Oral health is integrally linked to overall well-being. This article describes a research program focused on the contribution of poor oral health to systemic illness. Initial investigations examined factors related to streptococcal virulence that were important in dental caries and endocarditis and led to development of immunization strategies in animal models to reduce risk of endocarditis. Clinical investigations related to critically ill adults began with descriptive and observational studies that established the importance of dental plaque in development of ventilator-associated pneumonia (VAP) and examined existing nursing practices in oral care. Subsequent intervention studies sponsored by the National Institutes of Health (NIH) to test oral care protocols in critically ill adults have built on that foundation. The group’s first NIH-funded randomized clinical trial tested the effects of toothbrushing and use of chlorhexidine in reducing risk of VAP in critically ill adults and showed that VAP was reduced by topical application of chlorhexidine initiated after intubation, although toothbrushing did not reduce VAP. The study had a rapid and dramatic effect on clinical practice. Results of the study were published in September 2009 in the American Journal of Critical Care, and in May 2010, the Institute for Healthcare Improvement updated the recommendations for the care of patients receiving mechanical ventilation (the ventilator bundle) to include daily oral care with chlorhexidine, referencing the results of that study as evidence for the change. Chlorhexidine is now the standard of care for adults receiving mechanical ventilation. Because the effects of chlorhexidine after intubation were so beneficial, a second recently completed NIH-funded randomized clinical trial investigated the impact of chlorhexidine applied before intubation compared with after intubation. Currently a large randomized clinical trial is being launched to determine the optimal frequency of toothbrushing for critically ill patients receiving mechanical ventilation in an effort to maximize oral health benefits while minimizing systemic risks. The importance of collaboration and mentoring in building nursing science is discussed. Future directions for research also are explored. (American Journal of Critical Care. 2014;23:282-289)
The mouth is a complex ecological niche, and what happens in the mouth can have a profound affect on overall health and illness. Poor oral health can affect nutrition and hydration and has a direct impact on quality of life. Additionally, oral health problems have been associated with cardiovascular disease, endocarditis, poor glycemic control in diabetic patients, preterm delivery, upper respiratory infections, and pneumonia in outpatient and inpatient settings. Conversely, systemic disease or disease treatments can adversely affect oral health; an example is the xerostomia (dry mouth) commonly experienced by critically ill patients. Although biologically plausible mechanisms for these associations have been hypothesized, the relationships remain controversial, and direct evidence for a causal relationship between oral health and most specific systemic diseases is lacking. Nurses are responsible for provision of oral care to critically ill patients who cannot take care of themselves, and oral health is amenable to nursing interventions. This article describes the development of a program of research focused on oral health and its relationship to systemic health, with particular emphasis on reducing risk of ventilator-associated pneumonia (see Figure).

Preparing for a Career in Research

My preparation for a research career exemplifies how serendipity can influence one’s path. I have a photograph of myself at age 4, posing in a nurse’s costume: white uniform, cap, nurse’s cape on my shoulders, and nurse’s bag in hand. The frame is inscribed “I am fairly certain that given a cape and a nice tiara, I could save the world.” As a child, I viewed the nurse’s cap and cape as symbols of power to save the world. When I was in high school in the early 1970s, I shifted my aspirations from nursing to medicine. However, in my first year of college as a premed major, chance intervened in the form of an elective course, “Cultural Anthropology.” During the course, each student was assigned to field experience in an agency that was effecting social change. I was hooked on nursing again! Diploma preparation was the norm in nursing education at the time, and I left college to attend nursing school. I knew that I wanted to expand my abilities and contribute to nursing knowledge. I completed a baccalaureate degree through an RN to BS program and then enrolled in a master’s program immediately following graduation. I was advised not to enroll in the nurse practitioner (NP) track because the NP role was predicted to be less marketable than the clinical nurse specialist (CNS); following my PhD, I would rethink that career advice, and complete a

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I completed the master’s degree as a cardiopulmonary CNS. For my thesis, I studied the effect of performing a back massage just after transfer out of the intensive care unit on anxiety, randomizing patients to receive back massage or not by coin flip. Unsurprisingly, patients scored lower on a survey of anxiety following their back massage than did patients who did not have a massage.1 The master’s degree provided an essential foundation for my later work: the CNS preparation was heavy in basic science courses and oriented to improving bedside care, and the thesis sparked my enthusiasm for nursing research.

I chose a doctoral program that permitted me to complete a full curriculum in microbiology and immunology as well as 3 courses in nursing theory. Coursework important to my future research included prokaryotic and eukaryotic cell biology, molecular genetics, biochemistry, immunology, and a medical microbiology series of bacteriology, virology, and mycology. During a laboratory rotation in my first year of the program at Virginia Commonwealth University, I worked in the laboratory of Dr Francis Macrina, who was a leading researcher in oral microorganisms. His laboratory published groundbreaking basic research on both dental caries and periodontitis. I was assigned to a project involving genetic characterization of Streptococcus mutans, a viridans streptococcus responsible for dental caries. I completed the remainder of my predoctoral and postdoctoral training in the Macrina laboratory, and Macrina has been a lifelong mentor to me.

**Laboratory Research in Oral Health**

The oral cavity harbors a very complex microbial ecology. It is estimated that 700 to 1000 different kinds of microorganisms live in the mouth; many of these are found only in the mouth.2,4 Initial colonization of the tooth surfaces by bacteria occurs at the time of eruption of the child’s first tooth. In a healthy person’s mouth, 200 to 300 organisms form a stable microbiome; the number and species of organisms in dental plaque remain relatively constant throughout that person’s life. The predominant aerobic bacterial species are the viridans streptococci. Microbial flora are concentrated in dental plaque, which is a complex environmental niche of interdependent microorganisms embedded in bacterial and salivary products. Dental plaque is a biofilm found on tooth surfaces, and plaque accumulation is enhanced by bacterial aggregation between and among species. Calculus occurs when minerals are
deposited intracellularly and extracellularly in dental plaque; this calcified material is very resistant to removal. Oral debris is loose material (eg, food particles) that influences microbial carriage, in part by providing food sources for plaque organisms.

My early work in the Macrina laboratory focused on \textit{S. mutans} and its role in dental caries. \textit{S. mutans} has enzymes that can use sucrose (provided by the human host!) to produce substances called exopolysaccharides. These exopolysaccharides are foundational to formation and maintenance of the dental plaque biofilm, enabling \textit{S. mutans} (and other bacteria caught in the exopolysaccharide web) to remain on the tooth surface where acid byproducts of bacterial metabolism attack tooth enamel and cause dental caries. We used genetic techniques to inactivate each of the 4 \textit{S. mutans} genes involved in exopolysaccharide production, singly and in combination, and demonstrated in a rat caries model that these exopolysaccharides were critical to development of dental caries.

Here is where chance enters again! Although I was immersed in the basic sciences and not in a clinical position, I continued to stay connected to nursing through journals. In the March 1988 issue of \textit{Heart and Lung}, I was surprised to find a case presentation about endocarditis caused by \textit{S. mutans}. My previous cardiopulmonary training, combined with training in microbiology and immunology and my fortuitous connection with a premier laboratory researching \textit{S. mutans} meant that I was perfectly positioned to pursue an innovative line of research. I secured support for my dissertation research through a predoctoral award (F31 NR06498) from the National Institutes of Health (NIH) National Center for Nursing Research, which would later become the National Institute for Nursing Research (NINR). I found that \textit{S. mutans} exopolysaccharides also increased infectivity in rat and rabbit models of endocarditis. I have continued to collaborate with researchers in investigations of bacterial virulence factors. Dr Todd Kitten and I co-authored 14 papers focused on streptococcal virulence during a 13-year collaboration. In addition to the scientific discoveries we published, I learned about team science. Just as in the intensive care unit, scientists worked together to attain the best possible outcomes.

**Early Research in Oral Care for Adults Receiving Mechanical Ventilation**

I joined the faculty of the School of Nursing at Virginia Commonwealth University as a newly prepared PhD in 1992. In addition to continuing my bench research, I began looking for projects that would tie my oral health research back to patients’ problems. Dr Mary Jo Grap, a fellow assistant professor, introduced me to Julie Fitch, a nurse in the intensive care unit (ICU) who wanted to improve oral health in her patients. We found dental hygienists to collaborate in measuring oral health in critically ill patients and obtained internal research funds from the university and from the hospital. We conducted a small study of a toothbrushing protocol in the ICU. Sixty critically ill patients were included in the study; in half of the patients, oral care was performed by the bedside nurse who had been trained in the oral care protocol, and in the remainder, nurses who had not been trained in the oral care protocol provided care. The study was not focused on patients receiving mechanical ventilation, although such patients were included, and we focused on problems within the oral cavity rather than systemic consequences. Fitch went on to investigate other questions in ICU care, and I continued to develop research in oral care for critically ill patients.

Grap and I quickly recognized that her research on the care of patients receiving mechanical ventilation intersected with my oral health interests. Early on, we decided to work collaboratively to maximize each of our programs of research. A long-term research partnership has had many advantages, including exceptional opportunities to vet and develop our best ideas, unwavering mutual support, cross-coverage for research activities, and synergistic energy and enthusiasm. To date, we have published 35 papers together, with more in the pipeline.

When we began our collaboration in the mid-1990s, ventilator-associated pneumonia (VAP) was one of the most vexing clinical problems in the ICU. It occurred in 25% to 30% of patients receiving mechanical ventilation, and accounted for 90% of infections in patients who required mechanical ventilation. VAP was the leading cause of death from nosocomial infections, with reported mortality rates of 13% to 65% depending on the etiologic agent. There were tantalizing hypotheses that 2 factors amenable to nursing interventions might be pivotal in the development of VAP: first, head-of-bed elevation (of interest to Grap), and second, oral flora (of interest to me). Prior research had shown that potential respiratory pathogens such as methicillin-resistant \textit{Staphylococcus aureus} and \textit{Pseudomonas aeruginosa} could be cultured from the dental plaque of ICU patients and that colonization of dental plaque was associated with a variety of nosocomial infections.
Following descriptive studies of current backrest elevation and oral care practices, we designed the POE study (Pneumonia, Oral Health, and Backrest Elevation), which simultaneously permitted determination of the contribution of each of these factors to VAP. We were successful in obtaining funding in 1998 from NINR (R15 NR04730, principal investigator, Grap). We enrolled 66 patients within 24 hours of intubation and followed them for up to 7 days. A regression model was used to predict risk of VAP (measured by Clinical Pulmonary Infection Score, CPIS). The results confirmed our suspicion that oral health was an important risk factor for VAP. We found that dental plaque and oral organisms increased over time, and potential pathogens were identified in oral cultures for 6 patients before or at the same time as the appearance of the same organisms in tracheal aspirates. Higher dental plaque scores conferred greater risk for VAP, particularly for patients with greater severity of illness.

**Strategies to Prevent Pneumonia: The First SToPP Study**

At the conclusion of the POE study, we had evidence that oral health was a factor in development of VAP, and we reasoned that reducing the number of microorganisms in the mouth would reduce risk of VAP. There are essentially 2 mechanisms by which the number of organisms can be reduced in the oral cavity. One mechanism is direct pharmacological interventions using bactericidal agents. Topical oral antibiotics had been tested for VAP prevention with some success, but concerns about antimicrobial resistance and side effects have prevented translation to practice. In elective cardiac surgery patients, gargling with chlorhexidine started before hospitalization was effective in reducing nosocomial infections (including surgical and respiratory tract infections), but most patients receiving mechanical ventilation cannot self-administer several doses of chlorhexidine mouthwash before intubation. The other mechanism for reducing the number of oral organisms is mechanically removing them, and the most effective method of doing so is toothbrushing. However, our descriptive studies had shown that nurse-provided oral care is inconsistent, is generally directed toward patients' comfort rather than microbial removal, and is often neglected or performed by quickly swabbing the mouth.

We hypothesized that providing both chlorhexidine and toothbrushing would provide optimal reduction of oral microbial flora and thus reduce risk of VAP. We obtained funding for the first SToPP study (Strategies to Prevent Pneumonia) from NINR in 2001 (R01 NR07652, principal investigator, Munro). This was my first funded collaboration with Dr Curtis Sessler. Deborah Jones, who would later earn her PhD and become an independent investigator, was the project manager. We randomly assigned 547 adults receiving mechanical ventilation within 24 hours of intubation to 1 of 4 groups: (1) 0.12% solution chlorhexidine gluconate by oral swab twice daily, (2) toothbrushing protocol by study personnel 3 times a day, (3) both toothbrushing and chlorhexidine, or (4) a control group receiving usual care. We measured both risk of VAP (by CPIS) and amounts of dental plaque for 7 days. This 2 × 2 factorial experimental design allowed us to evaluate toothbrushing and chlorhexidine alone and also to determine if there was any interactive effect between the 2 interventions.

The results surprised us! In the 192 patients who were evaluated on day 3, we did not see a significant effect on VAP from either toothbrushing or chlorhexidine, even though toothbrushing did reduce the amount of dental plaque. However, 105 of the patients had CPIS values at or higher than the usual cutoff for pneumonia (CPIS ≥ 6) on the first day! When we analyzed data from the 87 patients who began the study with a CPIS less than 6, those who received chlorhexidine had a significantly lower risk of VAP. In the POE study, increased dental plaque was most predictive of VAP in those with lower baseline CPIS values. Our suspicion that patients in whom signs of pulmonary infection had not yet developed might derive the most benefit from plaque-reduction interventions appeared to be confirmed by the SToPP study data. Even in patients with a low CPIS on day 1, the toothbrushing protocol did not have a significant effect on VAP and toothbrushing did not enhance the effect of chlorhexidine. Although not statistically significant, there was a worrisome trend toward worse CPIS values in patients who received toothbrushing 3 times a day. In retrospect, the bactericidal activity of chlorhexidine provided durable suppression of microbial growth; because organisms were able to begin regrowth immediately after toothbrushing, the intermittent reduction in organism numbers achieved by toothbrushing was not sufficient to reduce VAP risk. We reported the results of the study in September 2009, and in May 2010, the Institute for Healthcare Improvement updated the recommendations for the care of patients receiving mechanical ventilation (the ventilator bundle) to include daily oral care with chlorhexidine, referencing our results as evidence for the change.
Chlorhexidine is now the standard of care for adults receiving mechanical ventilation.

Concurrently with the SToPP study, Grap led a randomized, controlled clinical trial (Strategies To Prevent Pneumonia In Trauma, SToPP-IT) funded by the US Department of Defense TriService Nursing Research Program (MDA-905-03-1-TS02) of a single dose of topical oral chlorhexidine applied within 12 hours of intubation to reduce oral microbial flora and VAP.® Trauma patients requiring endotracheal intubation were randomly assigned to receive a single dose of chlorhexidine (n = 71) or to receive usual care (n = 74); chlorhexidine was not yet the standard of care. Patients in the single-dose chlorhexidine group were significantly less likely to have VAP develop by 48 (P = .02) or 72 (P = .03) hours.

The Next Step: StoPP2

As we considered the results of the SToPP and SToPP-IT studies, as well as procedures for insertion of other tubes into sterile body cavities, we began to wonder whether earlier intervention with chlorhexidine could reduce VAP risk even further. In procedures such as insertion of vascular catheters, urinary tract catheters, and chest tubes, the insertion area is cleaned before tube insertion to reduce procedure-associated contamination. However, decontamination of the mouth is not included in the intubation procedure. Furthermore, gargling with chlorhexidine was known to be effective in reducing nosocomial infection in elective cardiac surgery, although a longer lead time was available in elective surgery than in emergency or urgent intubation.

We proposed an intervention study (SToPP2) to test the effect of delivering the first dose of chlorhexidine before intubation; NINR funded the study as a continuation of R01 NR07652 in 2008. We reasoned that reducing the number of microorganisms in the mouth before intubation by application of chlorhexidine, added to continual microbial suppression by chlorhexidine applied after intubation, would reduce the risk of VAP. Enrollment was initiated at Virginia Commonwealth University, and when I moved to University of South Florida in Tampa, in 2011, we opened a second enrollment site at Tampa General Hospital. A total of 314 patients were enrolled (214 in Virginia, 100 in Florida). Patients were randomly assigned to 1 of 2 groups; the intervention group (n = 157) received oral application of chlorhexidine gluconate 0.12% solution before intubation by swab to the oral cavity (administered by study personnel), whereas the control group (n = 157) received no intervention before intubation. All patients (both groups) received chlorhexidine twice daily after intubation, as chlorhexidine was now the standard of care. Again, the results surprised us! CPIS scores did not differ between the groups during the intervention period (manuscript in review). As evidence that risk of VAP has reduced substantially since we began this line of research (probably because of both daily use of chlorhexidine and better compliance with head-of-bed elevation), mean CPIS in both groups remained less than 6 throughout the study.

Toothbrushing As an Unresolved Problem

Nurses have a high level of enthusiasm for oral care as part of the care of patients receiving mechanical ventilation. Determining the optimal frequency for toothbrushing in adults receiving mechanical ventilation is an important unresolved issue and will have a significant impact on nursing practice and patients’ outcomes. No research has been published that addresses how often toothbrushing should be done to maximize benefits while minimizing risks and optimizing nursing effort. Frequencies of 2 and 3 times daily are reported in research and clinical literature, without any evidence of additional benefit or risk related to more or less frequent intervention.

Toothbrushing is a common nursing intervention that is routinely performed in critically ill adults, and clinical providers hoped that toothbrushing would reduce risk of VAP by reducing the microbial burden in the mouth. However, in the SToPP study we found that although dental plaque was reduced in patients who had their teeth brushed 3 times daily, the risk of VAP was not reduced and in fact trended worse. Additionally, we found that toothbrushing did not enhance VAP protection afforded by chlorhexidine. Although our data and those of others convince me that toothbrushing is not an effective strategy to control VAP, many questions about toothbrushing remain.

Toothbrushing has potential benefits that are important despite a lack of involvement in VAP prevention. Because previous toothbrushing research in the ICU has focused primarily on VAP risk reduction, examination of other benefits has been obscured. Toothbrushing reduces mucosal inflammation in healthy populations, and accumulation of dental plaque exacerbates mucosal inflammation. The effect of toothbrushing on oral inflammation in critically ill patients has not been well examined, nor has the
systemic effect of oral inflammation. Further, both dental plaque accumulation and mucosal inflammation may be a source of discomfort to patients. Although potentially beneficial through its reduction of dental plaque and subsequent oral inflammation, toothbrushing may have accompanying risks in adults receiving mechanical ventilation that are not well understood. Organisms dislodged from dental plaque during toothbrushing might increase risk of health care–acquired infections if they are aspirated (contributing to VAP) or translocate into the bloodstream (contributing to bacteremia and sepsis). Microbial colonization from toothbrush contamination is also a theoretical risk. Individual demographic and clinical factors may moderate both benefits and risks of toothbrushing, but these have not been examined in critically ill adults where the benefit/risk balance is likely to be different from that in healthy populations. Additionally, each episode of toothbrushing uses nursing time, effort, and supplies and displaces other care activities.

We have made considerable progress in reducing risk of VAP, including through administration of topical oral chlorhexidine. But at present, nurses are left without direction for toothbrushing practice, the contributions of toothbrushing to patients’ outcomes other than VAP remain unclear, and great variability in frequency of toothbrushing and in use of nursing time and resources continues to exist. We are currently initiating a randomized clinical trial of toothbrushing frequency (1, 2, or 3 times daily) focused on conclusively defining the benefit and risk of various frequencies and identification of moderating patient-level factors for risk and benefit. When completed, we will produce information about the efficacy and safety of each frequency of tooth-brushing, but these have not been examined in critically ill adults where the benefit/risk balance is likely to be different from that in healthy populations. Additionally, each episode of toothbrushing uses nursing time, effort, and supplies and displaces other care activities.

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More Oral Health Research Is Needed

Additional opportunities exist to improve oral health in critical care. Translation of findings into bedside nursing practice is imperative. Significant opportunities remain for development of strategies that improve nurses’ performance in toothbrushing. For example, would the use of a visible plaque-detecting agent assist nurses in administering oral care? Are modifications to oral care needed for special populations of patients (eg, patients with elevated intracranial pressure)? Do products used (including type of toothpaste or rinse solution) make a difference? How can costs of oral care (eg, nursing time and supplies) be controlled without sacrificing outcomes?

Answering these questions will give nurse researchers something to smile about!

FINANCIAL DISCLOSURES

None reported.

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