INVITED COMMENTARY

Early Childhood Caries: Future Perspectives in Risk Assessment

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Early childhood caries (ECC) is defined as tooth decay among children <6 y of age. It is a “family disease” in that ECC is highly infectious and transmissible (parents/caregivers can expose their children to caries-causing bacteria) and dependent on poor (sugar laden) dietary habits (Douglass and Clark 2015). ECC continues to be one of the most prevalent childhood diseases worldwide. In the United States, 23% of all preschoolers are affected by the disease (Dye et al. 2015), with more than half the cases occurring among low-income families and ethnic/racial minority backgrounds. Left untreated, ECC can result in rapid and rampant destruction of primary teeth and cause marked pain and systemic complications that require urgent attention. This often involves emergency room visits or hospitalization for surgical intervention under general anesthesia at towering costs; those who cannot access care suffer in other ways that can negatively affect their socialization, education, and overall well-being. Importantly, even after removal or restoration of carious teeth, children remain at high risk for future recurrences despite pharmacologic interventions,

such as topical antimicrobial and fluoride applications. Thus, early identification and early application of preventive measures are essential to help eliminate this costly and painful disease.

Pediatricians are often the first health professionals to encounter ECC and therefore could play a pivotal role in preventing childhood caries. Young children are far more likely to visit primary care physicians than dentists (Douglass and Clark 2015). According to the Medical Expenditure Panel Survey, 89% of children <1 y old had office-based physician visits annually, compared with only 2% who had dental visits. Both the American Academy of Pediatrics and the American Academy of Pediatric Dentistry recommend that primary care providers conduct counseling (e.g., to avert practices such as prolonged bottle-feeding with sugary fluids) and risk assessment by 6 mo, and they encourage referral to a dentist by 1 y of age. However, despite significant efforts to integrate children’s oral health into primary care and to enhance interactions between pediatricians and dentists (e.g., the American Academy of Pediatrics’ Oral Health Initiative), identification of children at risk for ECC before the onset of cavitation (a late stage of the disease) in the pediatric or even dental office settings remains

challenging. This limitation is due to the multifactorial (environmental, social, and behavioral) nature of ECC and the limited accuracy or poor validity of existing caries risk screening tests (Fontana 2015). Development of a reliable, accurate, and low-cost ECC risk assessment device for routine screening in the pediatric office would facilitate determination of individual-level caries activity, case identification, and early referral of high-risk patients to dentists for monitoring. Emerging biological insights into the pathogenesis of ECC and new technologies suggest that such screening devices may be available in the near future.

Besides *Streptococcus mutans*, a proven bacterial culprit of ECC, other microorganisms may act in concert with this pathogen in promoting the formation of tooth decay-causing dental plaque (biofilm; Hajishengallis et al. 2015). For example, the fungus *Candida albicans* is frequently detected in high numbers with *S. mutans* in plaque from ECC-affected toddlers. It has been demonstrated that *C. albicans* and *S. mutans* develop a synergistic relationship when a sucrose-rich diet is available, which boosts their ability to form plaque biofilms, leading to aggressive onset of ECC-like lesions in an animal model of dental caries. Other acidogenic and acid-tolerant

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bacteria (actinomyces, lactobacilli, bifidobacteria, *Scardovia* species), as well as additional microbial genera/species detected in plaque of children with ECC, may also contribute to the pathogenesis of the disease. Furthermore, lack of alkali production by specific members (e.g., *Streptococcus gordonii*) of the plaque microbiome may enhance caries susceptibility in children. All together, these observations reveal the complexity of the microbiology in the ECC-plaque and explain why determination of single-species (e.g., *S. mutans*) levels in saliva, used in some caries susceptibility tests, is not an accurate method for identifying children at risk for ECC.

In the mouth, microorganisms are constantly interacting with constituents of the host saliva, including salivary proteins and biomolecules secreted by oral microbiome. Many host-derived proteins/peptides and low molecular weight constituents in saliva bind to or are utilized by oral bacteria and may be associated with caries. Likewise, elevated levels of bacterial products associated with biofilm formation (e.g., glucosyltransferase B) in saliva have been linked with enhanced caries activity, while high activity of bacterial enzymes responsible for alkali production (arginine deiminase) in plaque may decrease the risk for caries in children (as reviewed in Hajishengallis et al. 2015). Detailed exploration of host-microbe interactions through (meta) proteomics and metabolomics could identify additional biomolecules for caries susceptibility in saliva and plaque, which should be then validated through carefully designed longitudinal clinical studies. These biomolecules, with caries-associated microbes, might form a panel of biomarkers that could be analyzed

simultaneously (multiplexed) with new screening devices to more accurately identify children at risk for developing ECC.

The advent of nanotechnology, such as ultrasensitive nanomaterials or nanostructured sensors/nanophotonics, combined with microfluidics has revolutionized biomarker analysis and molecular diagnostics. These technologies are capable of rapid, portable, and accurate detection of biomarkers at femtomole concentrations. The multiplexing capacity of microfluidics offers the potential for improving sensitivity and specificity by combining several markers for analysis into a single device and, indeed, has been already tested for respiratory disease (e.g., asthma) diagnostics using human saliva. Furthermore, low sample and reagent requirements, fast analytic times, and low-cost production make these devices well suited for detection of multiple microbes and simultaneous analysis of salivary and microbial biomarkers involved in the multifactorial etiology of ECC (Hajishengallis et al. 2015).

Once developed, microbiome and saliva analysis could be combined with behavioral risk assessments in predictive models (Divaris 2016) to improve the accuracy of the existing ECC risk screening and monitoring methods. Such a combined approach will help pediatricians and dentists to objectively identify, refer, and/or monitor children who have the behavioral traits and the microbial/salivary biomarkers at levels that put them at high risk to develop ECC before the clinical manifestations (white spot/cavitation) of the disease. This personalized approach, once validated, could help to implement early intensive preventive care, strengthen the medical-dental interaction, and

ultimately help to eliminate this costly and painful disease.

Author Contributions

E. Hajishengallis, contributed to conception, drafted the manuscript; C.B. Forrest, contributed to conception, drafted and critically revised the manuscript; H. Koo, contributed to conception and design, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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