RNA with PCR), ONT sequencing can detect base modifications, such as methylation, as well as noncanonical bases such as inosine (Garalde *et al.*, 2018, Tourancheau *et al.*, 2021, Begik *et al.*, 2022, Nguyen *et al.*, 2022). The ability to detect DNA and RNA modifications on a genome wide or transcriptome wide scale is a major advance and is likely to produce entirely new fields of microbiology research. Furthermore, the long RNA reads enable the detection of co-transcribed genes and novel RNA isoforms on a transcriptome wide scale (Garalde *et al.*, 2018, Grunberger *et al.*, 2022).

Lipidomics of bacteria, and unsaturated fatty acid production in Streptcococci

A special current emphasis of research in The Baker Lab is using lipidomics to better understand the ways in which bacteria modify their cell membranes to adapt to their environment, and in some cases, cause disease. All cells, and many viruses, have membranes, which are composed of lipid bilayers. The chemical properties of most membrane lipids render them notoriously difficult to study. As a result, lipidomics is perhaps the least utilized major 'omics discipline, and a relative deficiency exists in understanding the consequences of the lipidome in various contexts, despite certainty in its biological importance. Bacterial cells all have at least one membrane, while Gram negative organisms have two. Bacteria produce a diversity of lipids to the extent that many bacterial species can, in fact, be identified be their lipid profile alone (Abel *et al.*, 1963).

The Lactobacillales order of bacteria contains some of the most important pathogens and commensal organisms of the human microbiota. This includes the genera *Streptococcus*, *Enterococcus*, and *Lactobacillus*. Previous research has shown that a diversity of Lactobacillales increase the proportion of unsaturated fatty acids in their cell membranes in response to various environmental stresses including acid stress and oxidative stress (Fozo *et al.*, 2004). In the case of the caries pathogen, *S. mutans*, this shift to a membrane containing a greater percentage of unsaturated fatty acids was required to withstand further acid or oxidative stress, and crucially, cause disease in a rat model of dental caries (Fozo & Quivey, 2004, Fozo & Quivey, 2004, Fozo *et al.*, 2007). Our current research project on this topic seeks to address several questions and knowledge gaps raised by these observations: (1) although it is known how *S. mutans* and other Lactobacillales produce unsaturated fatty acids, it is not known how this system is regulated and controlled (i.e., how it is turned on when needed), (2) it is not known how the unsaturated fatty acids are protective, and (3) although a similar response appears to occur in all tested Lactobacillales, it is not known if it is protective and/or required for virulence in organisms other than *S. mutans* or other disease contexts. This is

a particularly important question, as Lactobacillales contains other devasting pathogens such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, and *Enterococcus faecium*, all responsible for significant human morbidity and mortality. The bacterial lipid biosynthesis pathway is quite different at the molecular level than its eukaryotic counterpart, therefore it presents attractive targets for the development of novel antibiotics (Radka & Rock, 2022). Indeed, one of the few novel classes of antibiotics discovered and utilized in the past 30 years, triclosan, targeted the reductase step in bacterial fatty acid biosynthesis (distinct from the steps involved in unsaturated fatty acid biosynthesis) (Radka & Rock, 2022). Beyond this specific study and application, the impact of the bacterial lipidome on bacterial physiology and pathogenesis more broadly is an understudied field, with advancements in mass spectrometry technologies opening the door to lipidomics studies with a level of resolution not possible previously.

RESISFORCE: partnering Norway, Brazil, India, Canada and the U.S. to further excellence in education, research and innovation in the study of biofilms and antibiotic research.

Resistance of pathogenic microbes to antibiotics is a growing worldwide concern, with global deaths due to antibiotic resistance predicted to overtake global deaths due to cancer and become the number one cause of death worldwide by 2050 (Brown *et al.*, 2017). Our RESISFORCE project, funded by the Research Council of Norway, partners research labs from the Norwegian Institute of Public Health, University of Oslo, TATA Consultancy Services (based in Delhi, India), University of Campinas (Piracicaba, Brazil), McGill University (Montreal, Canada), University of Illinois at Chicago, Forsyth Institute and Oregon Health & Science University to engage diverse trainees, clinicians and scientists in educational outreach regarding the accelerating antibiotic resistance crisis and antibiotic stewardship. The Baker Lab has been an active partner in this project since 2019, and has facilitated RESISFORCE outreach symposia at dental conferences in Brussels, Belgium (CED-IADR 2021) and Marseille, France (PER-IADR 2022), as well as intensive symposia and hands-on workshops for trainees at the University of Oslo (2023) and University of Campinas (2019, 2022). Our team has also produced a massive online open course (MOOC), titled “Exploring the Landscape of Antibiotic Resistance in Microbiomes,” available on FutureLearn. This free online course enables interested clinicians, researchers, students and members of the public, to discover how antibiotic resistance has emerged as one of the most urgent public health threats, explore how the study of antibiotic resistance genes helps us understand antibiotic resistance and get hands-on experience examining data using the ResistoXplorer online tool (**www.resistoxplorer.no**—itself produced as a collaboration initiated through the RESISFORCE project (Dhariwal *et al.*, 2021)). RESISFORCE has also sponsored several international researcher exchanges between labs participating on the project, provided networking opportunities, and fostered fruitful research collaborations between the participating labs (Junges *et al.*, 2018, Junges *et al.*, 2019, Junges *et al.*, 2019, Ricomini Filho *et al.*, 2019, Salvadori *et al.*, 2019, Dhariwal *et al.*, 2021, Bajalan *et al.*, 2022, Dornelas-Figueira *et al.*, 2023, Junges *et al.*, 2023). Since dentists account for approximately 10% of all antibiotic prescriptions, and antibiotic resistance and stewardship are frequently neglected topics in dental school curriculum, the unique dentistry-focused international outreach of this program is expected to be particularly impactful (Ramanathan *et al.*, 2023).

The Baker Lab will also be hosting our four-day annual RESISFORCE symposium at OHSU on Sept. 9 - 15, 2024. This symposium will include a day of formal presentations by faculty from the RESISFORCE project, OHSU faculty in related fields, and regional leaders in microbiology and antibiotic resistance research (change to Sept. 13, 2024). The symposium will also feature three days of interactive workshops for dental/graduate student and postdoctoral-level trainees (Sept. 10 - 12, 2024). The workshops will include group problem-based learning sessions and presentations, working with other trainees from Brazil, Norway, U.S. and Canada, as well as a hands-on bioinformatics workshop. The symposium will be a tremendous opportunity to learn about current research in antibiotic resistance and oral health, and to network and interact on an international level with oral health researchers.

Perspective

Personalized medicine, enabling significant improvements to oral health and overall health, is on the horizon. However, an incomplete understanding of the complex oral microbiota, and its impact, continues to obstruct progress toward actionable diagnostic metrics, as well as novel therapeutic and preventative strategies. Fortunately, emerging technologies are enabling discovery in these fields at an unprecedented pace, scale and level of resolution. It is an exciting time to be at the intersection of oral health research and microbiome research.

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Designing the future: exploring the potential of stimuli-responsive dental biomaterials for personalized therapies

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Abstract

Remarkable strides in dental biomaterial development over recent decades have dramatically improved patient care and clinical outcomes. Current efforts in the field are now to develop materials that not only resist harsh oral conditions but also act as dynamic platforms capable of sensing microenvironmental changes, processing them, and responding in a programmable, ordered, and orchestrated way. This short review provides an overview of novel stimuli-responsive biomaterials, highlighting their primary characteristics, challenges, and opportunities, particularly in applications in restorative dentistry and periodontal disease management. The expectation is that these biomaterial platforms will revolutionize the development of personalized, multifunctional dental care therapies, pioneering a new era in patient-centered dental treatments.

Introduction to stimuli-responsive dental materials

Fast, off-target effects-free, sustainable, and on-demand are the current objectives for biomaterials in pursuit of personalized patient care. The era of "one-size-fits-all" therapeutics is nearing its end, as individualized approaches have shown to be the sole path to advancing patient care. In this context, the new category of stimuli-responsive biomaterials has emerged as a promising strategy to facilitate this transition.

Stimuli-responsive biomaterials, by definition, are systems endowed with the inherent ability to detect changes in microenvironmental conditions, interpret this information effectively, and subsequently initiate organized and coordinated actions (1). These bioinspired synthetic therapeutic platforms strive to replicate the most perfectly responsive system ever developed—the human body (1).

Countless responsive processes occur within the human body each day. For instance, a simple paper cut on the fingers triggers a cascade of ordered events, initiating with hemostasis, followed by inflammation, leading to cell proliferation, and culminating in tissue remodeling (2). This sequential process is intricately guided by biomarkers and cytokines, orchestrating a rapid, predictable, localized, controlled, and autonomous response (2). These are precisely the characteristics that researchers aim to replicate in synthetic systems (1).

The design and development of stimuli-responsive systems typically follow a structured pathway comprising five main steps (3). The initial step involves an in-depth exploration of the microenvironment intended for the platform, enabling a comprehensive understanding of its characteristics and intricacies. The second step involves the identification of the stimulus or stimuli that will activate the synthetic system. Once the environmental understanding is achieved and the triggering stimulus is clearly defined, the third step involves selecting the most suitable model by considering the clinical application. Subsequently, the newly designed system undergoes rigorous and systematic optimizations to ensure appropriate activation

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under physiologically relevant conditions. Finally, in the last step, the platforms undergo extensive validation both *in vitro* and *in vivo* to ascertain their effectiveness and functionality (3).

The development of stimuli-responsive biomaterials is advancing swiftly in the medical field. In dentistry, it is still in its initial stages, offering abundant opportunities for growth and innovation (4). Therefore, this short-communication aims to present the current challenges and opportunities in the realm of stimuli-responsive dental biomaterials. Specifically, it focuses on their application in restorative dentistry and the treatment of periodontal disease.

Restorative dentistry: From space-filling to biologically instructive role

Since the introduction of polymer-based restorative materials, noticeable advances have been achieved in their mechanical resistance, physicochemical stability, and aesthetic properties, underpinning the principles of minimally invasive dentistry (5). However, dental restorations continue to experience failure rates much higher than desired (6). One of the primary reasons for such failures is the formation and propagation of microcracks induced within the body of the restorations due to thermal and masticatory stresses (7). The propagation of these microcracks can lead to the penetration of bacteria and subsequent recontamination of dental tissues or the catastrophic fracture of the restorations (7). In an effort to tackle this challenge, there has been a growing interest and effort in developing self-healing dental composites that rely on the concept of repairing microcracks as they are formed.

The primary challenge in developing dynamic polymeric networks for restorative materials is the rigidity and density of their polymer networks, which are required to withstand the harsh conditions of the oral environment (3). However, this environment is contrary to the conditions required for the responsive bonds to be broken and reformed (1). An alternative method to overcome this obstacle has been to encapsulate low-viscosity compounds, designed as healing agents, in microcapsules and add them to the resin composite formulations (8). The concept involves the microcapsules being ruptured as cracks form, leading to healing agent release and polymerization and, ultimately, the restoration of the material integrity (**Figure 1**) (8).

Although this microcapsule-based approach has shown promising results, extensive efforts have been dedicated to enhancing its potential for translation into clinical practice. These efforts include incorporating high-

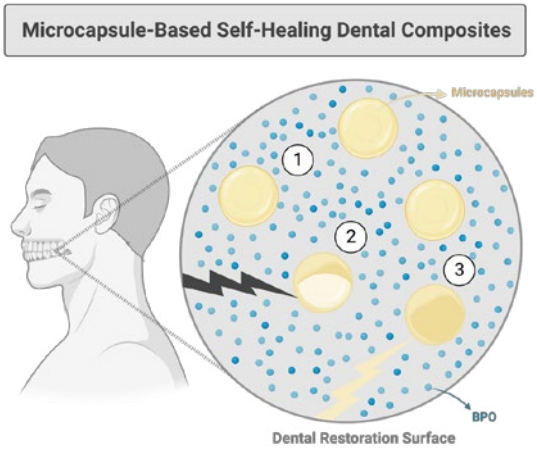

Figure 1. Illustration depicting the repairing mechanism of a microcapsule-based self-healing dental composite. The diagram showcases three primary scenarios: (1) an intact microcapsule, (2) a microcapsule ruptured by a newly formed microcrack, and (3) the cracked region covered by the healing agent. Upon contact with benzoyl peroxide (BPO), the healing agent polymerizes and seals the affected area. *Created with BioRender.com*

toughness additives into the healing agent compositions, functionalizing the shell walls to establish covalent bonding between them and the organic matrix, and introducing more robust and reliable techniques for promoting microcapsule synthesis (9). The incorporation of high-toughness agents has already demonstrated significant improvements in resin composite formulations. These modified systems could restore around 80% of the toughness after post-healing and enhance their resistance to crack propagation by increasing the energy required by 50% (10).

Periodontal disease: A complex microenvironment with high potential

The 2021 landmark report "Oral Health in America: Advances and Challenges," released by the NIDCR (National Institute of Dental and Craniofacial Research), highlights the accelerating aging of the U.S. population (11). In less than 15 years, individuals aged 65 and above will outnumber those under 18 for the first time (11). With aging comes increased health concerns, and presently, two-thirds of the U.S. population aged 65 and over struggle with chronic periodontal disease (11). Beyond the discomfort and pain resulting from tooth loss, difficulties in speaking and chewing lead to poor nutrition, affecting social interactions, emotional well-being, and overall quality of life (12). In addition, periodontal disease is intricately linked to over 50 systemic disorders such as diabetes, rheumatoid arthritis, Alzheimer's, cancer, and heart conditions (13).

Currently, treatment and diagnosis of periodontal disease faces important challenges. Treatment mostly consists of removal of contaminated and granulation-inflamed tissues through root planning and scaling (14). In advanced cases, use of systemic broad-spectrum and anti-inflammatory drugs are often linked to issues such as the development of antimicrobial resistance, off-target effects, and immune suppression (14). The only local therapy approved by the U.S. Food and Drug Administration is a hydrogel based on doxycycline, a broad-spectrum tetracycline (15). Regarding diagnostics, assessments primarily rely on bleeding upon probing and radiological findings, reflecting the history of the disease rather than their precise status at the moment (16). Moreover, these methods are invasive, painful, and potentially influenced by personal judgment (16).

The environment within periodontal pockets is intricate, housing a variety of microorganisms, various cell types, biomarkers, enzymes, and inflammatory cytokines (**Figure 2**) (17). However, it also presents numerous stimuli that can activate responsive therapeutic platforms that hold the potential to promote the local, on-demand, and sustainable release of therapies. Research endeavors have focused on developing biodegradable

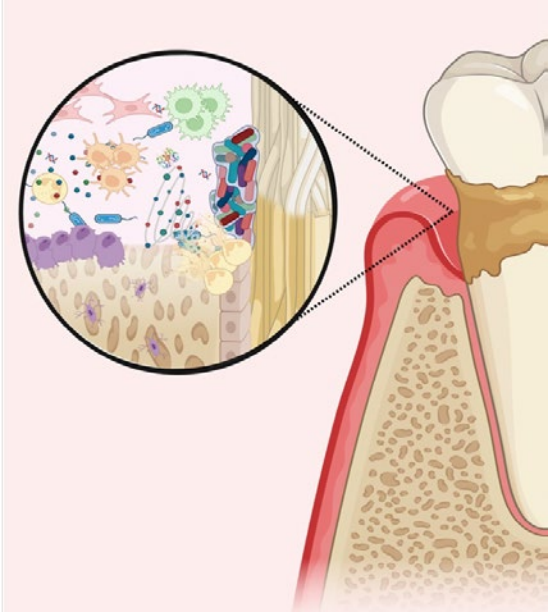

Figure 2. Cartoon representing the complex microenvironment of chronic periodontal disease, comprising a diverse array of microorganisms, various cell types, and components of the immune defense system. *Created with BioRender.com*

nanocarriers that can encapsulate therapeutic agents, engineered to be released when concentrations of targeted stimuli are out of the range of hemostasis levels (18). To address the clinical requirements for the effective translation of these designed platforms, injectable, biodegradable hydrogels have been specifically engineered to deliver and release the nanocarriers (18). Additionally, endowing these delivery vehicles with a therapeutic role has been representing an ongoing optimization of the systems, enabling them to serve as adjunctive therapeutic agents (18).

Prospects and future directions in stimuli-responsive dental biomaterials

The field of biomaterials designed to dynamically interact with the oral environment is still in its nascent stage yet holds significant promise. The convergence of multiple functionalities within a singular platform stands as a potentially transformative advancement in oral therapies (19). Such innovations have the potential to effectively engage with the complex oral environment, wherein many pathological conditions manifest due to the interplay of numerous factors. Furthermore, integrating therapeutic capabilities with diagnostic features presents a promising approach (20). This integration serves as a powerful tool, facilitating real-time assessment and accurate monitoring of treatment efficacy, and the progression or remission of specific conditions.

Endowing dental biomaterials with dynamic components while preserving their essential physicochemical stability in the harsh oral environment and ensuring their prompt response to specific stimuli is inherently difficult. Further, interdisciplinary collaboration is essential since comprehensive biological and mechanistic insights into the microenvironment, and a comprehensive understanding of available chemistries and the clinical requirements for achieving translational applicability are required. However, this advancement might initiate a new era in dental therapies, revolutionizing patient care. The prospect of customizing and personalizing dental therapies to accommodate the unique and specific needs of each individual can transform treatment outcomes.

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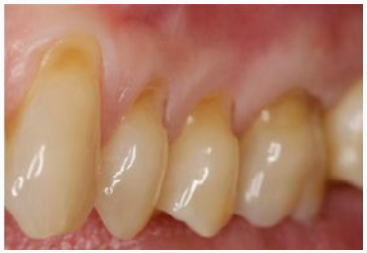
Which adhesive system is more effective for treating non-carious cervical lesions?

Students: Sehoon Park and Riley Smart
Mentor: Ahmad Alkhazaleh, B.D.S., M.S.

Case Scenario – With the school's shift to 2-step self-etch bonding (2SE) from 3-step etch-and-rinse (3E&R), it is important to explore the potential benefits and drawbacks of each adhesive. Historically, 3E&R has the most evidence supporting its success, while the 2SE is known to be less technique sensitive. To assess their effectiveness, non-carious cervical lesions (NCCL) were chosen for several reasons: they are highly prevalent in the patient population, involve both enamel and dentin, and the bond strength is critical for the retention of the restorations as the primary outcome while also considering the post-operative sensitivity and esthetics.



https://www.studiodentaire.com/en/conditions/abfraction.php

P	I	C	O
Problem	**Intervention**	**Comparison**	**Outcome**
Adult patients with NCCL	2SE	3E&R	Restoration retention

Clinical Question – For adult patients with non-carious cervical lesions, does 2-step self-etch adhesive display more clinical effectiveness than 3-step etch-and-rinse system?

Search Strategy

MeSH Terms: non-carious cervical lesions, adhesive

CAT (1)

Citation: Peumans et al. "Clinical effectiveness of contemporary adhesives for the restoration of non-carious cervical lesions." Dent Mater. 2014 Oct;30(10):1089-103.
Methods: 72 articles and 15 abstracts that evaluated at least 2 adhesives for at least 18 months were used. These articles recorded retention as a function of time for each adhesive strategy administered.
Results/Conclusions: 2SE had annual failure rate (AFR) of 2.5 (standard deviation (SD) = 1.50) while 3E&R's had AFR of 3.1 (SD = 2). The mean AFR scores of the two adhesives were relatively stable with time (>5 years). The difference in AFR between the two adhesive systems was insignificant. Instead, the clinical performance was highly product-dependent.
Validity/Applicability: Systematic Review of Randomized Controlled clinical trials and controlled clinical trials
Level of Evidence: Level 1 - Systematic Review

CAT (2)

Citation: Schroeder et al. "Influence of adhesive strategy on clinical parameters in cervical restorations: A systematic review and meta-analysis." J Dent. 2017 Jul;62:36-53.
Methods: 42 studies that evaluated at least 2 adhesives for at least 18 months were used evaluating retention rate and marginal discoloration. One meta-analysis was performed measuring the risk of post-operative sensitivity
Results/Conclusions: When comparing the retention of the restoration, no significant differences between groups (3E&R vs. 2SE) were observed in any post operative follow ups between 18 months to 60 months ($p > 0.21$). When comparing marginal discoloration, no significant difference between adhesive strategies could be detected at 1-year and 3-year follow-ups ($p > 0.08$), however this difference was statistically significant at 18 months to 2 years ($p = 0.0003$) and 4 to 5 years ($p = 0.0007$).
Validity/ Applicability: Systematic review and meta-analysis
Level of Evidence: Level 1 - Systematic Review

CAT (3)

Citation: Dreweck et al. "Adhesive strategies in cervical lesions: systematic review and a network meta-analysis of randomized controlled trials." Clin Oral Investig. 2021 May;25(5):2495-2510.
Methods: 66 randomized controlled trials evaluated primarily on restoration loss. Follow up periods ranged from 3 to 108 months, with age range of participants from 18 to 88 years
Results/Conclusion: When evaluating the loss of retention at 12 to 24 months, a significant difference was observed in the pair 2SE vs 3E&R (Risk Ratio = 0.72; 95% Confidence Interval = 0.52 - 0.99) in the meta-analysis in favor of the 2SE bonding strategy. No significant difference was found in the loss of retention after 36 months between the two adhesive strategies.
Validity/ Applicability: Systematic review and meta-analysis
Level of Evidence: Level 1 - Systematic Review

Case Significance

When restoring NCCL, 2SE and 3E&R are both viable treatment options for establishing a long-lasting composite restoration. However, the effectiveness of both systems is highly product dependent. The products that were most effective for 2SE and 3E&R are Clearfil SE Bond and OptiBond FL, respectively.

- When comparing 2SE and 3E&R adhesives, the retention rate and post-operative sensitivity are similar between these restorations. However, using 3E&R adhesives can reduce marginal discoloration.
- There is insufficient evidence to support the findings that enamel beveling or dentin roughening increases retention rate.
- When comparing the effectiveness of 2SE systems, using a milder acid greatly increases overall retention rate.

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The impact of maxillary skeletal expansion on objective measures of nasal resistance in adults and children

Student: Peter Lahti
Mentor: Jeffrey Nickel, D.M.D., M.Sc., Ph.D.

Case Background – Nasal breathing is crucial for living a healthy life. Though there are several ways to measure nasal airway resistance, rhinomanometry is the standard technique. The normal value for an adult is 0.30 (adults) and 0.40 (children) Pa/cm^3/s and with 0.80 being considered severe nasal obstruction.

P	I	C	O
Population	**Intervention**	**Comparison**	**Outcome**
Adults & Children	Maxillary Skeletal Expansion	No Maxillary Skeletal Expansion	Objective measures of nasal resistance

Clinical Question – Does maxillary skeletal expansion improve objective measures of nasal resistance in adults and children?

CAT (1)

Citation: Calvo-Henriquez, Christian, et. al. (2020) The Impact of Maxillary Expansion on Adults' Nasal Breathing: A Systematic Review and Meta-Analysis. *American Journal of Rhinology & Allergy,* Vol. 35(6) 923-934.

Methods: Pubmed, Cochrane library, EMBASE, and Trip Database used to collect relevant articles. The main outcome was the value prior to treatment, after expansion procedures, after the retention period, and after follow-up

Results/conclusions: Initial evidence is too limited to suggest maxillary expansion as a treatment option to target nasal breathing. However, the data suggest a positive role of maxillary expansion for improving nasal breathing in adults. Statistically significant reduction of 0.27Pa/cm^3/s in nasal resistance after palatal expansion.

Validity/applicability: This study examined several articles in which multiple types of expansion were used and multiple means of objective data were collected

Leval of evidence: Level I - Systematic Review

CAT (2)

Citation: Alyessary, Akram S, et. al. (2019). Effects of non-surgical rapid maxillary expansion on nasal structures and breathing: A systematic review. *International Orthodontics. 17,* 12-19.

Methods: Web of Sicence, Dentistry & Oral Sciences Source, and Pubmed databases were searched using terms "rapid maxillary expansion", "nasal," "airway," and "breathing" to collect studies.

Results/conclusions: Non-surgical rapid maxillary expansion was found to improve breathing, increase nasal cavity geometry, and decrease nasal airway resistance in children and adolescents.

Validity/applicability: This study focused specifically on non-surgical rapid maxillary expansion and its effects on both breathing and airway structures.

Level of evidence: Level 1 - Systematic review

CAT (3)

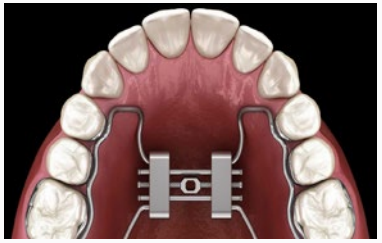
Citation: Calvo-Henriquez, Christian, et. al. (2020). The role of pediatric maxillary expansion on nasal breathing. A systematic review and metanalysis. *International Journal of Pediatric Otorhinolaryngology.* 135.

Methods: Pubmed, Cochrane Library, Embase, and Trip Database were used to collect relevant articles. The main outcome was the difference between resistance before nd after treatment.

Results/conclusions: There was a statistically significant difference of 0.12 Pa s/cm^3 mean reduction in nasal resistance after palatal expansion and a 29.9 cm^3/s increase in nasal flow after palatal expansion.

Validity/applicability: This study focused on the impact of palatal expansion in the pediatric population specifically.

Level of evidence: Level I - Systematic review



Null hypothesis – Maxillary skeletal expansion does not significantly improve objective measures of nasal resistance in adults and children.

Case Significance

Nasal breathing is very important for a healthy life! Nasal breathing is important in the prevention & treatment of sleep apnea, healthy body postures, and delivering oxygen to our bodies. Maxillary constriction is one of the most frequent craniofacial skeletal deformities, and it can lead to suboptimal nasal breathing. Nasal surgery fails to restore nasal breathing in some cases. Maxillary expansion is a common procedure that can be used to correct maxillary constriction. Though more studies are needed, the data suggest that maxillary skeletal expansion can improve nasal breathing, which can improve our patients' quality of life.

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Effective treatment of pediatric alveolar cleft lip and palate with rhBMP-2 bone graft

Student: Jonathan V. Nguyen
Mentors: Richard Grabowsky D.D.S., Rahul M. Visalakshan, Ph.D., and Luiz E. Bertassoni D.D.S., Ph.D.

Case Background - Autologous bone grafting is the gold standard for the repair of maxillary alveolar cleft defects, performed typically during mixed dentition phase and before permanent canine eruption. However, this procedure remains a challenge in clinic due to the shortcomings of harvesting bone tissue from the same patients: increased risk of infection, limited donor-site supply, and compromised ambulation. This CaseCAT aims to compare the performance on bone formation between autologous bone grafts and bone graft substitutes utilizing recombinant human bone morphogenetic protein-2 (rhBMP-2) among pediatric patients with alveolar clefts.

P	I	C	O
Population	**Intervention**	**Comparison**	**Outcome**
Pediatric patients with alveolar cleft (w/wo cleft lip and palate)	rhBMP-2	Iliac crest bone graft (ICBG)	Bone formation (volume, height, or filling percentage)

Clinical Question - Would the use of rhBMP-2 show similar outcomes regarding bone formation in alveolar defects when compared with iliac crest bone grafts (ICBG)?

CAT (1)

Citation: Da Rosa, W., et al. (2019) "Efficacy of rhBMP-2 in Cleft Lip and Palate Defects: Systemic Review and Meta-analysis." *Calcified Tissue International*: 104, 115-129.
Methods: Seven databases were screened: PubMed (Medline), Lilacs, Ibecs, Web of Science, BBO, Scopus, and The Cochrane Library for retrospective or prospective clinical trials.
Results/conclusions: Ten studies compared the use of rhBMP-2 and iliac crest bone graft (ICBG). Global analysis for bone formation volume and bone filling percentage showed that bioactive materials were similar to ICBG 6-month and 12-month periods of follow-up with a standardized mean difference of respectively 0.07 and 0.24.
Validity/applicability: Majority of found studies were clinical trials with low risk of bias evaluated by the Cochrane guidelines. Excluded studies were based on a strict inclusion criteria.
Level of evidence: Level 1 – Systemic Review (with Meta-analysis).

CAT (2)

Citation: Lee, K., et al. (2021) "Autogenous Iliac Crest Versus rhBMP-2 for Alveolar Cleft Grafting: A 14-Year Single Institution Experience." *J Oral Maxillofac Surg*: 79(2), 431-440.
Methods: 14-year retrospective study of patients with alveolar clefts treated at the Morgan Stanley Children's Hospital between 2006 and January 2020. Study sample included 115 patients (35 rhBMP-2 and 80 AICBG) with 130 alveolar clefts. Bone height was scored according to the Bergland scale.
Results/conclusions: No differences in success between materials (rhBMP-2:90.3%; AICBG: 89.1%). Compared with AICBG, rhBMP-2 produced similar height of bone and required less hospital resources.
Validity/applicability: Sufficient sample size and descriptive statistics were accounted for. Lack of CBCT measure due to institutional protocols.
Level of evidence: Level 4 – Retrospective Study

CAT (3)

Citation: Chen, K., et al. (2022) "Clinical Application of Allograft Bone of Alveolar Cleft Repair." *J Craniofac Surg.* 34(2): 178-182.
Methods: A total of 131 patients (66 males, 65 females) with unilateral alveolar cleft were divided into three groups. Group A (43 patients) were treated with autologous bone, Group B (41 patients) were treated with BIO-GENE group, and Group C (47 patients) were treated with rhBMP-2 + BIO-GENE group. Preoperative cleft volume and newly formed bone volume after 3+ months post-surgery was calculated by CBCT to measure osteogenic rate.
Results/conclusions: Osteogenesis rate of Group C compared to Group A was statistically significant ($p = 0.003$). rhBMP-2 significantly increases the osteogenic rate and bone volume
Validity/applicability: Sufficient sample size and justification for CBCT was discussed in the study design.
Level of evidence: Level 4 – Comparative Study

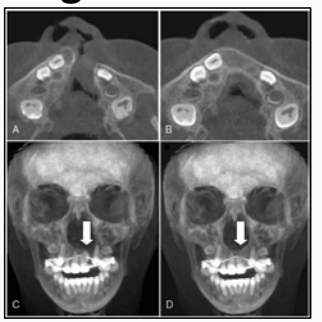

Figure 1. (**A**) and (**C**) Preoperative left alveolar cleft lip and palate defect. (**B**) and (**D**) Postoperative 6 months after GPP with rhBMP-2.
Scientific Figure on PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/31107382/

Search Strategy

MeSH Terms: Alveolar Cleft, rhBMP-2, Autologous bone graft

Case Significance

- ICBG has been reported to have success rates higher than 88% due to its essential osteoconductive and osteoinductive factors, and nonimmunogenic properties needed for bone healing and regeneration.
- Complications of autologous bone grafting from ICBG have been reported in 49% of patients experiencing pain, hemorrhage, or nerve injury post operation.
- While ICBG has provided one of the most biocompatible options for alveolar cleft defect repairs, its disadvantages have driven the search for minimally invasive alternatives.
- Use of rhBMP-2 present similar performance relative to bone formation in cleft lip and palate defects when compared with ICBG.

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Evaluation of clinical effectiveness of Hall technique for carious primary molars

Student: Stella Sonu
Mentor: Yifan Zhang D.D.S., Ph.D, M.Sc

Case Background – The CDC reports the prevalence of untreated caries in primary dentition: 10% among children aged 2-5 years, 16% among those 6-8 years (Oral Health Surveillance Report, 2019). Barriers in treating pediatric patients include behavior management and lack of resources (i.e. sedation). Thus, minimally invasive strategies are becoming the standard of care. These include 1) Atraumatic Restorative Treatment (ART), use of hand instruments to selectively remove carious tissue, and 2) the Hall Technique (HT), placement of preformed metal crowns (SSCs) over carious tissue.

P	I	C	O
Population	**Intervention**	**Comparison**	**Outcome**
Primary molars with proximal carious lesions with no signs and symptoms of pulpal involvement	SSCs placed by HT	ART or Conventional SSC Technique	Success (No signs or symptoms of pulp necrosis, no loss of restoration, no further treatment until exfoliation)

Clinical Question – How effective is HT in successfully treating carious lesions on primary molars with no pulpal involvement, compared to ART or conventional SSC technique?

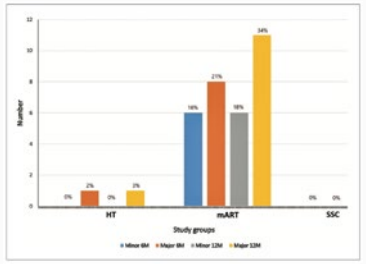

Figure. Number of major and minor failures in study groups after six months (6M) and 12 months (12M).*
* HT=Hall technique; mART=modified atraumatic restorative treatment; SSC=conventional stainless steel crown.

Search Strategy –

MeSH Terms: Hall technique, restorative, primary, randomized control trial

CAT (1)

Citation: Araujo MP, Innes NP, Bonifácio CC, Hesse D, Olegário IC, Mendes FM, Raggio DP. Atraumatic restorative treatment compared to the Hall Technique for occluso-proximal carious lesions in primary molars; 36-month follow-up of a randomised control trial in a school setting. BMC Oral Health. 2020 Nov 11;20(1):318. doi: 10.1186/s12903-020-01298-x. PMID: 33176756; PMCID: PMC7656501.

Methods: Randomized control trial (RCT) with 131 primary molars, allocated to ART (*n*=65) or HT (*n*=66). Primary outcome: restoration survival over 36 months. Success defined as no further intervention, no signs of pulp damage, and/or tooth exfoliation without failure. Secondary outcomes: OVD, child's discomfort, and treatment acceptability.

Results/Conclusions: Restoration survival rates: ART = 32.7%, HT = 93.4%. OVD returned to pre-crown measurements in HT within four weeks. No association and difference between child-reported discomfort before and after both interventions. Treatment acceptability high for children, but 24% of parents in HT disagreed with, "appearance doesn't bother me". HT restoration survival rates almost three times greater than ART, but need to consider parents' expectation regarding esthetics.

Validity/Applicability: High. Sample size determined with log-rank test and survival analysis, results evaluated with Kaplan-Meier survival analysis and Cox regression. Limitation: lack of radiographs to evaluate extent of caries prior to treatment.

Level of evidence: Level I Grade A, RCT

CAT (2)

Citation: Ebrahimi M, Shirazi AS, Afshari E. Success and Behavior During Atraumatic Restorative Treatment, the Hall Technique, and the Stainless Steel Crown Technique for Primary Molar Teeth. Pediatr Dent. 2020 May 15;42(3):187-192. PMID: 32522320.

Methods: RCT with 123 primary molars, allocated to HT (*n*=42), mART (*n*=42), or SSC (*n*=39). Primary outcome: presence of clinical major failure (i.e. sensitivity to percussion, spontaneous pain) at 6 and 12-month recalls. Secondary outcomes: time of treatment, child's behavior, and parental satisfaction.

Results/Conclusions: Major/minor failures significantly higher in mART than HT and SCC (refer to Figure). No significant difference between HT and SSC in major and minor failures at 12 months. Mean treatment time for HT, mART, and SSC were 8, 11, and 17 minutes, respectively. Patient's behavior significantly better in SSC than in HT and mART, with difference in latter insignificant. Parents report high degree of satisfaction with HT and SSC, but significant dissatisfaction for mART at both recalls. Overall, HT restoration survival rates similar to that of SSC, with shorter treatment time.

Validity/Applicability: High. Patient recruitment to fit sufficient sample size. Baseline/recall data analyzed with Fisher's exact, Kruskal-Wallis, Mann-Whitney, and Chi-square tests. Limitation: subjective evaluation of patient behavior by Frankl score.

Level of evidence: Level I Grade A, RCT

CAT (3)

Citation: Boyd DH, Thomson WM, Leon de la Barra S, Fuge KN, van den Heever R, Butler BM, Leov F, Foster Page LA. A Primary Care Randomized Controlled Trial of Hall and Conventional Restorative Techniques. JDR Clin Trans Res. 2021 Apr;6(2):205-212. doi: 10.1177/2380084420933154. Epub 2020 Jun 19. PMID: 32559403.

Methods: RCT with 570 primary molars, allocated to HT (*n*=149) or NHT (*n*=146). In NHT arm, operators chose restorative material, including SSC, glass ionomer, amalgam, or composite. Primary outcome: success, major failure, and minor failure defined by Innes et al. (2007) at 12 and 24-month recalls.

Results/Conclusion: At 12 months, 86.5% of all treated teeth successful, with no significant difference between treatment groups. In NHT arm, treatment material was significant predictor of minor failures, with more failures with glass ionomer. At 24 months, SSCs had greatest success regardless of treatment group, HT or NHT. In lesions treated by glass ionomer, 45.3% showed minor failure. HT restoration success rates are similar to that of SSC, but superior to that of glass ionomers.

Validity/Applicability: High. Sample size determined by conservative power analysis. Results analyzed with univariate descriptive statistics, cross-tabulations, and Chi-square tests. Limitation: 13 dental therapists, all with range of experience and given choice of restorative material in NHT arm.

Level of evidence: Level I Grade A, RCT

Case Significance

HT presents with:

- Restoration survival similar to SCC, but superior to ART.
- Variation in patient behavior due to discomfort of orthodontic separators.
- High patient and parent acceptability.
- Immediate OVD change and self-corrects in weeks.
- Shorter treatment time compared to SCC and ART.

Case selection is an important aspect upon determining treatment options for pediatric patients. HT is a successful, minimally invasive technique that should be considered for carious primary molars without pulpal involvement.

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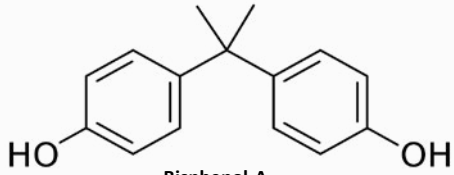
Clinical reduction of bisphenol-A leaching in dental restoration on younger patients

Students: Luke George, Sarah Wiskoski and Grayson Won
Mentor: Carmem Pfeifer D.D.S, Ph.D

Case Background – Currently, Bisphenol-A (BPA) is not used directly in the production of monomers used in dental composites. However, small transient amounts may remain as an impurity from synthesis of composites containing BisGMA or Bis-DMA. Though studies demonstrate that the trace amount of BPA and precursor compounds like BisHPP in composite restorations are safe and minimal, high concentrations of BPA have been shown to have adverse effects in children and young adults, whose bodies lack capacity to break down BPA. Because of this, patients and parents may fear that restorative materials containing Bis-GMA or Bis-DMA release BPA into the oral environment, especially for those at a young age. Therefore, it may be advantageous for a provider to offer treatment methods that reduce BPA when treating apprehensive patients or younger patients, despite the ambient environment providing far more exposure.



Bisphenol-A

P	I	C	O
Problem	**Intervention**	**Comparison**	**Outcome**
BPA leaching into younger patients from resin composite	Clinical methods that reduce levels of BPA	Placing restorations without using reductive methods	Reduced levels of BPA

Clinical Question – Are there evidenced-based methods to reduce levels of BPA released in the oral cavity of younger patients directly after dental restoration?

CAT (1)

Citation: Paula AB, Toste D, Marinho A, Amaro I, Marto CM, Coelho A, Marques-Ferreira M, Carrilho E. Once Resin Composites and Dental Sealants Release Bisphenol-A, How Might This Affect Our Clinical Management?-A Systematic Review. Int J Environ Res Public Health. 2019 May 9;16(9):1627. doi: 10.3390/ijerph16091627. PMID: 31075949; PMCID: PMC6539392

Methods: A systematic review of 20 studies was completed on literature databases, investigating BPA concentration in bodily fluids after composite placement.

Results/Conclusions: All studies on saliva showed an increase in BPA an hour after composite or sealant placement. Additionally, BPA increases as more composite surfaces are placed. Despite these increases, BPA levels return to base levels 24 hours after treatment. To reduce BPA exposure, the review suggests rubber dam isolation, use of glycerin gel barrier before polymerization, polishing with pumice or cotton, and limiting number of treatments per appointment.

Validity/applicability: This review explores studies that both measure BPA exposure levels and offer solutions to minimize exposure risk.

Level of evidence: Level 1 - Systematic Review

CAT (2)

Citation: Azarpazhooh A, Main PA. Is there a risk of harm or toxicity in the placement of pit and fissure sealant materials? A systematic review. J Can Dent Assoc. 2008 Mar;74(2):179-83. PMID: 18353205.

Methods: A systematic review was accomplished using 20 studies that evaluated the toxicity of BPA following sealant placement.

Results/Conclusions: No bis-GMA based sealants showed detectable BPA levels in systemic circulation. The review suggests that reducing the oxygen-inhibited layer of sealants via surface treatment prevents a detectable concentration. This review suggests finishing with a pumice abrasive, gargling tepid water, or deliberately washing the sealant following placement to limit BPA exposure.

Validity/applicability: This review emphasizes that mild abrasives after sealant placement can significantly reduce systemic exposure to BPA.

Level of evidence: Level 1 – Systematic Review

CAT (3)

Citation: Kloukos D, Pandis N, Eliades T. In vivo bisphenol-a release from dental pit and fissure sealants: a systematic review. J Dent. 2013 Aug;41(8):659-67. doi: 10.1016/j.jdent.2013.04.012. Epub 2013 May 1. PMID: 23643847

Methods: A systematic review was conducted on studies involving BPA release in bodily fluids in vivo. 6 interventional and 2 observational studies were included.

Results/Conclusions: High levels of BPA were found in saliva especially in samples collected directly after sealant placement. Following treatment, BPA concentration lowered with time. No detectable BPA was discovered in any blood samples. However, in urine, high levels of BPA were found even in long-term measurements after sealant placement. The review suggests removing the oxygen-inhibited layer with unreacted polymer through prophy cup and rinsing decreases salivary exposure risk.

Validity/applicability: Despite finding moderate evidence, this review finds that unpolymerized monomer in sealants is correlated with BPA detectability after sealant placement.

Level of evidence: Level 1 – Systematic Review

Case Significance

Because patient comfort is paramount, mitigating BPA exposure is possible to ease patient apprehension. Based on recent research, the most BPA released is immediately after the placement of a dental filling or sealant and will accumulate at the oxygen-inhibited surface of the placed material. Our reviews recommend a variety of clinical methods to reduce this potential exposure:

- Using rubber dams to isolate oral environment from unreacted monomer
- Proper polymerization by manufacturer instruction
- Finishing composite surface with mild abrasion for 30 seconds, especially with pumice
- Suctioning debris and rinsing restoration or sealant before rubber dam removal
- Rinsing mouth with tepid water for 30 seconds

Other sources:"Bisphenol A." American Dental Association, https://www.ada.org/resources/research/science-and-research-institute/oral-health-topics/bisphenol-a.

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Treatment and prevention of oral mucositis in adult patients undergoing chemotherapy treatment for leukemia

Student: Bryce Bothwell
Mentor: Jeffrey Nickel, D.M.D., M.Sc., Ph.D.

Case Scenario – While calling patients to schedule their appointments for the term, one of my patients informed me that he had been diagnosed with AML. He stressed that he would like to continue receiving dental care at OHSU to help give him a sense of normalcy and improvement while undergoing chemotherapy. While leukemia presents with its own side effects (anemia, infections, bleeding) oral mucositis is one of the most common and debilitating complications of chemotherapy treatment and can cause significant pain, difficulty eating, and increased risk of infection; I want to be prepared should this complication arise in this patient or any other patient of mine.

P	I	C	O
Population	**Intervention**	**Comparison**	**Outcome**
Adult patients with undergoing chemotherapy for leukemia	Administration of cryotherapy, honey, doxycycline	Placebo, zinc sulphate, glutamine, chlorhexidine, control (no treatment)	Reduction in incidence/severity/duration of oral mucositis

Clinical Question – For patients receiving chemotherapy treatment, what effective interventions can be implemented for the prevention and treatment of chemotherapy induced oral mucositis?

CAT (1)

Citation: Ramírez-Amador, V. et al. (2018). Journal of clinical pharmacy and therapeutics, 43(2), 202–208.

Methods: 147 Individuals greater than 15 years old were separated into multiple groups based on leukemia diagnosis. Each individual was then randomly assigned to either the doxycycline group (50 mg doxycycline tablet daily) or placebo group for 21 days.

Results/conclusions: Results were statistically insignificant; DG and PG groups were comparable.

Validity/applicability: Low-moderate. Low sample size - trial was stopped due to low incidence of OM.

Level of Evidence: Level 1 - RCT

CAT (2)

Citation: Yang, C. et al. (2019). International journal of nursing studies, 89, 80–87.

Methods: Network meta-analysis of RCTs 17 RCTs eligible from 22 analyses involving 1265 patients performed.

Results/conclusions: Honey was found to be an effective treatment in reducing severity of moderate-severe oral mucositis induced by chemotherapy/radiotherapy in adult patients(OR = 0.11, 95%CI: 0.06-0.22, I^2=52.7%).

Validity/applicability: Good-high quality

Level of Evidence: Level 1 – Meta-analysis

CAT (3)

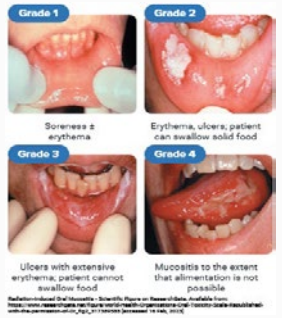
Citation: Wilairat, P. et al. (2020). European journal of hospital pharmacy : science and practice, 27(2), 103–110.

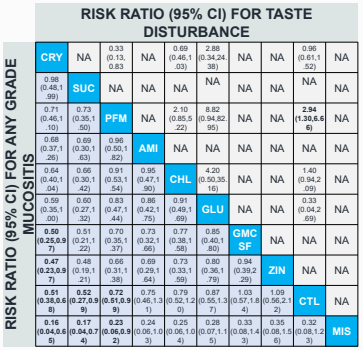
Methods: Network meta-analysis of RCTs evaluating interventions for the prevention of oral mucositis in adult cancer patients receiving chemotherapy. 29 RCTs with 2348 patients.

Results/conclusions: Cryotherapy was associated with a significantly lower risk of oral mucositis than GM-CSF, zinc sulphate, misoprostol and control.

Validity/applicability: Good-high.

Level of Evidence: Level 1 – Meta-analysis





Search Strategy

MeSH Terms: Antineoplastic agents / adverse effects*, Leukemia / drug therapy*, Mucositis , Mucositis / therapy*

Case Significance

- Cryotherapy and honey significantly reduced incidence/severity of oral mucositis
- Cryotherapy and honey are safe, effective, and readily accessible interventions
- Doxycycline did not have a significant effect

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Instructions for Authors | Call for submissions

We are currently accepting manuscripts and student posters for the spring edition of the Oregon Health & Science University School of Dentistry Anthology.

Student posters

For specifications and timelines, contact Samyia Chaudhry, D.M.D., assistant professor for restorative dentistry, at chaudhry@ohsu.edu

Manuscript submittals

OHSU Digital Collections instructions

Manuscript preparation

Technical specifications

Manuscripts submitted to the School of Dentistry Anthology must be prepared in Microsoft Word. Illustrations can be submitted as PDF, JPEG, TIFF or Microsoft PowerPoint files. If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply "as is" in the native document format.

Length

Word limits are dependent on the article type, exclusive of title page, abstract, acknowledgments, references and illustrations (tables, figures, text boxes).

Page setup

Pages should have 1-inch margins and must be numbered consecutively throughout the document.

Title page

Each manuscript should have a title page. The title page must include:

- The complete title of the manuscript and complete information for all authors
- Each author's full name, degrees, professional title and work affiliations including position
- Acknowledgments, if applicable

Tables and figures

- Tables and figures should augment, not repeat, the text or broad trends illustrated in a figure.
- Figures and tables should be numbered consecutively according to the order in which they are cited in the text.

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Tables

- Variables are to be clearly defined and include the unit of measurement and values for any categories.
- Tables are to use units and phrasing consistent with the manuscript's text.
- Abbreviations are to be defined in table footnotes. Unit of measure abbreviations do not need to be defined.
- Row and column headings are to contain any necessary units of measure that apply to data in the row or column. Measurement abbreviations should conform to the journal's style.

Figures

- Each chart, graph or photograph will be counted as a separate illustration.
- The School of Dentistry Anthology accepts digital files (see above for formats) of radiographs, magnetic resonance images and magnetic resonance angiograms.
- Images are to obscure any feature that can identify the patient, including unique physical characteristics, files labeled with patient names or other identifiers.

General points

- Use uniform lettering and sizing in the original artwork.
- Use a preferred font: Arial, Helvetica, Times New Roman, Times, Symbol, Courier.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for the artwork files.
- Indicate per figure if it is a single, 1.5- or 2-column fitting image.
- Submit individual figure files larger than 10 MB in separate source files.
- Include figure legends at the end of the manuscript file, not on the figure.

Formats for figures

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply "as is" in the native document format. Otherwise, regardless of the application used to create figures, the final artwork should be saved as or converted to one of these formats:

- TIFF, JPEG or PPT: Color or grayscale photographs (halftones): always use a minimum of 300 dpi
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Please do not:

- Supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG).
- Supply files that are too low in resolution.
- Submit graphics that are disproportionately large for the content.

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Supplemental data

This material should be submitted with each submission of the manuscript (original and revisions) to permit full review.

Manuscript style

Basic style/writing requirements

The School of Dentistry Anthology style is based on the 11th edition of the AMA Manual of Style. The purpose of any piece of writing is to deliver information. This requires authors to define their message and present it in a way that is readily understood by and engages the reader. Manuscripts should be written in active voice using declarative sentences for a clear, concise style. The overall tone of these reports should be factual and professional, and thus suitable for a scholarly journal. Authors are allowed to express a personal opinion as long as the basis for that opinion is stated plainly. For example, authors may express an opinion "based on long experience and intensive observation." Other statements of opinion and all statements of fact require references from the appropriate published literature (dental, medical, epidemiologic, practice management, etc.).

Manuscript title

The title should be brief while clearly conveying the main point or purpose of the article. Short subheads also should be used throughout the article to highlight key points. All submissions, including titles and subheads, are subject to change during the editing process.

Statistical methods reporting

Research manuscripts should include an a priori calculation of the sample size necessary to discern a minimally detectable and clinically meaningful effect and include a description of the methods used for primary and secondary analyses. A pre-specified analysis plan is preferred. Interpretation of observational studies should arise from the results of multivariable models or other methods controlling for potential confounding effect modification and dependencies in the data. Interpretation of data from a randomized clinical trial should arise from the primary outcome measure, as analyzed in the pre-specified statistical analysis plan.

References

All published references should be cited in the text and numbered consecutively in the order in which they are referenced in the text. No references should be cited in the abstract. Each reference should be numbered only once; on subsequent citations, the original number should be used. Personal communications and unpublished data should not be numbered, but should be cited in the text as follows:

(O SoDA, D.M.D., oral communication, November 2023)

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Examples:

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1. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *J Sci Commun*. 2010;163(1):51-59. https://doi.org/10.1016/j.Sc.2010.00372

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3. Strunk W Jr, White EB. *The Elements of Style*. 4th ed. Longman; 2000.

Reference to a chapter in an edited book:
4. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, eds. *Introduction to the Electronic Age*. E-Publishing; 2009:281-304.

Reference to a website:
5. Zika travel information. Centers for Disease Control and Prevention. January 26, 2016. Updated August 11, 2016. Accessed June 18, 2019. https://wwwnc.cdc.gov/travel/page/zika-travel-information

Reference to software:
7. Coon E, Berndt M, Jan A, et al. Advanced Terrestrial Simulator (ATS) v0.88 (Version 0.88). Zenodo; 2020, March 25. https://doi.org/10.5281/zenodo.3727209

Journal abbreviations source

Journal names should be abbreviated according to the **List of Title Word Abbreviations**.

Data References

The School of Dentistry Anthology encourages authors to cite underlying or relevant data sets in the text and include a data reference in the reference list. Data references should include author names, data set title, data repository, version (where available), year, and global persistent identifier. Add "[data set]" immediately before the reference so we can properly identify it as a data reference. The [data set] identifier will not appear in the published article.

Example

[data set] 5. Oguro, M, Imahiro, S, Saito, S, Nakashizuka, T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. **http://dx.doi.org/10.17632/xwj98nb39r.1**

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Author responsibilities

Ethical approval of studies and informed consent/assent

The School of Dentistry Anthology requires that all manuscripts reporting data from studies involving human participants, human specimens, animals or animal specimens include a description (blinded in the Methods section and in full detail on the separate title page) of formal review and approval or, if appropriate, formal review and waiver by an appropriate institutional review board or ethics committee. Authors may be asked to request that the institutional review board or ethics committee responsible for oversight of the study provide, directly to the editor, documentation of its formal review and recommendation. For investigations involving human participants, authors must state in the Methods section that study participants provided informed consent/assent.

Personal communications and unpublished data

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Author contributions

All authors are to have made substantial contributions to:

- Conceptions and designs of the study, acquisition of data, or analysis and interpretation of data.
- Drafting the article or revising it critically for important intellectual content.
- Final approval of the version that is submitted.

All authors should be listed with their affiliations including positions, their academic degrees, and their scientific or clinical contributions to the article. The editor and publisher reserve the right to ask for justification for each author's inclusion.

Practical implications

Authors must ensure that the article describes the practical implications of the findings, answering the question, "What does this mean for oral health care?" This should be included in the abstract.

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- Only use these technologies to improve readability and language, not to replace key researcher tasks, such as interpreting data or drawing scientific conclusions.
- Apply the technology with human oversight and control, and carefully review and edit the result, as AI can generate authoritative-sounding output that can be incorrect, incomplete or biased.
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