Safety and efficacy of oral care for intubated neuroscience intensive care unit patients.

Prendergast, Virginia

2012

Department of Health Sciences, Faculty of Medicine, Lund University, Sweden,
Bulletin No. 37 from the Unit of Caring Sciences, 2012

SAFETY AND EFFICACY OF ORAL CARE FOR INTUBATED NEUROSCIENCE INTENSIVE CARE UNIT PATIENTS

Virginia Prendergast

LUND
UNIVERSITY

ISBN 978-91-86871-75-8
ISSN 1652-8220
Lund University, Faculty of Medicine
Doctoral dissertation Series 2012:13
Printed in Sweden by Media-Tryck

Be a lamp, or a ladder, or a lifeboat

Rumi

CONTENT

ABSTRACT 6
ABBREVIATIONS AND DEFINITIONS 9
ORIGINAL PAPERS 10
INTRODUCTION 11
BACKGROUND 12
Oral health 12
Components of oral health 13
Maintenance of oral health 15
Oral health assessments 16
Threats to oral health 17
Exogenous threats 19
Endogenous threats 20
Self-care deficit: hygiene 21
Neurological dysfunction 21
Complications of poor oral health and hygiene 22
Oral complications 22
Cardiovascular disease 23
Pulmonary Disease, Ventilator Associated Pneumonia 23
Infections of the Central Nervous System 24
Oral Hygiene Interventions 24
Oral care products 24
Safety 25
Efficacy 27
Comprehensiveness 27
AIMS 29
METHODS 30
Design 30
Setting and Sample 31
Data collection and instruments 33
Neurologic assessment tools 33
Oral Health Assessments 34
Oral and sputum cultures 36
VAP Criteria 36
Procedure 36
Paper I 36
RCT: Papers II – IV 37
DATA ANALYSIS 40
Data Preparation 40
Statistical Analyses 40

ETHICAL CONSIDERATIONS 43
FINDINGS 46
Safety during oral care 46
Changes in oral health 48
Microbial changes and VAP rates during intubation 52
DISCUSSION 53
Methodological considerations 53
Internal Validity 53
Construct Validity 55
Statistical Conclusion Validity 57
External Validity 58
Reliability 59
General discussion of the findings 60
Safety of oral care 60
Oral Health 61
Microbial flora and VAP 63
CONCLUSIONS AND CLINICAL IMPLICATIONS 65
FURTHER RESEARCH 67
ACKNOWLEDGEMENTS 69
REFERENCES 71
PAPER I - IV

ABSTRACT

The overall aim of this research was to investigate the safety of oral care in terms of intracranial dynamics and changes in oral health during intubation and 48 hours after extubation among neuroscience intensive care unit (NICU) patients. Additional aims included comparison of a comprehensive oral care protocol (i.e., tongue scraping, electric toothbrush, non-foaming toothpaste, and application of oral moisturizers) to a standard protocol (pediatric manual toothbrush, standard toothpaste, lubricant) with respect to safety and efficacy to promote oral health and to reduce the incidence of oral nosocomial bacteria and ventilator-associated pneumonia (VAP) in NICU patients.

First, a 12-month prospective cohort study with data from 45 intubated patients in an NICU was conducted to identify changes in oral health during intubation until 48 hours after extubation. Specifically, changes in oral health, intracranial pressure (ICP) recorded during non-specified oral care, the prevalence of oral nosocomial bacteria, and the incidence of VAP were analyzed. The results from the cohort study (Paper I) reflected significant deterioration in oral health during intubation and improved oral health 48 hours after extubation, as measured by the Oral Assessment Guide (OAG). During unspecified oral care methods, normal ICP recordings remained stable while ICP values greater than 20 mm Hg before oral care decreased after care ($p<0.001$). Progressive colonization of oral nosocomial bacteria was documented during intubation, and the overall rate of VAP was 24%. Based on literature and the results of the cohort study (Paper I), it was then hypothesized that a comprehensive oral care protocol would be safely tolerated by NICU patients, oral health would improve, and a decrease in oral nosocomial bacteria and the frequency of VAP compared to NICU patients receiving standard oral care would be observed.

A two-year randomized controlled trial (RCT) was therefore conducted to compare the outcomes of intubated NICU patients undergoing a standard oral care protocol or a comprehensive oral care protocol. Outcome variables included changes in ICP and cerebral perfusion pressure (CPP) among 47 patients (Paper II); changes in oral health among 56 patients (Paper III); and changes in oral and sputum nosocomial bacteria and the frequency of VAP among 78 patients (Paper IV).

During standard and comprehensive oral care (Paper II) ICP increased significantly (mean increase 1.7 mm Hg, $p<0.001$), while ICP decreased significantly (mean decrease 2.1 mm Hg) after oral care ($p<0.001$). Neither change was clinically significant. There were no changes in CPP before, during, or after oral care. Based on the total OAG score and all item measurements ($p<0.001$), oral health deteriorated significantly in patients receiving the standard protocol and large effect sizes were present (Paper III). The total OAG score of subjects receiving the comprehensive oral care protocol also deteriorated ($p<0.004$), but no deterioration was noted in the individual item scores for teeth, tongue, gingiva, or mucous membranes. During the first week of intubation, there were no significant differences in the oral and respiratory nosocomial colonization between groups (Paper IV). However, patients in the comprehensive group tended to have fewer nosocomial colonized oral and sputum samples. VAP rates were equivalent between the two treatment groups ($p=0.61$).

A comprehensive oral care protocol appeared to be safely tolerated in NICU patients with normal ICP values. Four key components of oral health (i.e., teeth, tongue, gingiva, and mucous membranes) were supported by the comprehensive oral care protocol. Further research is necessary to refine the psychometric properties of the OAG for intubated patients and to define optimum oral care practices for this at-risk population.

ABBREVIATIONS AND DEFINITIONS

AACN	American Association of Critical Care Nurses
CHX	Chlorhexidine gluconate
CPP	Cerebral perfusion pressure
CXR	Chest X-ray
ETT	Endotracheal tube
EVD	External ventricular drain
GCS	Glasgow Coma Scale
GNB	Gram negative bacteria
ICP	Intracranial pressure
ICU	Intensive care unit
KES	*Klebsiella, Enterobacter, Serratia marcescens*
NICU	Neuroscience intensive care unit
OAG	Oral Assessment Guide
PI	Principle Investigator
RCT	Randomized controlled trial
S. aureus	*Staphylococcus aureus*
SLS	Sodium lauryl sulfate
VSC	Volatile sulphur compounds
VAP	Ventilator associated pneumonia
Oral health:	Homeostasis of the mouth based upon intact physiologic, biologic, and functional integrity
Oral hygiene:	The process whereby debridement, hydration, and moisturizing of oral tissues is performed to promote and maintain oral health

ORIGINAL PAPERS

This research is based on the following papers referred to in the text by their Roman numerals:

I Prendergast, V., Hallberg, I.R., Jahnke, H., Kleiman, C., Hagell, P. (2009) Oral health, Ventilator-acquired pneumonia, and intracranial pressure in intubated patients in a neuroscience intensive care unit. American Journal of Critical Care July; 18(4):368-76.

II Prendergast, V., Hagell, P., Hallberg, I.R. (2011) Electric versus manual tooth brushing among neuroscience ICU patients: Is it safe? Journal of Neurocritical Care 14(2):281-6.

III Prendergast, V., Jakobsson, U., Renvert, S., Hallberg, I.R. (2012) Effects of a standard vs. comprehensive oral care protocol among intubated Neuroscience ICU patients: Results of an RCT. Accepted for publication in Journal of Neuroscience Nursing

IV Prendergast, V., Hallberg, I.R., Jakobsson, U., Renvert, S., Moran, A., Gonzalez, O. (2012) Comparison of oral and respiratory nosocomial colonization between 2 methods of oral care among neuroscience ICU patients: an RCT. Submitted

INTRODUCTION

Providing oral care to an orally intubated patient is difficult. A review of literature and health care initiatives identified practices of oral care historically related to treating side effects of chemotherapy or more recently, galvanized in response to associations between poor oral health and ventilator associated pneumonia (VAP) (Eilers et al. 1988; Miller & Kearney 2001; Sole et al. 2002; Scannapieco et al. 2003; Eilers & Million 2007). Yet optimum oral care practices to support or maintain oral health while a patient is critically ill, intubated, or both are lacking despite results indicating a significant relationship to overall health (Kshirsagar et al. 2005; Demmer & Desvarieux 2006). Furthermore, studies are lacking that establish the safety of oral care practices for the critically ill (Ames 2011), a crucial aspect to be addressed before trials of oral care efficacy can begin.

Poor oral health among intensive care unit (ICU) patients has been identified as a source of increasing bacterial virulence of oropharyngeal secretions and subsequent development of nosocomial pneumonias (Scannapieco 1999; Paju & Scannapieco 2007). Despite the widely acknowledged importance of oral care for critically ill patients, there is a paucity of evidenced based oral hygiene protocols for intubated patients. While ICU nurses rate oral care as important, most oral care practices consist of only foam sticks, saline as a rinse, and standard tooth pastes (Feider et al. 2010). Although tooth brushing has been advocated, in fact purported to be the standard of critical care by the American Association of Critical Care Nurses (AACN) (AACN 2006), fewer than 44 % of critical care nurses report brushing teeth (DeKeyser Ganz et al. 2009).

Oral hygiene, although a technical challenge to perform for intubated patients, is critical to perform for the overall health, safety, and comfort of the patient. To render good oral care, the nurse must incorporate knowledge of the patient's clinical condition, oral health status, threats and barriers to oral health, and provide comprehensive oral care aimed at minimizing oral health problems that impact the patient's well-being. Within the ICU setting, multiple factors demand the staff's attention. Technical requirements related to equipment, invasive lines and procedures, medication administration and titrations all require the vigilance and proficiency of the bedside nurse. Common aspects of bedside care, such as oral hygiene, may be performed with ineffective products, a perceived lack of time, or a general reluctance on part of the staff (McNeill 2000; Rello et al. 2007). When oral cleansing and care are insufficient, progressive accumulation of dental plaque and resultant formation of biofilms can lead to degradation in overall gingival tissue health and the development of periodontal disease (Jenkins 1989; Paju & Scannapieco 2007). These factors contribute to a greater pathogenic environment among the already critically ill, further emphasizing the need for oral assessments and comprehensive care within the ICU.

Measures of oral health status for ICU patients are under reported in critical care literature. While there is a growing consensus that oral care is a component of critical care, scales to provide a baseline and ongoing assessments of oral health in the ICU

are lacking. Oral health assessment scales used in neurology, oncology, nursing homes, and outpatient settings provide information on key aspects of oral health such as overall condition of teeth, gums, mucous membranes, lips, and the tongue (Westergren et al. 1999; Andersson et al. 2002a; Chalmers et al. 2005; Talbot et al. 2005). In contrast, when a patient is admitted to the neuroscience ICU (NICU), attention is initially directed towards the assessment of vital functions and central nervous system impairments. Focus is directed towards the reduction of pathophysiological deterioration and avoidance of complications related to the primary insult. For patients in an NICU, the performance of nursing care activities must be balanced with the goal of preserving and maintaining a patient's intracranial hemodynamic status. Preservation of cerebral perfusion pressure (CPP) and avoidance of sustained elevations of intracranial pressure (ICP) require monitoring during care and procedures to avoid the possible deleterious effects (Mitchell & Mauss 1978; March 2000).

Barriers to providing oral hygiene to intubated patients include the presence of the oral endotracheal tube (ETT), oral gastric tubes, bite blocks, and the adhesive tape to secure such devices in place. The access to the oral cavity is obstructed by these necessary devices which further hampers adequate oral care (Wardh et al. 2000). As a result, a difficult task may be delayed due to concerns of safety or completed by inadequate care and result in a worse pathogenic state.

During the time of intubation, the conversion of normal oropharyngeal flora to a pathogenic state by proliferation of nosocomial bacteria increases the risk of pneumonia (Garcia et al. 2009; Berry et al. 2011). For patients on mechanical ventilation, the diagnosis of VAP signifies a serious threat to patient outcomes. Associations between dental plaque and pathogenic oropharyngeal flora to VAP have led investigators to explore strategies to reduce the oral bioburden of nosocomial bacteria (Shay et al. 2005; Restrepo et al. 2010). Oral care is critical care and practice patterns need to address the assessment of oral health and the delivery of safe, effective oral care in order to minimize potential complications for intubated patients in the NICU and promote health and well-being.

BACKGROUND

Oral health

References to oral health and bad breath have been noted in scientific and religious literature with references in the Bible, Talmud, and Koran (Rosenberg 1996; Shifman et al. 2002). Suggestions on treatment and promotion of oral hygiene with descriptions of crudely constructed toothpicks appeared in the Ebers Papyrus compiled in 1500 B.C. from ancient Egyptian writings dating to 4000 B.C. (Weinberger 2005). By the 20th century, new varieties of manual toothbrushes were developed to provide oral hygiene (McCauley 1946). Traditional concepts of health were based on a mechanical model metaphor in which the body is viewed as a machine with health and

illness viewed as biologic phenomena (Slade 1997). As such, the tendency had been to treat the oral cavity as though it were an autonomous structure, isolated from the body and the person (Locker 1997). Challenges to traditional concepts of health and disease have resulted in a move away from an atomistic way of viewing the body to a greater holistic perspective on health and illness with a logical extension to oral health care and promotion (Coulter et al. 1994; Watt 2002).

Oral health has been defined as a 'state of the mouth and associated structures where disease is contained, future disease is inhibited' (Yewe-Dyer 1993, pg 224). Good oral health today is considered a component of overall health and as such, merits the commitment by societies to ensure good health for all individuals (Haden et al. 2003). Good oral health has been studied from a health-related quality of life perspective as defined by functions and impairments (Cohen 1997; De Palma et al. 2005). In an exploratory study, factors such as accumulated oral neglect, self-reported problems, reparable oral diseases, and oral health values were found to be basic dimensions of reported good oral health (Gift et al. 1997). While advancements in oral health have dramatically improved in the United States during the past 25 years, the need for further collaboration among health providers in dentistry, medicine and allied health care providers has been identified (Haden et al. 2003). Such collaboration is fundamental in hospitalized patients where the status of oral health has gained heightened awareness within the realm of health promotion and disease prevention.

Components of oral health

There is a complex integration of functional oral components necessary to maintain oral health and wellness. Structures of the oral cavity include the lips, mucosal lining, hard and soft palate, gingiva, teeth, saliva, and the tongue. The mouth is the primary portal for the alimentary system as it is within the oral cavity that hydration and food are tasted, and together with saliva and mastication, ingested for digestion (Moore & Dalley 2006). A synergy exists between nutrition and oral health suggesting the need for optimal intake and oral health to be mutually beneficial (Touger-Decker & Mobley 2007). Oral intake is necessary to support the hydration of mucous membranes, support nutrition, and as a contributor to the complex infrastructure of microbes which exists in the mouth and gut (Kau et al. 2011). The ability to use nutrients is fundamental in the maintenance of an effective immune response and the relationship between diet, nutrition, and the gastrointestinal microbial configuration has been investigated as symbiotic relationship which contributes to health and disease (Wu et al. 2010; Kintscher et al. 2008). The mouth is a secondary entry route for the respiratory tract which is important in respiration and the production of speech (Seidel et al. 2006). The structural components of the mouth need to be healthy in order to meet basic needs of eating, breathing, and speaking as well as to promote comfort and a healthy self-esteem.

The lips, normally pink and supple, function as the entry and exit for the mouth, upper alimentary and respiratory tract. They are covered externally by skin with an abundant, superficial blood flow and internally by a mucous membrane (Moore & Dalley 2006). The mucous lining extends from the inner lips and lines the soft tissues, hard and soft

palate, and tongue. In states of good health, the mucous lining should appear pink, moist, and free of surface disruptions (Hallberg & Andersson 2011). On the surface there is a thin layer of saliva providing a physical barrier to establishment of biofilm and invading organisms (Brailsford & Beighton 2005).

In the healthy mouth, saliva is produced and secreted by the salivary glands at a rate of 500 milliliters to 1.5 liters per day, with production noted to be highest when standing and lowest when recumbent (Bruya & Madeira 1975; Dawes 1996). The composition of saliva, of which 99% is water, includes electrolytes, glycoproteins, antimicrobial enzymes, and immunoglobulins which together serve a number of important functions (Amerongen & Veerman 2002; Stonecypher 2010). When saliva is normal in quantity and composition, it acts to cleanse the mouth, maintain moisture of mucous membranes, lubricate food during mastication, and act as a removal mechanism for microorganisms thereby maintaining integrity of the teeth and soft tissues (Fitch et al. 1999; Dennesen et al. 2003). The antimicrobial property of saliva is attributed to salivary gland secretions rich in immunoglobulins, e.g., immunoglobulin A produced by lymphoid tissue, as well as mucin, lysozymes, and lactoferrin (Mandel 1987; Munro & Grap 2004). Saliva further contributes to the antimicrobial process by maintaining a neutral pH within the mouth to discourage the growth of pathogenic organisms and together with its mechanical washing properties, aid in the clearance of oral bacteria (Addy et al. 1992; Brailsford & Beighton 2005).

The gingivae, fibrous tissue covered by the mucous membrane, are attached directly to the alveolar bone surface covering the neck of each tooth (Seidel et al. 2006). In a healthy state, the gingiva is pink and stippled in appearance and has a clearly defined margin at each tooth (Seidel et al. 2006; Hallberg & Andersson 2011). The crown of each tooth projects from the gingival margin and the root is anchored in alveolar bone by periodontium (Moore & Dalley 2006). The main functions of the teeth include the chewing and mixing of food with saliva during mastication and the articulation of speech. The tooth surface is uniquely defined by its non-shedding characteristics as compared to the natural shedding surface of oral mucosa (Mager et al. 2005). Consequently, the teeth may harbour organisms leading to the development of thick biofilms. Cleaning the tooth surface provides the necessary desquamative effects to decrease microbial burden of pathogens (Marsh & Devine 2011).

The tongue, a thick mobile, striated muscle covered by mucous membrane, is involved in chewing, swallowing, oral cleansing, and speech production (Barkauskas et al. 2001). It is anchored posteriorly within the oral cavity at its base and to the floor of the mouth by the frenulum (Seidel et al. 2006). The dorsal surface of the tongue is covered by a thick mucous membrane and should appear as dull red, moist, and glistening (Seidel et al. 2006). When the mouth is closed, the tongue occupies the majority of the oral cavity (Moore & Dalley 2006).

The term, microbial homeostasis, is used to describe the stable microbial environment of the mouth in an ever changing environment (Alexander 1971). The mouth is aerobic with a neutral pH and various, interrelated mechanisms maintain normal oral flora by

being simultaneously engaged in cellular metabolism based on functional genomics of more than 600 prokaryote species as identified by the human oral microbiome database (Brailsford & Beighton 2005; Li et al. 2008; Dewhirst et al. 2010). General factors such as the oral mucosa, saliva, and phagocytes, as well as specific factors such as lymphocytes, immunoglobulins, and T cells (Bagg et al. 2006) contribute to a stable microbial state.

Intact functioning of the central nervous system via multiple sensory and motor cranial nerve components is necessary for optimal function of the oropharynx and gag reflex. Cranial nerves V (Trigeminal) and VII (Facial) innervate the muscles used for facial expression and mastication (Barkauskas et al. 2001). Efferent function of both cranial nerves V & VII are required for mouth closure and opening, teeth occlusion and mastication, and innervation to submandibular and sublingual salivary glands (Wilson-Pauwels et al. 2002; Seidel et al. 2006). The tongue should protrude midline without fasiculations or atrophy and is innervated by the hypoglossal nerve, cranial nerve XII (Seidel et al. 2006). Sensory receptors for taste located on the dorsal surface of the tongue are carried by cranial nerves VII and IX (Barkauskas et al. 2001).

The glossopharyngeal and vagus nerves (cranial nerves IX and X) innervate the soft palate and uvula to assist with the gag reflex, swallowing and vocalization (Hickey 2009). The gag reflex protects the upper airway from foreign bodies and results from pharyngeal skeletal muscle action combined with smooth muscle contraction (Briar et al. 2003).

Maintenance of oral health

The maintenance of oral health is dependent upon a triad of factors: hydration of tissues, the cleansing, microbial properties of saliva, and debridement of the teeth and tongue (Sweeney 2005). Oral care regimens to support and enhance these interrelated components have been well developed in the out-patient setting, but less well-developed for the critically ill. Hydration of oral tissues is attributed to oral intake as well as the lubrication properties of saliva (Stonecypher 2010). Among healthy individuals, an intact thirst mechanism will prompt individuals to drink fluids, thereby receiving direct moisture to oral tissues while maintaining a positive fluid balance. During times of fever, stress, hypovolemia, or with ingestion of certain medications (e.g., narcotics, anti-hypertensives, benzodiazepines), the subjective complaints of ‘dry mouth’ among the general population can be ameliorated by sucking sugar-free candies, or sipping water (Thurgood 1994; Blumenfeld 2002). Chewing gum is also advocated as a way to produce saliva and thereby increase hydration of tissues and stimulate the flow of saliva. And while none of these strategies work with the intubated patient, artificial saliva, oral moisturizing agents, and various rinses have all been promoted as ways for the ill to maintain oral hydration with varying degrees of success (DeKeyser Ganz et al. 1999; Hsu et al. 2011).

Twice daily tooth brushing with fluoridated toothpastes together with instruction on tooth brushing techniques during dental visits have been promoted since the 1970’s as effective in the maintenance of good oral health for the general population (Greene &

Vermillion 1971). Tooth brushing twice daily to reduce oral debris and dental plaque remains the mainstay of oral health, and has been described as the single most important oral hygiene activity (Sweeney 2005). During the past decade, several investigations have reported electric toothbrushes superior to manual toothbrushes in plaque reduction and improved gingival health (Haffajee et al. 2001; Heanue et al. 2003; Deshmukh et al. 2006). Flossing, encouraged by outpatient dental care teams, has been proven effective in the reduction of plaque formation and gingivitis (Bader et al. 2001; Stefanc & Nesbit 2007) yet has not been introduced as an oral care practice for hospitalized patients. Debridement of the tongue via scraping is advocated in the outpatient setting, as a means to reduce halitosis due to bacterial load along the dorsal surface of the tongue (Rosenberg 1996). However, its use among hospitalized patients has not been reported.

Oral health assessments

Oral health assessments can be considered as a descriptive health measurement focused on the mouth as an organ system, designed for clinical evaluation and sensitive to changes following treatments (McDowell & Newell 1996). Patients' oral health status on admission to the hospital can be viewed as an indicator of their pre-hospitalization oral health status and the overall oral health can be viewed as a continuum scale ranging from poor health to excellent health. Oral health assessments conducted during hospitalization can provide a surrogate marker for oral health since detailed dental check-ups are neither feasible nor practical to perform due to the often critical nature of the patient.

An assessment of oral health is needed in order to establish the patient's baseline oral health status, changes during the course of care, and response to interventions (Abidia 2007). Although nurses are responsible for conducting assessments and performance of interventions for other body systems, such as hemodynamic monitoring and administration of blood pressure medications, oral health assessments and research-based oral care practices are not routinely performed (Adams 1996; Munro & Grap 2004; Berry & Davidson 2006). The oral health assessment is akin to assessment of other targeted areas and should include a general observation and an intra-oral examination (Davies et al. 2003). Techniques used during the examination should include visualization, palpation of tissues and relevant lesions, and olfaction (Davies et al. 2003). Efficiency of reducing overall gram negative bacteria (GNB) loads from the mouth can be evaluated by odor, β-galactoside activity in the saliva, or both, with evaluations of malodour between examiners found to be reliable (Sterer et al. 2002; Greenman et al. 2005). With early assessment and detection of oral health disturbances, oral care may be modified or frequency of interventions adjusted to prevent the incidence and further deterioration which negatively impacts the patient's overall health (Chan et al. 2011).

Measures of oral health targeting a specific patient population or oral problem are described in the literature. Such examples include the Index of Oral Cleanliness for orthodontic assessments (Bearn et al. 1996), various scales to evaluate effects of mucositis following radiation therapy (Eilers et al. 1988; Sonis et al. 1999;

Harris et al 2008), periodontal disease in pregnant and post-partum women (Silness & Loe 1964), and a ‘0’ to ‘5’ scale used for rating oral malodor (Greenman et al. 2004). Oral assessment scales for use among hospitalized and institutionalized geriatric patients have been introduced with the increased focus of the impact of oral health on systemic health. Dewalt (1975) described an oral tissue assessment scale for institutionalized geriatric patients receiving different methods of oral care. A ten item, brief oral health assessment examination (BOHSE) was developed (Kayser-Jones et al. 1995) to use by nurses caring for cognitively impaired nursing home residents. Similarly, the Oral Health Assessment Tool was developed for the geriatric population and included examination of dentures and patient behaviors reflective of dental pain (Chalmers et al. 2005).

Daily oral assessments have been previously recommended as means to guide oral care in critical care settings. Treloar (1995) developed an oral assessment tool for intubated ICU patients based on examination of saliva, soft tissues, dentate status, dental plaque, and gingiva. No measures of reliability or validity were provided. An ICU oral assessment scale, developed by a dental hygienist, targeted aspects of poor oral health such as dental plaque, inflammation, saliva, calculus, caries, and other items using a 100 – mm visual analog scale for each item (Fitch et al. 1999). The BRUSHED Assessment Model (Hayes & Jones 1995) is based upon a mnemonic to aid nursing staff in the detection of clinical signs of impaired oral health, i.e., bleeding, redness, ulceration, saliva, halitosis, external factors, and debris. Its incorporation into ICU assessments is not well-documented in the literature (Labeau & Blot 2011).

The Oral Assessment Guide (OAG) (Eilers et al. 1988) was developed for assessing the oral health of patients receiving stomatotoxic treatments. Guiding principles in developing the OAG were reliability, validity, and simplicity in rating. The OAG is based upon eight items: voice, swallow, lips, tongue, saliva, mucous membranes, gingiva, and teeth with each item rated on a three-point scale. A score of "1" is a normal finding, "2" reflects a mild change, and "3" reflects significant compromise. Stratified scoring based on all items to indicate severity of good, or poor, overall oral health based on the OAG has not been reported.

Oral health, as defined as homeostasis of the mouth, is based upon intact physiologic, biologic, and functional integrity of multiple oral structures. Promotion and maintenance of oral health is achieved through debridement of plaque and debris from the surface of teeth, gingival, and tongue in combination with hydration of tissues and the cleansing properties of saliva. Oral assessments can serve as a surrogate marker of oral health upon which care and interventions may be instituted.

Threats to oral health

When oral cleansing is insufficient, heavy biofilms form along tooth surfaces, gingival tissue degrades, and periodontal disease develops. The pre-existing oral health status of some patients, such as the homeless or drug addicted, may reflect suboptimal care

as evidenced by heavy plaque accumulation, loss of bony attachment, and fewer teeth (Scheutz 1984; De Palma et al. 2005). Pre-hospitalization neglect or trauma, ineffective oral care during hospitalization, or a combination of both results in a greater oral pathogenic environment among the already critically ill, further emphasizing the need for comprehensive oral care.

Hospitalization has been found to negatively impact overall oral health as evidenced by increased dental plaque accumulation together with deterioration in mucous membranes and gingival inflammation (Terezakis et al. 2011). For the intubated, unconscious patient the importance of good oral health reflects the dimension of preventive oral care in reducing colonization of potential respiratory pathogens (Furr et al. 2004) as well as promoting holistic patient care (Malkin 2009). While ICU nurses report recognition of oral care as important, it is frequently underperformed in the ICU (Fitch et al. 1999; Furr et al. 2004). Oral care is a complicated task in critical care requiring performing and understanding oral assessment findings, providing safe and effective care, and evaluating the results (Wilkin 2002). Changes in oral health among intubated patients have been documented in a number of studies (Fourrier et al. 1998, Dennesen et al. 2003, Munro 2006b) and may have an adverse impact on patient outcome (Terezakis et al. 2011). Problems related to oral health and oral care have been attributed to the direct and indirect effects of disease, the treatment of the primary or co-existing disease(s), or a combination of both (Davies et al. 2003). (Figure 1).

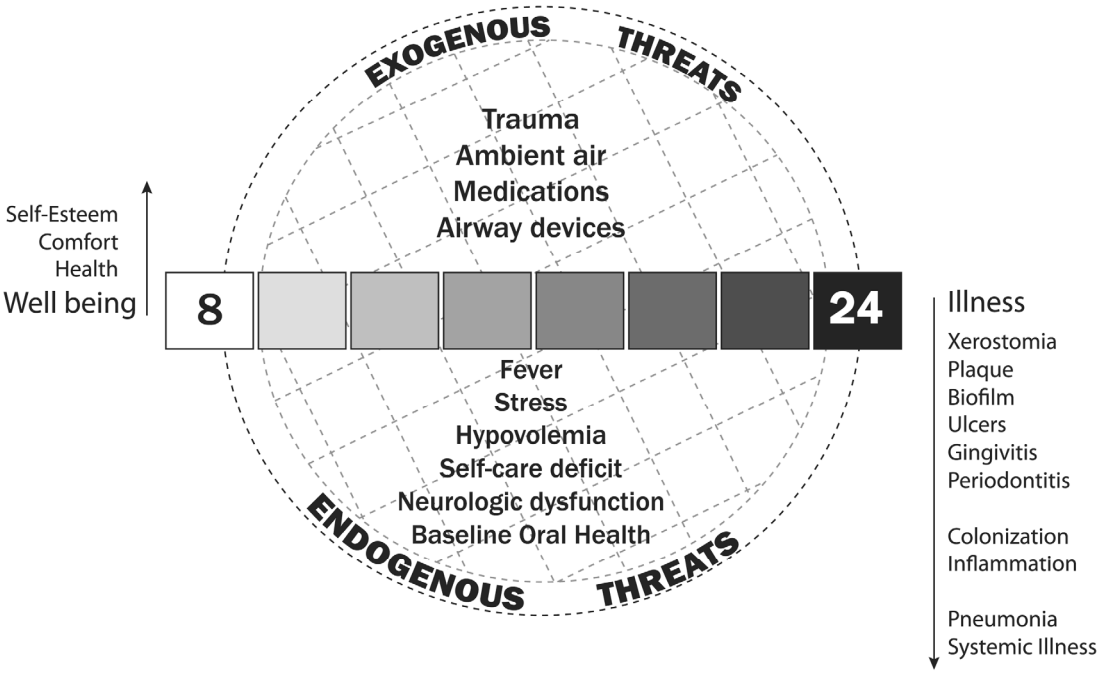


Figure 1. Threats to oral health during hospitalization and intubation. Numerical scale represents the OAG scale for oral health assessments, '8' indicates good oral health.
Figure used with permission from Barrow Neurological Institute

Exogenous threats

External threats to oral health can generally be classified into main groups of airway devices, ambient air, direct trauma from airway device or initial injury, effects of medications and hygiene products such as sodium lauryl sulfate (SLS), a common detergent ingredient in many tooth pastes. The presence of oral airways, the ETT, and oral gastric tubes all present a barrier to oral hygiene (Fitch et al. 1999). The ETT is key for protection of the airway in the most critically ill neuroscience patients. The tubes used in most adults have an internal diameter of 7.5 mm with an inflatable cuff to seal the trachea from aspiration of oral and gastric secretions, and some tubes have a small port above the cuff which allows for sub-glottic suctioning (Labeau & Blot 2011). Direct trauma to the tongue and mucosal surfaces has been noted to occur and are attributed to the tube's presence (Abidia 2007). Dried mucosal areas under the ETT have been reported to tear when the tube is removed (Schweiger & Lang 1981). Due to the altered mental status of many NICU patients, gastric decompression is required necessitating placement of a nasal or orally inserted gastric tube. Furthermore, the patient may have increased oromotor tone or during periods of agitation may bite the ETT and an oral bite block is inserted to prevent clamping down on the artificial airway. These devices, necessary to maintain a patent airway, mandates the mouth to be constantly exposed to air which dries oral mucosal surfaces and tongue, and worsens dental plaque (Munro & Grap 2004).

This constant exposure to ambient air and retraction of lips for placement of the ETT subjects the lips and oral mucosa to additional stress. Disruption of lip integrity and redness of oral mucosa was noted in a healthy volunteer after four hours of the mouth being artificially maintained in an open position with no lubrication to tissues during that time (DeWalt & Haines 1969). Nasal and oral gastric tubes have been shown to contribute to dried oral tissues challenged by the lack of direct hydration by oral intake (Harrell & Damon 1989).

Medication administration, an additional exogenous threat to oral health, may result or worsen a xerostomic state by commonly administered medications such as narcotics, anticonvulsants, benzodiazepines, and antihypertensives (Munro & Grap 2004). For patients with increased ICP due to mass lesions or cerebral edema from brain compression, the administration of hypertonic saline, diuretics, or both may further worsen xerostomia (Bratton et al. 2007). Drugs which exert a sympathomimetic action such as phenylephrine for hypotension, or an anticholinergic such as scopolamine for nausea, reduce salivary flow contributing to xerostomia (Porter & Scully 2000). For patients admitted with a new onset of a seizure, a number of antiepileptic medications result in xerostomia, gingival hyperplasia, and oral ulcerations (Greenwood & Meechan 2003). Gingival hyperplasia is also seen with calcium channel blockers such as nifedipine, a medication commonly used in the treatment of patients with aneurysmal subarachnoid hemorrhage (Allen et al. 1983; Little et al. 2008). Finally, medications that suppress lymphocytic function with consequent impairment on the immune system may also indirectly affect oral health via dampening of the normal oropharyngeal flora. This includes anticonvulsants and dexamethasone used in the

treatment for central nervous system neoplasms and propofol, an intravenous anesthetic, used as a sedating agent (Neuwelt et al. 1983; Song & Jeong 2004).

Finally, the very use of some oral care products themselves may be perceived as external threats to a healthy oral status. Toothpastes, many manufactured with SLS, a common detergent agent in many dentifrices, results in a foaming action to help rid the mouth of plaque. If the toothpaste is not adequately cleared from the mouth, residual amounts dry and harden on the mucosal surface thereby blunting efforts to clean the mouth and associated structures (Herlofson & Barkvoll 1996). Mouthwashes, many containing alcohol, may further contribute to local desquamative effects and chemical burns and have not been uniformly recommended (Roth & Creason 1986; Hayes & Jones 1995).

Endogenous threats

Hemodynamic instability, fever, and stress seen during critical illness constitute additional threats to oral health integrity. Patients that have experienced volume loss from traumatic or operative procedures will have decreased tissue perfusion (Labeau & Blot 2011) which results in xerostomia. While euvolemia is a desired goal of hemodynamic monitoring, additional critical care complications such as fever and diarrhea, combined with an inadequate fluid intake, can result in a decreased production of saliva (Dennesen et al. 2003).

A patient's baseline oral health status may also be considered a threat to oral health if there has been trauma, neglect, or abuse. During a grand mal seizure or closed head injury, blunt force craniofacial trauma with associated fractures, tongue lacerations, and oral trauma may result (Benbadis et al. 1995; Hohlrieder et al. 2004). Disadvantaged patients may present to the hospital with poor baseline oral health due to neglect, dental disease and caries (King & Gibson 2003). Among the homeless, untreated caries have been reported as high as 92% (Kaste & Bolden 1995). Drug abuse, most notably seen with methamphetamine, results in rampant dental caries due to drug induced xerostomia and poor oral hygiene during periods of drug abuse (Shaner 2002; Hamamoto & Rhodus 2009).

As a consequence of these threats, the oral mucosa becomes dry, the saliva viscous, and the lack of saliva's antimicrobial properties contribute to an increasing vulnerability to potential respiratory pathogens and pyrexia (Berry & Davidson 2006; Saito et al. 2008). Disruption to oral mucosal membranes, together with a reduction in salivary immunoglobulin A, stimulates a cascade of increased receptors for bacterial adherence during an acute illness (Grap et al. 2004). By the very nature of a critical illness, patients' resistance to oral colonization decreases thereby increasing the risk of pathogenic organism colonization (Labeau & Blot 2011). Such colonization may occur within the oral cavity and dental surfaces, particularly surrounding dental caries, and may result in rapid multiplication of oral nosocomial bacteria with consequent destructive action (Kolenbrander 2000).

Self-care deficit: hygiene

The ICU population in the United States is expected to increase given the overall aging of the population. In 2004, there were 55,000 dedicated beds for ICU care, that number had risen to approximately 99,955 dedicated ICU beds by 2010 (Ely et al. 2004; Halpern & Pastores 2010). Self-care deficits are seen in ICU and general ward patient populations as well as residential treatment facilities and palliative care settings (Forsell et al. 2011; Milligan et al. 2001; Chan et al. 2011). The nursing diagnosis of Self Care Deficit may be applied to those individuals with an impaired ability to perform self-care hygiene practices due to cognitive or physical impairments (Dochterman & Bulechek 2004; NANDA 2005). With poor oral hygiene, the patient may further develop disruptions in tissue integrity of the lips and oral mucous membrane (NANDA 2005). Together with the decline in physiologic and oral health status, there is a concomitant decline in comfort from the pain of tissue damage (NANDA 2005). Altered oral mucous membranes require frequent oral assessments for signs of oral health deterioration and the need for frequent oral care (Hickey 2009). Critically ill or neurologically compromised patients may be unable to perform oral care due to altered level of consciousness, sensorimotor deficits, or both and bear the burden of oral health deterioration and pain if their hygiene needs are unattended.

Neurological dysfunction

An altered level of consciousness, a recurrent theme for many NICU patients mandates the bedside nurse to be responsible for protecting the patient from injury (Hickey 2009). Due to the underlying neurological disturbance, patient responses to actual or potential health problems are multiple and frequently co-exist. Commonly used nursing diagnoses for critically ill NICU patients include Ineffective Cerebral Tissue Perfusion, Risk for Aspiration, and Impaired Verbal Communication (NANDA 2005). Central nervous system dysfunction as seen in stroke, brain stem tumors, closed head injury, and neurodegenerative diseases commonly result in impaired cognition and cranial nerve function as manifested by the risk for aspiration and dysphagia (Blair & Lapinski 2007). Dysphagia, an impairment of swallowing, can be caused by muscle dysfunction, lesions of cranial nerves IX, X, or XII or their nuclei, dysfunction at the neuromuscular junction, or in descending motor pathways (Blumenfeld 2002). Such disruptions within the central nervous system impairs cranial nerve functioning and results in poor oropharyngeal muscle control or muscle fatigue leading to aspiration, a common cause of death in disorders of the nervous system (Blumenfeld 2002; Blair & Lapinski 2007).

Patients in the NICU are frequently maintained on paralytics and sedative drips for control of increased ICP or decreased CPP (Hsaing et al. 1994; Hlatky et al. 2005). Due to resultant pharmacologic paralysis, these patients are unable to protect their airway, produce an effective cough or gag, or communicate their needs. Furthermore, deteriorations in oral health result in pain for the neuroscience patient population (Cohn & Fulton 2006). Consequently, patients with impaired cognition and physical impairments depend on care givers to anticipate needs and provide comfort and are at greater risk for worsening oral health if staff performs inadequate oral care.

Given the presence of the ETT at a minimum, and in some cases, multiple oral devices, visualization of the oral cavity is difficult to achieve unless a nurse is motivated to do so and understands how to assess the oral cavity. The very critical nature of the illness predisposes patients to a host of additional factors which threaten oral health. If deterioration of oral tissues is not appreciated, interventions cannot be instituted, thereby increasing the likelihood of further oral tissue degradation and worsening oral health.

Complications of poor oral health and hygiene

When oral hygiene is ineffective or neglected, the focal disturbances in oral health are manifested in an array of disturbances. Complications can be observed orally and if left untreated, can be manifested systemically (Treloar & Stechmiller 1995; Scannapieco & Mylotte 1996).

Oral complications

The lips may become dry and ulcerated as evidenced by fissures or crusted areas due to improper moisturizing, local trauma, or poor nutrition thereby providing a vector for secondary infections (Little et al. 2008). Xerostomic tissues are noted to be dry and pale, or red and atrophic and results in ulcers of the mucous membranes creating a portal for opportunistic bacterial and fungal infections, inflammation and edema of the tongue, and periodontal disease (Little et al. 2008; Hallberg & Andersson 2011). As the mucosal surface of the tongue dries, sharply defined fissures over the dorsum and lateral aspects of the tongue serve as a retention area for pathogenic bacteria most notably among those with periodontitis, poor oral hygiene, hyposalivation, and the elderly (Ralph 1987; Yaegaki & Sanada 1992). The resultant proliferation of bacteria leading to malodor is attributed to the presence of volatile sulphur compounds (VSC) (Tonzetich 1977; Roldan et al. 2003) coating the dorsum of the tongue and has been theorized to account for translocation of pathogenic bacteria to other micro-environments such as the lungs (Miyazaki et al. 1995; Greenman et al. 2004).

In addition to the xerostomic tissues, dental plaque composed of several bacterial cell layers thick organized around the tooth surface as a biofilm, thickens when left undisturbed with poor oral hygiene (Kolenbrander 2000; Sweeney 2005). This biofilm can be viewed as a matrix enclosure which provides bacteria with protection, nutrients, and niches from which to proliferate and is the most common cause of most periodontal disease (Stefanc & Nesbit 2007). Additionally, mucosal membrane lesions that are in contact with bacterial plaque present on teeth surface may be come infected (Little et al. 2008). With improper or poor oral hygiene, bacterial deposits along gingival crevices develop causing inflammation (gingivitis), manifested by redness and swelling of the gums (Loe et al 1965; Moore & Dalley 2006). If left untreated, gingivitis may serve as a portal for infection and further result in subgingival inflammation and destruction of the bone (periodontitis) (Labeau & Blot 2011). Periodontitis has been implicated as a factor contributing to the worsening of a number of systemic diseases, including but not limited to cardiovascular disease, bacterial

pneumonia, diabetes mellitus, and pre-term labor (Li et al. 2000; Fowler et al. 2001; Brailsford & Beighton 2005; Stefanc & Nesbit 2007; Labeau & Blot 2011).

Cardiovascular disease

Periodontal disease, as seen with poor oral health, results in a 2 fold increase in cardiovascular disease (Fowler et al. 2001). The relationship between oral bacteria and byproducts of periodontitis resulting in inflammatory vascular smooth muscle changes, intravascular coagulation, and platelet dysfunction has been explored with cardiovascular diseases such as atherosclerosis and acute myocardial infarction (Rams & Slots 1992; Pesonen et al. 1981). The relationship between infective endocarditis and poor oral hygiene has been explored as the mechanism by which transient bacteremia from dental procedures is a causative factor for bacterial endocarditis for those individuals with abnormal heart valves (Bayliss et al. 1983). The recognition that periodontal infections are a risk factor for cardiovascular disease underscores the relevance of oral health and systemic health (Li et al. 2000; Demmer & Desvarieux 2006).

Pulmonary Disease, Ventilator Associated Pneumonia

Pneumonia remains a leading cause of death in America (Xu et al. 2010). In patients with poor oral hygiene, the increased oral bioburden of potential respiratory pathogens has been theorized to play a role in aspiration pneumonia among those hospitalized and residents of care facilities (Scannapieco & Mylotte 1996; Terpinning et al. 2001; Shay 2002; Renvert 2003). Oral mucous membranes, inflamed by poor oral hygiene, may stimulate an inflammatory response which in turn, contributes to the pathogenesis of pneumonia (Scannapieco et al. 2001). The oropharyngeal nosocomial colonization and resultant inflammatory response has also been observed among those with dentures which may provide a harbor for increased bacterial loads when hygiene is substandard (Sumi et al. 2003).

Hospital acquired pneumonia, may occur as early as 48 hours following admission to the hospital and is purported to be responsible for 15% of all hospital infections (CDC 2004). Pneumonia among ventilated patients, i.e., VAP, is reported as high as 78% with an average incidence ranging from 17-25% (Cook et al. 1998; Bauer et al. 2000; Pace & McCullough 2010) and an associated mortality rate ranging from 24-50% (Chastre & Fagon 2002). In a systematic review of 24 cohort studies, a significant association between pneumonia and dental plaque or dependency in oral hygiene was reported (Scannapieco et al. 2003). With dental plaque as an indicator of poor oral hygiene, Munro et al., (2006b) reported a greater risk for VAP among those ICU patients with heavy dental plaque. The bacteriology of hospital acquired pneumonia or VAP is attributed to *Staphylococcus aureus* (*S. aureus*), or GNB (Bartlett et al. 1986; A'Court & Garrard 1992). The most common offending GNB organisms include enteric gram negative bacilli (eg, *Klebsiella, Enterobacter, Serratia marcescens, Escherichia coli,* and *Pseudomonas aeruginosa*) (Bauer et al. 2000; Craven 2000).

Infections of the Central Nervous System

The oral cavity has been reported as the source of systemic spread of pathogenic bacteria which may involve the cranial or intraspinal compartments (Rams & Slots 1992). Destructive periodontal disease, oral abscesses, or both have been identified as a causative factor in various reports of cerebral abscess development (Rahamat-Langendoen et al. 2011; Mueller et al. 2009). Injury from circulating oral microbial toxins and transient bacteremia has been theorized to result in brain abscesses, cavernous sinus thrombosis, cerebral infarctions, and chronic meningitis (Rams & Slots 1992; Gendron et al. 2000; Sabbatani et al. 2004; Mueller et al. 2009). Recommendations for treatments of such abscesses have included aspiration or resection of the abscess followed by removal of the destructive periodontal source of infection if indicated and targeted antibiotics for treatment of the offending organism (Mylonas et al. 2007; Ewald et al. 2006). In addition to dissemination of oral pathogens to the central nervous system, the relative risk of pneumonia in patients undergoing a craniotomy was reported 3.5 times greater among individuals with periodontal disease compared to those with good periodontal health (Bagyi et al. 2009).

Oral Hygiene Interventions

Oral care for the intubated patient must include the fundamental triad of hydration, debridement, and moisturizers at a minimum for optimal oral hygiene given the host of threats to oral health in the ICU. While few oral care protocols have been identified in the literature targeting critically ill patients (Stiefel et al. 2000; AACN 2006), various agents have been used in a variety of hospital settings to promote oral health (Beck 1979; Dudjak 1987; Milligan et al. 2001). However, support to validate various products or a combination of mechanical and pharmacological interventions has not substantiated by oral assessments in the literature.

Oral care products

Hydration and moisturizing of the lips, mucous membrane and tongue has been attempted through a variety of agents, including several unsubstantiated by research. These interventions include compounded mouthwashes containing mixtures of cinnamon and menthol, cider and water, and effervescent ascorbic acid solutions (Milligan et al. 2001). Mixtures of hydrogen peroxide and those of sodium bicarbonate which may appear beneficial at first glance, cause superficial burns to oral tissues (Crosby 1989). Lemon and glycerin have been used in past nursing care protocols but the use of lemon can cause decalcification of teeth and irritation to tissues, and glycerine has been found to absorb water and is therefore drying to tissues (Bruya & Madeira 1975; Crosby 1989). Thymol, a compound made from thyme oil has been reported as a useful agent in European protocols during the 1980's but no recent reports reflect its use (Milligan et al. 2001). Lips have been hydrated with water and protection of lip integrity was purported through the use of paraffin wax (Crosby 1989).

Saliva substitutes, usually compounded from carboxymethylcellulose or hydroxyl-methylcellulose, have been reported useful for the treatment of xerostomia yet many do not provide for naturally occurring antibacterial or immunological properties that are present in organic saliva (Buglass 1995). A gel substitute, Oral Balance® has been recommended for mucous membranes as it contains two antimicrobial enzymes normally found in saliva, lactoperoxidase and glucose oxidase (Jones 2005; Little et al. 2008). Oral Balance Gel® studied in conjunction with Biotene® dry mouth toothpaste to treat xerostomic effects of radiation for head and neck cancer has been found effective (Warde et al. 2000). Other investigators have reported significant relief of xerostomia from the combined use of these products and attributed results to the antibacterial effects of the product's enzymes and lactoferrin which is also present in human saliva (Epstein et al. 1999; Shadad et al. 2005; Givens 2006).

Tooth brushing with toothpaste has long been promoted as the mainstay for promotion of tooth and gingival health for hospitalized patients (Howarth 1977; Schweiger & Lang 1981; Addy et al. 1992; AACN 2006). However, ICU nurses continue to use foam swabs as the main tool for cleansing of teeth, gingival, and mucous membranes (Grap et al. 2003; Cutler & Davis 2005). This practice persists in the United States and Europe despite ICU nurses acknowledging the superiority of a tooth brush over a swab (Binkley et al. 2004; Jones 2005; Rello et al. 2007; Feider et al. 2010). In Israel, 218 critical care nurses report using gauze pads or tongue depressors for debridement and fewer than half use toothbrushes (DeKeyser Ganz et al. 2009). While foam swabs may provide stimulation of mucous membranes, they are not indicated for debridement of plaque (Fitch et al. 1999). Powered toothbrushes have demonstrated superiority in plaque removal and better cleaning in gingival crevices when compared to manual tooth brushes (Terezhalmy et al. 2005). Due to the reported effectiveness in plaque removal, electric tooth brushes should be explored as a part of oral care for intubated patients (Needleman et al. 2011).

Tongue scraping has been advocated for treating the oral malodor that results from xerostomia, limited oral intake, VSCs, and dried secretions noted on the dorsum of the tongue (Tonzetich 1977). Deep tongue scraping of the posterior aspect of the tongue can be performed by a tongue scraper or a toothbrush but evidence supports a tongue scraper as more effective in reducing VSC levels (Outhouse et al. 2006). Gentle, deep tongue cleaning has been recommended on a daily basis in the outpatient setting for maintaining oral hygiene (Rosenberg 1996).

Safety

Oral care practices must be safe so as not to undermine the already critically ill patient. A key component of safety is protection of the airway. The fear of dislodging the ETT has been noted to be a concern of ICU nurses when performing oral care and may account for less thorough practices as evidenced by continued use of foam swabs for routine care (Cutler & Davis 2005; Sona et al. 2009). A second issue of safety concerns possible transient bacteremia occurring following tooth brushing (Ames 2011). Yet in a preliminary microbial analysis of timed blood and oral cultures

obtained during and immediately following tooth brushing with a manual tooth brush, no evidence of transient bacteremia was detected (Jones et al. 2010).

ICP measurements may be obtained directly with intraventricular or intraparenchymal brain tissue monitoring. In a landmark paper published in 1965, Lundberg and colleagues described placement and monitoring of ICP via a ventricular catheter placed within the cerebral lateral ventricle (Lundberg et al. 1965). This is the first mention of real-time ICP recordings used to monitor minute-by-minute ICP, evaluate responses to treatment, and guide patient care. ICP monitoring has become part of the standard of care for patients admitted to the NICU with a suspected mass lesion or at risk for developing increased ICP (Yanko & Mitcho 2001; Bratton et al. 2007; Daley et al. 2008). The attention focused on ICP has expanded to include CPP, which is equal to the mean arterial blood pressure minus mean ICP and represents the pressure gradient for cerebral blood flow (Novak et al. 2003; Smith 2008; White & Venkatesh 2008). Measurement of CPP has been identified as an important physiologic parameter to be included in the monitoring of NICU patients (Young et al. 2003; Rangel-Castilla et al. 2008).

For the neuroscience patient, careful attention must be simultaneously directed towards maintenance of normal ICP, i.e., 0-15mm Hg, with 15 mm Hg as an upper limit of normal ICP, and CPP maintained greater than 60 mm Hg (Smith 2008). Therefore, in patients with central nervous system pathology, care is directed towards optimal blood flow and oxygenation while minimizing real or potential threats to neuronal integrity regardless of the underlying etiology. Patients admitted to the NICU with diagnoses of traumatic brain injury, intracranial hemorrhage, hydrocephalus, and other less common diagnoses may require ICP monitoring in cases where increased ICP is known or suspected (Bader & Littlejohns 2010). The ability of the brain to maintain cerebral blood flow may be distorted, i.e. impaired cerebral autoregulation, following injury and remains an area of investigation for researchers (Reinhard et al. 2010; Nakagawa et al. 2011).

Nursing care activities such as bathing, repositioning, and suctioning have been found to influence ICP and CPP to varying degrees and close observation by staff during care is essential (Mitchell et al. 1981; Parsons et al. 1985; Ersson et al. 1990; Olson et al. 2007). In a 1978 exploratory study, Mitchell and Mauss reported increased ICP among patients who had coughing episodes, restless movements, or conversations at their bedside. Further explorations of reduced CPP and increased ICP values lead to the formation of the nursing diagnosis “decreased adaptive capacity - intracranial” (Mitchell 1986, pg 171). This diagnosis has provided nurses the framework to assess and plan care in terms of maintaining normal ICP and CPP perfusion pressures. Monitoring ICP in relation to various nursing care practices such as passive range of motion (Koch et al. 1996), suctioning and bathing (Rising 1993), and bathing and oral care (Parsons et al. 1985) have resulted in unstained elevations of ICP in the absence of intracranial hypertension. Studies examining ICP and CPP during periods of oral care performed in a comprehensive or standard manner among NICU patients are lacking.

Efficacy

Oral care intervention strategies are targeted to promote and maintain oral health with a dual role of preventing systemic disease (Fowler et al. 2001). As such, oral care protocols and products to provide such care need to reflect best practices in oral hygiene during the stress of illness and intubation.

While clinical efficacy studies of ICU oral care practices are few, there is extensive out-patient literature addressing best products for removal of plaque and biofilms. Investigations of manual compared to powered toothbrushes have concluded oscillating rotating or counter rotational brushes are the most effective in the removal of plaque biofilm and the prevention and treatment of periodontal disease and gingivitis (van der Weijden et al. 1994; Sicilia et al. 2002; Stefanc & Nesbit 2007). This finding was underscored in a Cochrane Review of 42 published studies comparing manual and powered toothbrushes in the outpatient setting, where powered toothbrushes with a rotating, oscillating head were judged to be more effective in the removal of plaque and prevention of gingivitis than the manual tooth brush (Robinson et al. 2005). Foam swabs, while ineffective in removing plaque, have been described as effective stimulation of mucosal tissues (Day 1993; Abidia 2007). Improving mucosal and gingival health and reducing the risk of periodontitis has demonstrated improved glycemic control among diabetic patients (Mealey & Rose 2008).

The choice of oral care cleansing and hydrating agents has been examined in the out-patient and oncology literature with the call for products that do not result in or worsen existing xerostomia (Tombes & Gallucci 1993; Eilers 2004). Xerostomic effects and desquamation of oral mucosal tissue has been noted to occur when products containing SLS have been used (Herlofson and Barkvoll 1993; Herlofson and Barkvoll 1996).

Frequency of oral hygienic measures has also been explored as a means to provide adequate hydration of tissues. In a study of oral care effectiveness based on oral care rendered every two, three, or four hours using a soft toothbrush and tap water no significant difference in condition of oral tissues was reported (DeWalt 1975). In a study investigating benefits of every four hour mouth rinses with boiled water vs. a green tea solution, the overall health of mucosal surfaces was noted to be better in the boiled water group (Hsu et al. 2011). Yet evidence to support frequency and which type of mouth washing agents are superior for ICU patients remains unclear (Berry & Davidson 2006).

Comprehensiveness

The various structures of the mouth require combined interventions to maintain oral health, prevent conversion to an oral pathogenic state, and promote comfort for the intubated patient. Thus, a comprehensive approach to oral care, incorporating fundamental elements of efficacy, is required for intubated ICU patients who are at greatest risk for oral health deterioration. As the mouth is considered a repository for nosocomial bacteria, oral care protocols targeting bacterial laden plaque and the

corresponding biofilms have been suggested as a means to reduce the incidence of bacterial pneumonia (Scannapieco & Mylotte 1996).
Fitch et al. (1999) described an oral care protocol using a pediatric manual tooth brush twice daily with Biotene® toothpaste and mouthwash followed by Oral Balance Gel® as effective in reducing dental plaque. Powered toothbrushes compared to foam swabs, each used for two minutes four times a day with Chlorhexidine gluconate (CHX) demonstrated significant reductions of dental plaque in the powered tooth brush group but no significant difference in respiratory pathogens among critical care patients (Needleman et al. 2011).

CHX has been used due to its bacteriocidal, antimicrobial effects in attempts to reduce occurrence of VAP (Hayes & Jones 1995). The incidence of VAP among patients orally swabbed with 2% CHX was 5% compared to 11% in patients receiving normal saline swabs for oral care (Tantipong et al. 2008) and is in accordance with previous published reports that suggest CHX should be part of oral care protocols (Koeman et al. 2006; Sona et al. 2009). In contrast with more recent reports, CHX has been equivocal in reduction of total respiratory pathogens and reduction of VAP among ICU patients (Jacomo et al. 2011; Panchabhai et al. 2009; Scannapieco et al. 2009). No mention of oral health assessments were provided in any of the trials. Furthermore, there has been the suggestion that CHX may pose an occupational hazard to health care workers in light of recent reports describing CHX as an IgE mediated allergy (Garvey et al. 2007; Nagendran et al. 2009).

In summary, care providers must attend to oral hygiene needs of patients unable to independently perform oral care. While care givers recognize the importance of oral care, they may experience difficulty performing oral hygiene due to limited access to the mouth, expressed feelings of disgust, repulsion, and possible psychosexual undertones (Eadie & Shou 1992; Wardh et al. 2000; Trieger 2004). Nevertheless, care providers are charged with meeting the needs of the dependent individual. To provide safe, effective oral care mandates implementation of best practices. Given the unsubstantiated current oral care practices (Munro et al. 2006a) and increasing awareness of the connection between oral health and systemic health, nursing research within the realm of oral hygiene is essential in order to delineate evidence-based oral care practices.

AIMS

The overall aim of this research was to investigate the safety of oral care in terms of intracranial dynamics and changes in oral health during intubation and 48 hours after extubation among neuroscience intensive care unit (NICU) patients. Additional aims included comparison of a comprehensive oral care protocol (i.e., tongue scraping, electric toothbrush, non-foaming toothpaste, and application of oral moisturizers) to a standard protocol (pediatric manual toothbrush, standard toothpaste, lubricant) with respect to safety and efficacy to promote oral health and to reduce the incidence of oral nosocomial bacteria and ventilator-associated pneumonia (VAP) in NICU patients.

The specific aims were:

- Study I: To explore changes in oral health as indicated by the OAG; the prevalence of oral nosocomial bacteria; and the frequency of VAP in orally intubated patients throughout the period of intubation and 48 hours thereafter. The effect of oral care on patients' ICP during and after completion of oral care was also assessed.
- Study II: To determine the safety of tooth brushing in intubated patients with acute neurological injuries by measuring the effects of specified oral care protocols on the intracranial and cerebral perfusion pressures.
- Study III: To investigate and compare changes in oral health during intubation through 48 hrs after extubation among patients enrolled in a standard versus a comprehensive oral care protocol.
- Study IV: To investigate and compare changes in oral and respiratory nosocomial colonization during intubation from admission through the first week of hospitalization among NICU patients randomized to a standard versus comprehensive oral care protocol. Furthermore to compare the incidence of VAP between the two groups.

METHODS

Design

The study designs used in this thesis were a prospective cohort study (Paper I) followed by a two year, randomized controlled trial (RCT) (Papers II, III, and IV). The descriptive approach was chosen for Paper I as a preliminary study to obtain data on the pre-selected variables of oral health, ICP during oral care, nosocomial oral flora, and VAP rates (Table 1). Such an approach would allow the description and documentation of these variables during the time of intubation and serve as the foundation for hypotheses testing (Melnyk & Fineout-Overholt 2010). The RCT was chosen to evaluate and compare the effects of a standard oral care protocol to a comprehensive oral care protocol and provide evidence which may be used to change and improve clinical practice (Polit & Beck 2008).

Table 1. Design and sample overview for Papers I-IV

Study	**I**	**II**		**III**		**IV**	
Design	Prospec-tive Cohort Study	Randomized Controlled Trial		Randomized Controlled Trial		Randomized Controlled Trial	
Sample		Std	Comp	Std	Comp	Std	Comp
N	45	27	20	31	25	40	38
Male (%)	21 (47)	11 (40)	9 (45)	14 (45)	15 (60)	23 (58)	19 (50)
Age, mean (SD)	49 (16)	47 (18)	51 (19)	52 (19)	51 (19)	51 (18)	54 (18)
Data Collection	GCS Oral cultures Mean ICP OAG CXR	GCS Admit diagnosis Mean ICP CPP		GCS OAG Oral care frequency Adverse responses		GCS Oral cultures Sputum cultures CXR	

Std – standard oral care protocol
Comp – comprehensive oral care protocol
GCS - Glasgow Coma Scale
ICP - intracranial pressure
OAG – Oral Assessment Guide
CXR - Chest x-ray
CPP – cerebral perfusion pressure

Setting and Sample

The setting for each study was an NICU in a 517-bed Level I Trauma and Stroke Center in the Southwestern United States. The hospital is a regional referral center for critically ill neuroscience patients. The most common admission diagnoses include stroke, brain tumor, and closed head or acute spinal cord injury or both. The NICU is staffed with a nursing ratio of 1 to 1 or 1 to 2 in addition to a clinical supervisor. Patient care technicians are available to assist with bedside patient care tasks. The hospital is an academic facility with residency programs in neurosurgery and neurology. The prospective study was conducted from January – December 2006, the RCT was conducted from August 2007- August 2009.

Patients eligible for study inclusion were at least 18 years old who were admitted intubated on arrival to the NICU or within the first 24 hours of admission to the unit, had a primary diagnosis consistent with neurological injury or dysfunction, and had a legally identified decision maker available to sign informed consent forms. Exclusion criteria were an unstable cervical spine injury, fewer than six teeth, facial or oral fractures, pregnancy, expected extubation within 48 hours, or those not anticipated to survive according to the attending physician's documentation. Patients already admitted to the hospital, those in a sub-acute or acute rehabilitation, or a nursing home setting and transferred into the NICU were excluded due to the possibility of pre-existing oropharyngeal colonization (Craven et al. 2002). Inclusion and exclusion criteria were held constant for each study. Flowchart of patient enrollment during the RCT is depicted in Figure 2.

In the cohort study (Paper I), the sample consisted of 45 patients aged 49 ±16 years old (mean ± SD) and 47% were men (Table 1). The admitting diagnosis included stroke (64%), traumatic brain injury (20%), brain tumor (9%), and miscellaneous (7%). The median admission Glasgow Coma Scale (GCS) score was 9 (7-10), and 49% had a GCS score of 3-8 reflecting severe neurological impairment, of which 34 patients underwent placement of an ICP monitor. There were 34 patients that had enrollment, pre-extubation, and 48 hours post-extubation data available for oral health, oral flora, and VAP analyses.

An interim safety analysis of 47 patients that had been randomized (27 in the standard oral care protocol and 20 in the comprehensive care protocol) was performed (Paper II). All patients had an external ventricular drain (EVD) verified for placement by a post – procedure computerized tomography of the brain and interpreted by the neurosurgical staff. Baseline demographics were similar in both groups (Table 1). The admission GCS score was severe for 78% in the standard group and 75% in the comprehensive group. The admission diagnosis of stroke was documented in 85% of those randomized to the standard group compared to 70% in the comprehensive group with the difference not significant (p=0.58). An arterial line for blood pressure measurement as required by NICU policy for patients with an EVD was present in all 47 patients.

Analysis of 56 patients (31 in the standard oral care protocol and 25 in the comprehensive care protocol) was reported on patients with OAG scores on NICU admission and every 48 hours thereafter through 48 hours following extubation (Paper III). The sample consisted of 31 patients aged 52 ±19 years old (mean ± SD) in the standard protocol and 25 patients aged 51 ±19 years old (mean ± SD) in the comprehensive protocol (Table 1). There was no significant difference in tobacco use between the 2 groups (p = 0.27).

Patients with documented oral and sputum cultures upon enrollment and every 48 hours thereafter during the first six days of hospitalization or until extubation were analyzed (Paper IV). The sample consisted of 40 patients aged 51 ±18 years old (mean ± SD) in the standard protocol and 38 patients aged 54 ±18 years old (mean ± SD) in the comprehensive protocol. Baseline demographics of gender, admission diagnosis, and admission GCS were similar in both groups (Table 1). There were no significant differences in co-morbidities of cardiac, respiratory, diabetes, or other secondary diagnoses (p=0.41).

Compliance with the hospital VAP prevention program, i.e. elevation of the head of the bed greater than 30 degrees, mandated daily interruption from sedation, peptic ulcer prophylaxis, and deep vein thombosis prophylaxis, was achieved in greater than 96% for all patients in each study (Papers I – IV).

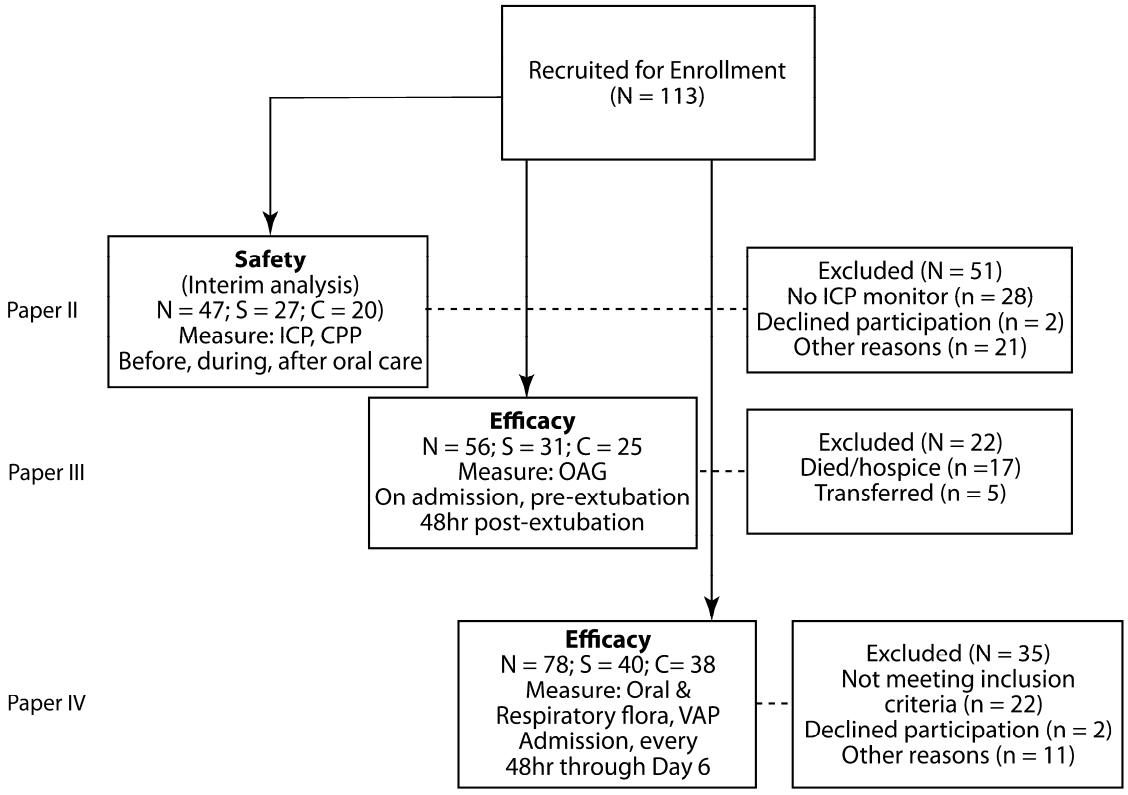


Figure 2. Overview of RCT enrollment and data measurements
S – Standard oral care protocol
C – Comprehensive oral care protocol

Data collection and instruments

During the cohort study (Paper I), the Principle Investigator (PI) or a co-investigator acquired all physiologic, radiographic, and intracranial hemodynamic recordings via the hospital electronic medical record on a daily basis. Furthermore, they conducted all oral health examinations using the OAG and obtained simultaneous oral cultures.

For patients enrolled in the RCT (Papers II-IV), five teams of individuals collected data for analyses. The bedside nurses who performed oral care recorded patient and intracranial responses 30 minutes before, during and 30 minutes after oral care; a designated group of nurses performed all OAG evaluations and obtained oral cultures; respiratory therapists obtained sputum cultures; pulmonary critical care physicians reviewed patient chest x-rays (CXR); and nurse co-investigators recorded demographic and daily biometric data. Data collection followed the timeline as outlined in Table 2.

Table 2. RCT Data collection for Papers II-IV

	Study Day					
Component	Admission	1	2	3	4…	48˚ post extubation
ICP/CPP*	x	x	x	x	x	
Bedside RN record†	x	x	x	x	x	x
OAG‡	x		x		x	x
Oral Culture§	x		x		x	
Sputum Culture§	x		x		x	
Biometric data‖	x	x	x	x	x	x
CXR¶	x		x		x	

* Mean ICP, CPP obtained 30 minutes before, during, and 30 minutes after oral care while ICP monitored
† Documentation of oral care and patient adverse responses
‡ Oral Assessment Guide performed
§ Oral, sputum cultures obtained
‖ Demographics on admission, daily biometric data
¶ Chest x-ray

Neurologic assessment tools

The GCS, a standard measurement of level of consciousness in acutely ill, NICU patients was used as the clinical scale for altered level of consciousness and neurologic impairment (Bader & Littlejohns 2010). The GCS scale score ranges from a 3 – 15 with 15 indicating no impairment of consciousness. The scale provides independent measures of eye opening, verbal performance, and motor responsiveness which are summed for a total score (Teasdale & Jennett 1974). The GCS has been evaluated for use in emergency rooms and ICUs and despite inconsistencies when used by

inexperienced personnel, it has been found reliable when used by qualified personnel with a reliability coefficient of 0.8-1 (Rowley & Fielding 1991; Prasad 1996).

ICP and CPP were used as the principle indicators of intracranial response to patient care (Mitchell & Mauss 1978; Boortz-Marx 1985; Hickey 2009). ICP was measured exclusively via an EVD and recorded as mean ICP values. All patients with an ICP monitor had an arterial line for blood pressure monitoring used for calculation of the CPP. The ICP and CPP signals were acquired from the bedside computerized system (Philips Intelliview NP 5, Irvine, CA, USA), which continuously displayed analog wave forms and digital values.

Oral Health Assessments

The total OAG score ranging from 8-24 is based on summed scores of one to three in eight item categories. The higher the score indicates the worse the oral health although there are no established cut-off scores for interpretation. Inter-rater agreement between nurses has ranged from 0.91 to 0.73 (Eilers et al. 1988; Holmes & Mountain 1993) and the OAG is viewed as a valid measure of oral health for hospitalized patients (Hallberg & Andersson 2011).

All oral assessments were performed using a modified version of the OAG (Eilers et al. 1988) (Table 3). The item category of 'voice' in the OAG was omitted in the cohort and RCT (Paper I, III) as all patients were intubated. The total OAG scores (Paper I) could range between 7 (excellent oral health) and 21. The 'voice' item was replaced with the category of 'odor' (Paper III) as an indicator of VSC responsible for halitosis due to microbial activity (Rosenberg & McCulloch 1992; Greenman et al. 2004). Consequently, total OAG scores could range between 8 (excellent oral health) and 24 representing the worst in all categories. For all intubated patients, the assumption was made that there was some pain on swallow due to the presence of the ETT. For patients maintained on paralytic drips, patients were scored the maximum score in the swallow category since they were unable to swallow. The total OAG score was used as the primary measure of oral health, but item level data were also examined for exploratory purposes.

Table 3. Modified OAG Assessment Scale

Category	**Tools for Assessment**	**Methods of Measurement**	**Numerical and Descriptive Ratings**		
			1	2	3
Swallow	Observation	Ask patient to swallow. To test gag reflex, gently place blade on back of tongue and depress *(may move ETT to test gag)*	Normal swallow	Some pain on swallow; impaired *(Assume intubated patient has pain = minimum score of 2)*	Unable to swallow *(CN IX, X, XII; sedated, or absent gag)*
Lips	Visual/palpatory	Observe and feel tissue *(Lubricate finger and palpate)*	Smooth and pink and moist	Dry or cracked	Ulcerated or bleeding *(HSV, candidiasis, and/or cheilitis)*
Tongue	Visual/palpatory	Feel and observe appearance of tissue	Pink and moist and papillae present	Coated or loss of papillae with a shiny appearance with or without redness	Blistered or cracked *(bleeding, lacerations, ulcers)*
Saliva	Mouth mirror	Insert blade into mouth, touching the center of tongue and floor of mouth *(Slide a mouth mirror along the buccal mucosa)*	Watery *(No friction between the mirror and mucosa)*	Thick or ropy *(Slightly increased friction, no tendency for the mirror to adhere to the mucosa)*	Absent *(Significantly increased friction, the mirror adhering or tending to adhere to mucosa)*
Mucous Membranes	Visual	Observe appearance of tissue	Pink and moist	Reddened or coated (increased whiteness) without ulcerations	Ulcerations with or without bleeding
Gingiva *(rate the worst)*	Tongue blade and visual	Gently press tissue with tip of blade *(press triangle gum area between teeth)*	Pink and stippled and firm	Edematous with or without redness	Spontaneous bleeding or bleeding with pressure
Teeth	Visual	Observe appearance of teeth *(Wait at least 1 min after applying disclosing solution w/ swab)*	Clean and no debris	Plaque or debris in localized areas (between teeth if present) *(< 50% surface areas; >50% surface area with thin biofilm coating)*	Plaque or debris generalized along gum line or denture bearing areas *(> 50% surface areas; heavy plaque and debris)*
Odor*	Nose	Smell	Normal	Slight to moderately foul	Strong, foul odor

Permission granted to use table by University of Nebraska. *Italics* indicate suggestions to oral evaluators for assessment. *Used in Paper III only

Oral and sputum cultures

All oral cultures, obtained in conjunction with OAG evaluations, were acquired using a sterile swab rubbed along the lower gingival margin. Oral swabs were plated on the following agar media: sheep's blood agar to isolate *S. aureus*, chocolate and MacConkey agar for isolation of Gram negative bacilli followed by incubation in CO_2 at 35^{o} C (Scannapieco et al. 2009). After 48 hours, microbiology technicians interpreted the agar plates using the Gram Stain technique. The results noted by the microbiology lab were *S. aureus*; *Klebsiella, Enterobacter, Serratia marcescens* (KES) group; and Pseudomonas. If other organisms were seen, they were reported as mixed gram positive or mixed gram negative. Following organism classification, semi-quantification was performed using a 0 - +3 range, i.e., none, light, moderate, and heavy (Tortora et al. 2006). Sputum cultures, obtained on the same day as the OAG oral cultures, were collected by respiratory therapists and sent to the laboratory for identical microbial analysis. Culture results were analyzed as non-colonized indicating none to light growth, or colonized indicating moderate or heavy growth.

VAP Criteria

The diagnostic criteria used for VAP was based upon the following clinical parameters: fever, leucopenia or leukocytosis, the development of purulent sputum together with radiographic evidence of a new or progressive pulmonary infiltrate (Bauer et al. 2000; CDC 2004). Biometric data obtained on enrollment and daily thereafter included white blood cell counts and maximum and minimum temperature recordings. A portable, upright CXR was obtained on enrollment and every 48 hours while intubated. Information on the sputum color was obtained from the respiratory therapists' documentation recorded at same time the sputum culture was obtained.

Procedure

Paper I

The recruitment of subjects in the cohort study (Paper I) was achieved by a morning review of all patients admitted the previous 24 hours. The medical chart was accessed to determine eligibility requirements, and if met, the legally identified decision makers were approached for enrollment per study protocol. The patient's chart was accessed each morning to obtain data points of the GCS as recorded by neurosurgical staff, the temperature, white blood cell count, sputum color, and the transcribed radiologist interpretation of CXR findings. Notation of a new or progressive pulmonary infiltrate was recorded as a positive CXR finding for the definition of pneumonia. The nursing documentation of oral care was identified and ICP values were obtained from the electronic chart for the 30 minutes before, during, and after oral care. The NICU standard of oral care at the time included brushing teeth twice daily with a manual pediatric toothbrush, fluoridated tooth paste, and rinsing the mouth with sterile saline. Moisturizers were applied to the lips as needed. Foam swabs were used at the nurses' discretion to provide cleaning or debridement. The bedside nurse determined use of a tooth brush or foam swab for debridement, and the frequency of oral care and hydration of tissues.

A registered dental hygienist provided instruction to the PI and co-investigators on oral health examinations using the OAG. A pilot group of 10 patients, seven were intubated, was then independently examined by the registered dental hygienist and co-investigators to establish inter-rater reliability. The nurse investigators subsequently performed the baseline OAG on enrollment and every 72 hours thereafter until the patient was extubated or underwent a tracheostomy. Approximately 48 hours following extubation, the post – extubation OAG assessment was repeated.

RCT: Papers II – IV

The following procedures were used for reported results during the RCT (Papers II – IV).

Recruitment and enrollment

Each morning, all patients admitted to the NICU during the previous 24 hours were reviewed for eligibility by the PI or co-investigator together with the clinical supervisor. After obtaining informed consent, patients were randomized into one of two methods of oral care using a computer-generated randomization list. The list was maintained in a locked room, separate from informed consent forms to prevent manipulation of group assignment. Individuals who obtained consent were not directly involved in the patients' oral care. Upon enrollment, the study logo was placed on the patient's door and the box with the designated oral care supplies was placed in the patient's room and the assigned protocol was reviewed with the bedside nurse.

Each patient was assigned a subject number and two envelopes for data collection with the subject number on a pre-printed label were issued. The first envelope, labelled 'Data Records' was kept in a locked drawer and accessible only to the PI and co-investigators for completion. This envelope contained data sheets for demographics, CXR interpretations, daily biometric data, and a copy of the signed informed consent form. The second envelope, labelled 'OAG Evaluations' was placed in a separate locked cabinet, accessible only to the PI and oral health evaluators. Inside were the data sheets for recording OAG results and pre-printed laboratory requisitions for oral and sputum cultures. A set of data sheets was placed with the bedside nurses' chart for recording intracranial data together with information related to length of time spent in delivering oral care, number of personnel required, and any complications related to the procedure. These sheets were kept on the nurses' clipboards and viewed only by the PI or co-investigators involved in daily data collection.

Oral care supplies

All supplies for oral care, regardless of group assignment, were placed inside an opaque, white cardboard box with the study logo pasted to the top of each box. On the inside flap of each box, a pre-printed label with the specified oral care protocol was placed for staff reference. Supplies for the standard oral care included a manual pediatric toothbrush, Freshmint fluoridated toothpaste (Product of India, distributed by NWI Inc, Nashville, TN, USA), sterile normal saline, and a biologically inert, water-based, water-soluble lubricant (K-Y Jelly, Johnson & Johnson, New Brunswick, NJ, USA) as the moisturizing agent for oral mucosa and lips. For patients randomized to

the comprehensive oral care protocol, supplies included a low profile tongue scraper, an electric toothbrush with a small, oscillating, rotary head (Oral B Vitality® toothbrush, Newark, NJ, USA) with a built-in two minute timer, Biotene® toothpaste, and Oral Balance® (both products from GlaxoSmithKline, Moon Township, PA, USA) as the moisturizing agent for oral mucosa and lips (Figure 3).

Figure 3. Comprehensive oral care supply box with oral care logo noted on lid, and protocol pasted on inner flap.

Instructions and provision of oral care

Prior to initiation of the RCT, educational sessions were conducted to explain the study protocol, how to perform the two oral care protocols, and completion of ICP and oral care records by the nurse bedside. Additionally, the dental hygienist provided a PowerPoint® presentation and hands-on demonstration of how to perform oral care for an intubated patient. At the conclusion of each educational session, attendees were paired and practiced brushing teeth on each other as per the protocol. Mandatory attendance was required of all nursing and patient care technicians.

For both groups, the assigned oral care protocol was performed twice daily, i.e., once during the day shift and once during the night shift. Wall-mounted bedside clocks were set to zero at the beginning of tooth brushing. At the conclusion of each oral care episode, the bedside nurse recorded performance of tooth brushing, total time spent in

performing oral care including patient preparation, cleaning hygiene supplies, and any adverse events noted during the procedure. The dental hygienist made twice weekly rounds during the RCT to answer questions by bedside nurses regarding technical difficulties in performing oral care.

ICP and CPP documentation

The bedside nurse recorded the ICP and CPP values 30 minutes before, during, and 30 minutes after oral care (Paper II). If the EVD was ordered open to drain, the system was turned to monitor mid-way through brushing to obtain the mean ICP. The CPP value, calculated automatically by the bedside monitor, was similarly recorded by the bedside nurse for the corresponding time periods as the ICP. The bedside nurse also recorded transient episodes (lasting fewer than 5 minutes) of physiologic changes, patient agitation, and any mechanical issues with the toothbrush during oral care.

Oral Assessment

The baseline OAG was obtained on enrollment and repeated every 48 hours during intubation. Approximately 48 hours following extubation or tracheostomy, a post–extubation OAG assessment was repeated. OAG assessments were performed the between the hours of 05.00 – 07.30 on the scheduled day for examination. Bedside nurses kept oral supply boxes closed to prevent the evaluators from seeing the contents and maintain blinding of the oral evaluators to group assignment. To conduct the assessment, the bedside bright light source, a disposable dental mirror, tongue blades, cotton-tipped applicators, and a vegetable dye-based plaque disclosing solution were used. Protective patient care equipment, i.e., goggles and gloves were used by the OAG evaluators. Odor was the first item to be assessed, followed by: swallow, lips, tongue, saliva, mucous membranes, and gingiva. Immediately following evaluation of these items, the plaque disclosing solution was used to coat the teeth surfaces. Approximately 60 seconds following application of the dye, teeth were assessed for plaque or debris.

Oral and sputum samples

All oral cultures (Papers I, IV) were obtained prior to performing the OAG and the procedure was identical for each oral culture. Using a sterile, cotton-tipped culture swab, the evaluator rubbed the swab along the buccal gingival margin of posterior teeth on the lower jaw. Standing orders for sputum cultures were left with the respiratory therapist to obtain on the same day as the oral culture. Both oral and respiratory culture swabs were hand carried to the microbiology lab. Laboratory technicians, blinded to group assignment, interpreted the plates using the Gram Stain technique and bacteria counts (none, light, moderate, heavy).

Chest X-ray

A pilot interpretation of 20 CXRs was conducted with two pulmonary critical care physicians, board certified in pulmonary critical care, for reliability testing (Paper IV). All CXR interpretations (Paper IV) were performed by these same two physicians blinded to group assignment. CXR interpretations were conducted in a darkened room and viewed on the hospital's radiographic data base. Each subject's CXR was judged

on a yes/no category on the presence of the following criteria: clear, infiltrate, atelectasis, and effusion. Infiltrate was the only criteria used for the diagnosis of pneumonia. Interpretations were performed at regular intervals throughout the study.

Biometric data
The medical chart was accessed to obtain the required data points. If there was an omission of data in the chart, a co-investigator clarified the issue in point with the nurse, resident, or attending physician. Envelopes containing data collection sheets used for the daily review were maintained in a separate, locked cabinet from the OAG assessment envelopes to avoid revelation of group assignment to the oral evaluators. Following collection of daily data, the oral care box of supplies was checked and restocked as needed. During this time, the family members were asked if they had any questions regarding the protocol. When requested, additional information on oral health, a review of the protocol, or both was provided.

DATA ANALYSIS

Data Preparation

The data gathering phase was marked by four keys stages as outlined by Lewis-Beck (1995): sample; measures; coding and entry; and checking. A pilot test of ten patients for the cohort study (Paper I) was conducted in December 2005. A pilot test of ten patients was performed for the RCT (Papers II – IV) in May of 2007 to discover problems with data entry and coding. Length of intubation time was established by admission day as the first day of intubation through extubation or performance of a tracheostomy. VAP diagnosis was based on the following four criteria: white blood cell counts <4000/ul or >12,000/ul; body temperature <36.6C or > 38.5C; purulent sputum secretions, and together with documented findings of a new or worsening infiltrate on CXR. If three of the four criteria were met, including the CXR result as one of the three, a diagnosis of probable VAP was made. When all four of the criteria were present, a diagnosis of definite VAP was established. For group analyses, probable and definite VAP categories were combined to result in one category of VAP.

Statistical Analyses

No sample size estimates were calculated for the prospective cohort study (Paper I). Determination of sample size for the ICP responses during and after oral care (Paper II) was not performed due to lack of published trial data with this intervention and an interim safety analysis was performed.

In preparation for the RCT, power analyses were conducted *a priori* to determine the sample size for the OAG (Paper III) and VAP rate (Paper IV) (Cohen 1977; Cohen 1988). Using an estimated sample based on the OAG results obtained in Paper I, the

estimates for 50 subjects in each group to provide 90% power with $p<0.05$ to detect a difference of 80% between groups was established. A power analysis, conducted *a priori* to determine the sample size for the VAP rate was estimated following discussions with clinical experts, a review of literature for nationally reported VAP rates, and the hospital's quarterly reports of VAP. With VAP as the categorical predictor and a predicted VAP rate of 20% for the comprehensive protocol, and a 40% VAP rate for the standard protocol, a sample size of 100 patients in each group was estimated for an alpha level of $p<0.05$ (2 tailed) with 85% power.

Data were coded and SPSS for Windows (SPSS Inc., Chicago, Illinois, USA) was used for all data analysis. SPSS Version 14.0 was used for the cohort study (Paper I) and version 17.0 used for the RCT (Papers II – IV). For all analyses, where descriptive statistics were used, frequency distributions and cross-tabulations were executed. Differences between groups were analyzed using Student's t-test for interval and ratio data, chi-square test or Fischer's exact test for nominal data and Mann-Whitney U-test for ordinal data. Two-tailed p-values <0.05 were considered statistically significant (Table 4).

Table 4. Statistical analysis used in Papers I-IV

Study	**I**	**II**	**III**	**IV**
Analyses	Kendall's Coefficient Friedman test Wilcoxon signed rank	Student's t-test Chi-square Fisher exact ANOVA Wilks' lambda Confidence interval Effect size	Kendall's Coefficient Student's t-test Chi-square Fisher exact Mann-Whitney U Friedman test Wilcoxon signed rank Effect size	Student's t-test Friedman test Fisher exact Chi-square Kappa

Analyses of mean ICP changes in the cohort study (Paper I) was conducted with the Freidman test. During the RCT, repeated measures analyses of variance (ANOVA) was performed to investigate changes in ICP and CPP (Paper II) over time with Bonferroni adjustments. Effect sizes for changes in ICP and CPP were calculated for the mean differences in measurements at comparison points between all three oral care time periods and interpreted based on the nomenclature of 0.2 for small, 0.5 as medium, and 0.8 for large (Cohen 1977; Cohen 1988).

Kendall's Coefficient was used as a measure of reliability between the raters for OAG evaluations (Papers I, III). Nonparametric tests were used to test for changes over time and differences between groups. A repeated measures model was used to compare changes in mean scores for each item and the total OAG score during admission, last day of intubation, and 48 hours following extubation. Repeated measures of the total

OAG score were analyzed using the Friedman test followed by Wilcoxon signed - ranks test to analyze the difference between each time point. The p - values were corrected by using the Bonferroni method to avoid the risk of mass significance (Bland & Altman 1995). The effect size was calculated for changes in OAG score changes (total and item category) as the mean change at each time point divided by the standard deviation at the first time point for the corresponding variable. The results were converted from positive to negative and vice versa to illustrate deterioration in oral health. Effect size interpretation was again based on nomenclature of 0.2 for small, 0.5 as medium and 0.8 for large (Cohen 1977; Cohen 1988).

Bacterial growth was measured with colony forming units observed on oral and sputum cultures using the 0 - +3 range, i.e., none, light, moderate, and heavy. Chi Square was used to compare differences between groups with Fischer's exact test for statistical significance. Two-tailed p-values <0.05 were used. Friedman's test was used to compare changes in bacteria prevalence over time between groups. Chi-square test with Fisher's Exact test was used for comparing between protocol differences for the diagnostic category of VAP.

ETHICAL CONSIDERATIONS

Ethics, and the study of ethics as an art and science, are necessary to apply rules of correct conduct (Miltner 1948). The necessity of conduct within medical ethics was highlighted by judgments made by the war crimes tribunal in Nuremberg following World War II (Mitscherlich & Mielke 1949). Standards for human experimentation, known as the Nuremberg Code, mandated voluntary informed consent protecting the right of the individual to control his/her own body during the course of experiments (Mitscherlich & Mielke 1949). The World Medical Association, developed in 1947 in response to the war crimes, ratified a statement of ethical principles for medical research involving human subjects known as the Declaration of Helsinki in 1964 and most recently updated in 2008 (Puri et al. 2009). The foundation of ethical clinical research is based upon respect for and upholding of autonomy, maximizing welfare through beneficence, minimizing harm through non-maleficence, promoting fair and equal treatment of patients or justice, and maintaining honesty through the principle of veracity. Prior to the cohort and RCT, each of these aspects were reviewed and incorporated into the specific study design.

The principle of autonomy declares that each person is in control of their own person including their mind and body (Beauchamp & Childress 2001). If examined in its purest form, there is the presumption that no other person or institution should overrule the person's choice. This includes whether or not the choice is 'right' as judged from an external perspective (Furrow et al. 2008).

Autonomy is based on the individual's ability to understand risks, benefits, and alternatives to treatment. Accordingly, a person must manifest sufficient ability to understand these aspects in order to provide informed consent (Furrow et al. 2008). Within the neuroscience field, patients rendered comatose or with an altered level of consciousness, are often urgently admitted to the hospital. Neuroscience patients recruited for studies often have an inability for decision making due to a lack of capacity. As a result, their decision making rights fall to the legally identified decision maker, usually a designated family member or medical power of attorney. The process of informed consent is designed to provide clear information to participants of trials to allow decisions to be made regarding participation. During the cohort and the RCT, the designated person for consent was approached in a non-threatening manner and the study explained. The entire informed consent was explained on a page by page detail, concluding with the ancillary version of informed consent written in easy to understand English and ratified by questions and answers. A certified Spanish informed consent was also available for individuals whose native language was Spanish. Furthermore, explanations regarding voluntary participation and the ability to defer consent or withdraw from the study at any time without prejudice were provided. All individuals that obtained consent had undergone the Collaborative Institutional Training Initiative program and attained certification in research ethics (Braunschweiger & Goodman 2007).

Principles of beneficence and non-maleficence are interwoven and addressed simultaneously. Beneficence implies that what is best for each person is the course of action to follow (Beauchamp & Childress 2001). The corollary definition of non-maleficence incorporates the obligation of "primum non nocere" – "first do no harm" which is the foundation of the Hippocratic Oath (Furrow et al. 2008). In the prospective cohort study (Paper I), beneficence would be an indirect measure of study participation since findings may lead to improved oral care for future patients. Given the study relied on observations versus an intervention, there was not a direct threat to harmful effects of the study. Indirectly, patients may have been harmed should their health information be traced back to the subject. To avoid this problem, anonymity of each subject's personal identity and medical information was protected by having a single master list of enrolled subjects secured in a locked drawer and known only to the PI. Beneficence was addressed during the RCT as the aspect that oral care would be performed at regularly scheduled times using the AACN protocol for ICU patients. Subjects enrolled in the RCT would be the direct beneficiary of the oral care intervention as would patients in the future. Non-maleficence was a potential concern regarding the implementation of the oral protocols since there was the possibility of exacerbating poorly compliant intracranial hemodynamics resulting in increased ICP or lowered CPP. While not captured during the study, a second aspect of non-maleficence would be pain experienced by the patient during the oral care procedure. To ensure compliance with beneficence and non-maleficence, each bedside nurse had the option to medicate the patient for pain or abort oral care if outward signs such as facial grimacing were detected during the procedure. Finally, the possibility of systemic spread of periodontal pathogens was a potential risk to enrolled subjects. While unclear as to the likelihood of such bacteremia, it was nevertheless a threat to non-maleficence.

The principle of justice refers to participant recruitment in a non-discriminatory fashion on the grounds of age, gender, and nationality (Beauchamp & Childress 2001). As such, subjects must be adequately informed and free from coercion or under influence. Justice acknowledges that some individuals may be unable to claim their rights of self-determination, so-called vulnerable populations, due to possible exploitation. While such groups have traditionally included children and prisoners, comatose patients are also vulnerable since they cannot claim nor defend their rights (Thompson 1987). Therefore, all eligible subjects' legally identified decision makers were approached in the same, non-threatening manner and provided extensive explanations during the RCT. No patient enrolled in any of the reported studies survived or regained a level of cognition to give informed consent during the acute care hospitalization.

Advancements in medicine, biology, and technology have resulted in a heightened awareness of adherence to ethical principles in the conduct and reporting of study results to biomedical journals (ICMJE 2004). Consequently, the International Committee of Medical Journal Editors requires registration of clinical trials in a public trials registry before submitted research will be considered for publication (De Angelis et al. 2006). To assist in reporting RCTs, the Consolidated Standards of

Reporting Trials (CONSORT) issued a 22 item checklist which requires full disclosure of all aspects of an RCT to improve presentation and interpretation of results (Moher et al. 2001). In accordance with mandates from the International Committee of Medical Journal Editors, the RCT was registered at ClinicalTrials.gov (NCT 00518752). Furthermore, the cohort and RCT received IRB approval at St. Joseph's Hospital and Medical Center (Cohort - IRB #05NU044; RCT - IRB #07NU018) and mutual data use agreement forms were signed by the committee representative of Lund University.

The PI, co-investigators, and research assistants completed the Collaborative Institutional Training Initiative program and attained certification (Braunschweiger & Goodman 2007). In addition, the PI completed the National Institutes of Health Protecting Human Research Participants Program. Since enrolled patients had an impaired level of consciousness, informed consent was obtained from legally identified decision makers. A signed copy of the Informed Consent Form containing contact information of the PI was provided to all legally identified decision makers.

FINDINGS

The findings are presented in accordance with the aims of this research, i.e., the safety of oral care as demonstrated by intracranial dynamics and patient responses; changes in oral health during intubation and after extubation, and the effectiveness of oral care protocols on oral health; and lastly, by changes in nosocomial flora and VAP rates.

Safety during oral care

One aspect of safety was detection of compromised intracranial hemodynamics, as noted by elevated ICP, decreased CPP, or both among participants during and following oral care as compared to readings before the oral care procedure. Documentation of ICP measurements were the sole method used to evaluate intracranial safety during non-specified oral care the cohort study (Paper I). Within the sample, there were 849 recordings of mean ICP less than 20 mm Hg values at all three time points related to oral care (Figure 4). No significant differences were detected in ICP values among these reading across the time points ($p=0.24$, Friedman test). ICP was greater than 20 mm Hg prior to oral care in 13 patients, accounting for a total of 30 instances. Following oral care, ICP decreased to less than 20 mm Hg in 20 instances (67%) during oral care and 23 instances (77%) at 30 minutes following non-specified oral care ($p=0.24$, Friedman test). At the 30 minute time period following oral care, 3 patients had persistent ICP elevations greater than 20 mm Hg.

During the RCT, ICP values were obtained among patients in the standard and comprehensive groups during verified episodes of tooth brushing performed during the initial 72 hours of ICU admission (Paper II). Within the comprehensive and standard sample there were 352 and 455 ICP recordings respectively obtained over time. The ICP values did not differ significantly between groups ($p=0.86$). Accordingly, pooled data from both groups yielded a significant difference with a mean ICP elevation of 1.7 mm Hg from the time before to the time during oral care ($p<0.001$). A statistically significant decrease in ICP of 2.2 mm Hg was noted between time of oral care and 30 minutes following the procedure ($p<0.001$). There was no difference between mean ICP recordings when before oral care ICP values were compared to 30 minutes after oral care ICP values ($p=0.72$) (Figure 4). Fourteen instances of ICP greater than 20 mm Hg were recorded from four patients 30 minutes before oral care. Nurses' discretion resulted in oral care being performed twice in two patients, one in each group. No significant increase of ICP or decrease of CPP was detected in either patient during or after oral care. The CPP values did not differ between oral care groups ($p=0.68$) and remained greater than 60 mm Hg at all times points in both groups during and after oral care.

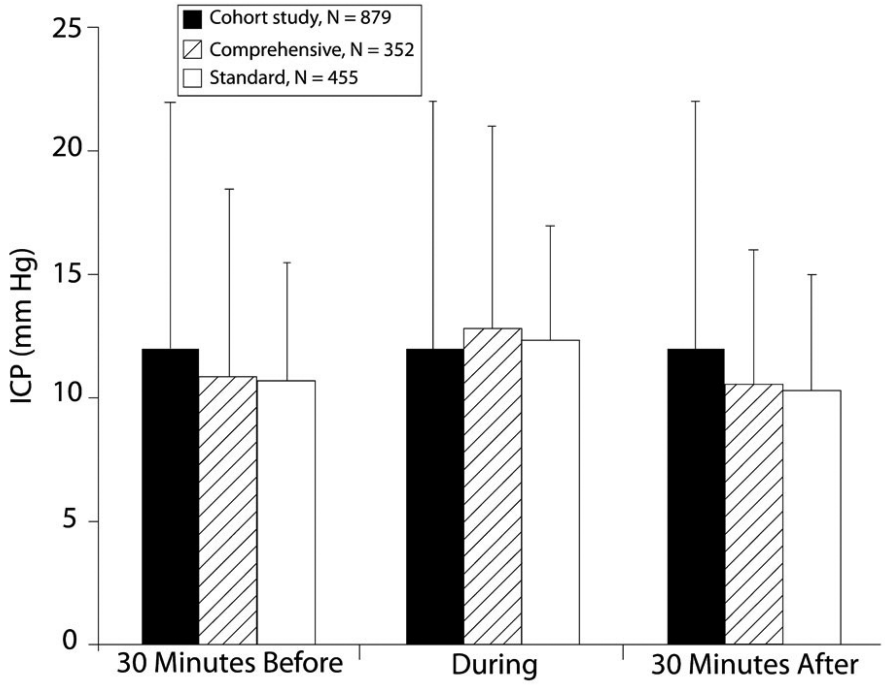


Figure 4. Mean (95% CI) ICP changes 30 minutes before, during, and 30 minutes after oral care from the cohort and RCT studies (Papers I and II). *Used with permission from Barrow Neurological Institute*

Exploratory analysis of adverse reactions during oral care among patients in both protocols during the RCT (Paper II) were categorized as changes in physiologic variables (ICP, blood pressure, oxygenation; bleeding); patient responses (agitation, uncooperative, biting); and mechanical issues with the toothbrush (Table 5). Bleeding along the gum line was noted more often among those in the standard group (p=0.02), while biting the ETT during oral care appeared more frequently among those in the comprehensive group (p=0.01). The mean number of individual adverse reactions, during the initial 72 hours, (standard protocol 1.2; comprehensive protocol 1.5) did not differ significantly between groups (p=0.61; Fisher's exact test).

Nursing activities related to oral care were reported for 161 and 127 separate oral care procedures for the standard and comprehensive group respectively. Documented nursing interventions for changes in ICP among patients in the standard (6.1%) and comprehensive (5.1%) groups (Paper II) were equivalent (p=0.54; Fisher's exact test). There was no significant difference in self-reported nursing interventions such as positional changes, pharmacologic interventions, or device manipulation during the peri-procedural intervention.

Table 5. Adverse patient responses noted during oral care

	Standard N=27 patients 161 OC procedures	Comprehensive N=20 patients 127 OC procedures	P-value[b]
Adverse responses[a] *(%)*			
Transient IICP	7 (4.3)	8 (6.2)	0.59
Increased blood pressure	3 (1.8)	3 (2.3)	1.00
Decreased oxygen	0 (0)	0 (0)	--
Bleeding	10 (6.2)	1 (0.7)	0.02
Agitation	8 (4.9)	3 (2.3)	0.35
Uncooperative	2 (1.2)	0 (0)	0.50
Biting endotracheal tube	4 (2.4)	12 (9.4)	0.01
Biting toothbrush	7 (4.3)	6 (4.7)	1.00
Mechanical problem with toothbrush	0 (0)	3 (2.3)	0.84

[a]Adverse responses: transient changes lasting less than five minutes and required no intervention; some patients had more than one adverse response
[b]Fisher's exact test
OC = Oral care
IICP = Increased Intracranial Pressure

Changes in oral health

For the cohort and RCT, two separate pilot groups of 10 patients each (7 intubated, 3 not intubated) was examined independently by the RDH and oral evaluators prior to initiation of each study. Inter-rater reliability was 86% and 88% in both pilots (Papers I and III) respectively. Since the OAG is an ordinal scale, additional analyses for reliability were conducted using the non-parametric measure of association, Kendall's coefficient of concordance (Norman & Streiner 2000). Among the three oral evaluators (Paper I) and the four oral evaluators (Paper III), with Kendall's W as the main overall measure of strength, agreement among raters was 0.76 (Table 6). When the RDH was used as the gold standard for calculation of Kendall's W for each pilot (Papers I and III), the overall concordance was 0.76 and 0.77 respectively.

Table 6. Kendall's coefficient of concordance (Kendall's W) among nurse raters

Item	Kendall's W Paper 1/ Paper 3
Swallowing	0.93/ 0.91
Lips	0.75/ 0.72
Tongue	0.66/ 0.63
Saliva	0.59/ 0.58
Mucous Membranes	0.85/ 0.85
Gingiva	0.75/ 0.66
Teeth	0.82/ 0.91
Odor	0.70*
Total Score	0.76/ 0.76

* Used as an item in Paper III only

The categorical item of voice in the original OAG scale was omitted in both studies because intubated patients are unable to speak. Odor replaced the item of 'voice' in the original OAG (Paper III). The content validity of odor as an item to the OAG (Paper III) was rated for relevance by five experts: an RDH, two expert NICU nurses, and two physicians in pulmonary critical care. The item content validity index for odor was acceptable at 0.91 (Davis 1992).

OAG assessment scores were reported on the day of admission, the last day of intubation, and 48 hours following extubation for 24 patients (Paper I). The total OAG score increased during intubation reflecting deterioration in all items of the OAG. There were significant differences between the total OAG score on admission compared to the last day of intubation ($p<0.001$) and between the last day of intubation and 48 hours after extubation ($p=0.03$). No significant difference was detected in the total OAG score on admission compared to 48 hours post-extubation. In item analysis following extubation, swallowing was noted to improve, while saliva deteriorated. All other items: lips, tongue, mucous membranes, gingiva and teeth remained unchanged from admission scores when compared to 48 hours after extubation.

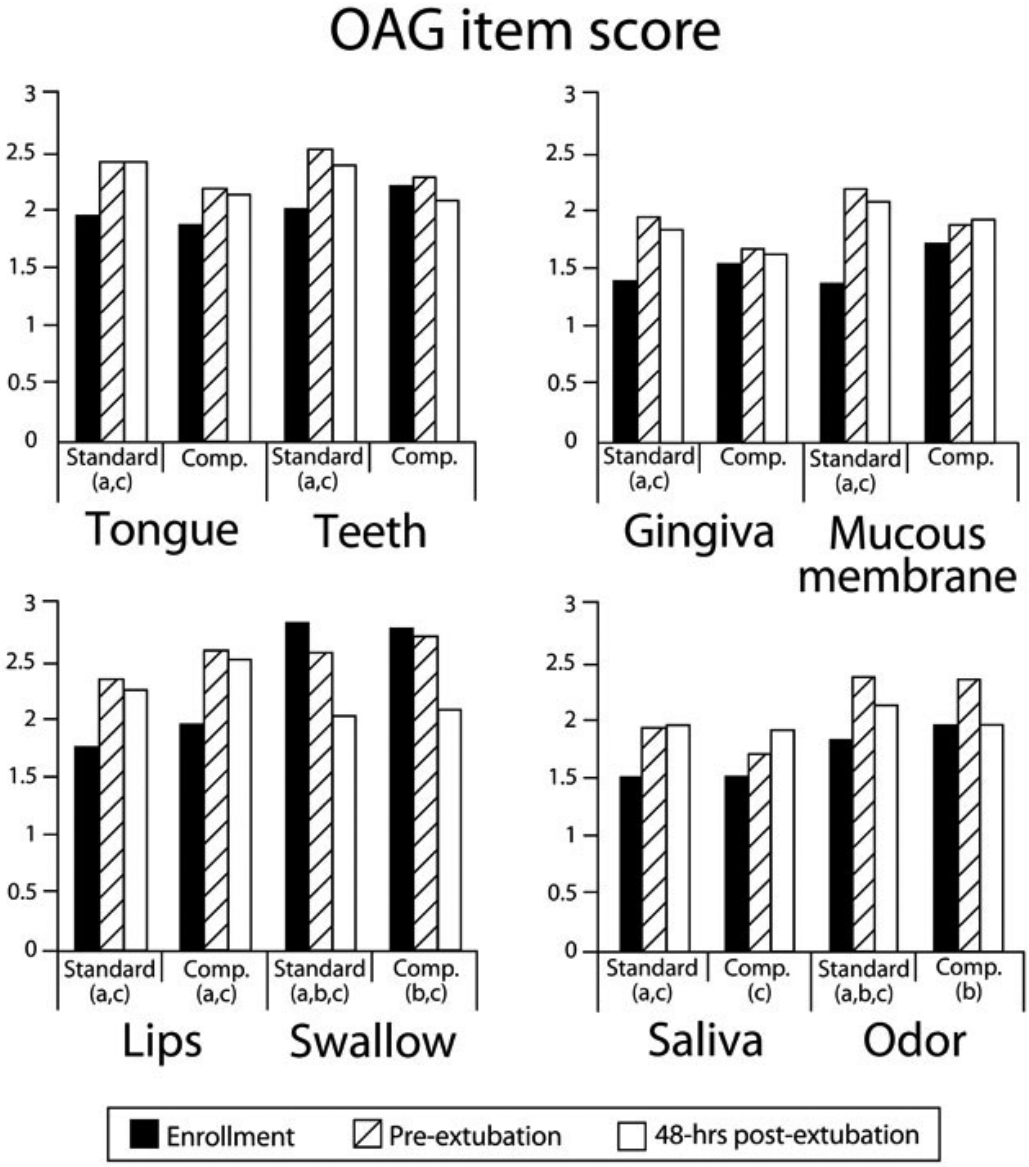
Results reported from the RCT (Paper III), with 31 subjects in the standard group and 25 subjects in the comprehensive care group, yielded differences between total OAG scores from admission through 48 hours following extubation. While *a priori* calculations predicted a sample size requirement of 50 subjects in each group, statistical significance was achieved with 31 and 25 subjects respectively. Among those in the standard group, total OAG scores deteriorated throughout the time of intubation and remained worse 48 hours following extubation. Within the comprehensive oral care protocol, total OAG scores deteriorated during the time of intubation, but there was no significant difference between scores from admission to

48 hours following extubation. Large effect sizes signifying deterioration in total OAG scores were noted in both protocols from enrollment to pre-extubation with 1.72 and 3.52 reported for the comprehensive and standard oral care group respectively. When effect size was examined from the time of enrollment to 48 hours following extubation, a modest deterioration in total OAG was noted in the comprehensive group (0.52), while a large effect size was found in the standard group (2.32).

In the comprehensive group analyses of item OAG scores over all three time periods no significant deterioration in the categories of tongue, teeth, gingiva, and mucous membranes were detected (Figure 5). Small effect sizes for these same four categories were noted at all three time comparison points, i.e., enrollment to pre-extubation, pre-extubation to post-extubation, and enrollment to post-extubation. From admission through the pre-extubation, a modest effect size representing deterioration was obtained for the lips. All intubated patients were assigned a minimum rating score of 2 since intubation is associated with pain; a rating a three was assigned to patients with no swallow due to neurological impairment or full sedation. Swallow was noted to improve between admission and extubation. Odor deteriorated as evidenced by modest effect size of 0.40 from admission to pre-extubation, and had an equal effect size in improvement between pre-extubation and 48 hours following extubation. There was no difference in odor between admission and 48 hours post-extubation with a corresponding effect size of 0.00.

In contrast, significant deterioration was noted in all item categories among those in the standard protocol from enrollment to pre-extubation and enrollment to post-extubation (Figure 5). As rated in the comprehensive protocol, all intubated patients were assigned a minimum rating score of 2 since intubation is associated with pain; a rating a three was assigned to patients with no swallow due to neurological impairment or full sedation. Furthermore, the total OAG, swallow, and odor had significant deterioration over time at all three points ($p<0.001$). During the time of intubation (enrollment to pre-extubation), a medium to large effect size reflecting deterioration was detected in all categories with the exception of swallow which was small.

When the effect size was analyzed for deterioration between enrollment and post-extubation, a small effect was observed for odor; a modest deterioration in lips, tongue, saliva, gingiva, and teeth; and large effect size for deterioration in mucous membranes was observed.



a= Significant difference between enrollment to pre-extubation
b= Significant difference between pre-extubation to 48 hours after extubation
c= Significant difference between enrollment to 48 hours after extubation
Used with permission from Barrow Neurological Institute

Figure 5. Mean OAG item scores for both protocols during intubation through extubation

No difference in the time spent in brushing teeth, i.e., two minutes brushing per episode in both groups was noted (p=0.53); nor was there a difference in the number of times brushing was performed per shift (p=0.89). The number of oral swabs used in a 12 hour shift was equivalent between groups (p=0.91). Neither the standard nor the comprehensive protocol required additional personnel aside from the bedside nurse to complete the protocol. One additional minute was required to complete the comprehensive oral care protocol, which was a significant difference from the standard group (p=0.01).

Microbial changes and VAP rates during intubation

Oral colonization was reported on admission in 22% of patients in the prospective study (Paper I). Oral cultures from the initial 10 days of hospitalization demonstrated a steady increase in colonization of GNB over time with prevalence rates of 38%, 46%, and 50% on days 4, 7, and 10 respectively. Colonization with *S. aureus* was noted to increase from an enrollment prevalence of 12% to 36% by day 4, and subsequently decreasing to 16% and 13% on days 7 and 10 respectively.

During the RCT, admission oropharyngeal cultures revealed moderate to heavy colonization among 25% of enrolled subjects in each protocol. For the remaining 75% of patients in each protocol, there was conversion to colonized oral cultures during the first week of intubation. While patients enrolled in the comprehensive protocol, colonized and non-colonized on admission, had a trend of less colonization in oral and respiratory cultures during the first six days no significant differences were noted when compared to those in the standard protocol.

Colonization with the gram positive bacteria, *S. aureus,* during the RCT was noted to be less in the standard and comprehensive groups compared to colonization among those in the descriptive study. By day four of the RCT (Paper IV) among those not colonized on admission, *S. aureus* was documented in 5% of all oral samples compared to the reported 36 % among those in the descriptive study. There was no report of *S. aureus* in the oral cultures of those in the comprehensive sample compared to 11% in the standard and 16% in the descriptive study. Similarly, there was no *S. aureus* in any oral samples among the comprehensive group on days 2, 4, or 6 among those colonized on admission compared to 11%, 29%, and 17% on the same days for those in the standard group.

Diagnosis of VAP was made on the basis of documentation of three or four of the established clinical criteria, i.e., derangements in white blood cell counts; body temperature; sputum secretions, and a new or worsening infiltrate on CXR. The CXRs in the RCT (Paper IV) were reviewed by two board certified pulmonary critical care physicians. The Kappa coefficient, used as the measure of agreement between the two physicians, was .84 (Landis & Koch 1977; Viera & Garrett 2005). The incidence of VAP during the prospective study yielded a steady increase over time. While 26% of patients had documented findings consistent with VAP on day four, that number rose to 46% by day 10. During the RCT, VAP incidence was noted to be slightly less for patients in both groups when oral cultures were not colonized on admission and ranged from 8% to 42% by day six. Among colonized patients on admission, VAP rates from 33-50% for the standard protocol compared to 11-38% for the comprehensive protocol over time with no significant difference between groups detected. Antibiotic usage was not significantly different between patients in either protocol, whether admission cultures were colonized ($p=0.78$) or not ($p=0.69$).

DISCUSSION

Methodological considerations

A prospective cohort study (Paper I) provided observations of exposure to oral care among NICU patients and outcomes of interest, i.e., ICP, oral health, oral nosocomial flora, and incidence of VAP. Such prospective cohort studies are useful for the exploration of new concepts and to aid in formulation or generation of hypotheses (Melnyk & Fineout-Overholt 2010). Based on literature and the results of Paper I, it was hypothesized that a comprehensive oral care protocol would be safely tolerated resulting in improved oral health and fewer diagnoses of VAP compared to patients receiving standard oral care in an NICU. Therefore, an RCT was performed to investigate and establish the effects of the proposed comprehensive oral care intervention compared to a published standard oral care protocol for the critically ill (AACN 2006). An RCT provides allocation of subjects to treatment and monitoring for development of outcome(s) allowing for group comparison and testing of hypotheses (Hennekens & Buring 1987). The degree to which observed findings lead to correct inferences about the phenomena in this research requires a methodologic examination of statistically relevant issues; namely, validity and reliability.

Internal Validity

Internal validity refers to the degree the independent variable represents the results and to what extent alternative explanations may have contributed to the findings (Hulley et al. 2007). Prospective descriptive cohort studies, as reported in Paper I, do not have strong internal validity since there is no control over the independent variable. The strength of a cohort study lies in the description of the problem, its incidence, and possible causes (Melnyk & Fineout-Overholt 2010). An RCT, as used for Papers II, III, and IV, is a robust design to test an intervention on a dependent variable(s) to provide evidence upon which clinical practice may improve (Melnyk & Fineout-Overholt 2010).

Threats to the internal validity are alternative explanations that may have influenced or caused a change in the dependent variable. Among threats to internal validity in this thesis are attrition, history, confounding variables, and bias (Shadish et al. 2002). Attrition refers to the loss of subjects to treatment or measurement which can result in artificial effects if the loss is correlated with conditions. In this thesis, attrition of study participants, recordings of ICP and CPP, OAG evaluations, or cultures occurred during the RCT due to patients being out of the ICU for procedures during data collection, death or early extubation, or patient transfers to an outside facility, such as hospice or rehabilitation. The attrition rate calculated for ICP and CPP findings was 6% (Paper II), and for the oral health comparison 28% (Paper III). Attrition rates progressively increased over time for nosocomial analysis (Paper IV). Within the standard group on days two and six, the attrition was 13% and 40% respectively. On days two and six for the comprehensive protocol, the attrition was 5% and 47% respectively. Attrition of subjects does not allow for determination of the independent variable effects and with attrition rates exceeding 20% there is a greater possibility of

bias (Polit & Beck 2008; Melnyk & Fineout-Overholt 2010). The RCT design would have represented equivalent groups allowing for analysis since there was an equal chance that attrition would have occurred in either group.

Bias, which affects internal validity, is a form of systematic error with a number of causes and should be considered as a function of the study design and methods (Hennekens & Buring 1987; Szklo & Nieto 2000). While potential for bias may be greater in a cohort study, such as Paper I, there are also forms of bias that may influence RCTs and hence validity (Concato et al. 2000). The attrition rates may have influenced the results of nosocomial analyses since those individuals that were the most critically ill required prolonged intubation; this however is the population of interest. There was no significant difference between the two groups regarding attrition rates on sampling days. The attrition was predominately due to extubation or death, evenly matched between the two groups. Selection bias exists when criteria for study participation influences the study's outcome (Shadish et al. 2002). In this thesis, consistent inclusion and exclusion criteria were used to achieve a study sample that most closely reflected the population of interest. Indicators of pre-existing poor oral health, such as oral disease or decay, were not exclusion criteria. Referral bias, occurring when a subset of the general population is referred, may have been a factor since the study was conducted at a tertiary care academic center. Reviewer bias may occur when the person collecting the data is inappropriately blinded. During the cohort study (Paper I), investigators collected data on variables of interest with no specified intervention and accordingly, such reviewer bias could be expected to be minimal. During the RCT, it was impossible to blind the bedside RN from ICP/CPP recordings during oral care and results therefore should be interpreted accordingly. Throughout the RCT, the nurse investigators that performed the OAG, the microbiology technicians that analyzed microbial growth, and the physicians that evaluated the CXRs were blinded to participant protocol allocation. Therefore the risk of reviewer bias was reduced.

History, another threat to internal validity, refers to concurrent, external events which occur during the experiment and may influence the outcome (Melnyk & Fineout-Overholt 2010). The RCT was conducted over a two year period, during which time newly-hired RN's were responsible for providing oral care. While they did not benefit from the initial instruction on oral care protocol techniques, the protocol was affixed to the inside flap of each oral care kit; furthermore, daily rounds by research assistants and rounds by the RDH afforded the opportunity to clarify techniques. Neurosurgical junior residents rotate through the NICU on a yearly basis. Their responsibilities include placement of EVDs and providing initial management directives for all NICU patients. Since the RCT was conducted over two years, there were two separate groups of residents that cared for patients enrolled in the study. There is a senior and a chief resident that provide assistance for the junior residents and the attending neurosurgeon has ultimate authority for ICP management. There were no changes in referral patterns nor hospital designation as a trauma or stroke center during the cohort or RCT.

Confounding variables are those that may have an effect on the dependent variable and should be handled in such a way as to avoid being related to independent or dependent variables (Polit & Beck 2008). Common confounding variables such as age, gender, diagnosis, and co-morbidities were addressed during the intervention by randomization. The PI and co-investigators underwent mandatory certification in obtaining informed consent, enrollment, and allocation to groups occurred without bias (Melnyk & Fineout-Overholt 2010). Furthermore, the intervention was applied consistently and monitored on a daily basis. It is possible that variations in the prescribed protocol occurred despite the educational sessions and having the protocol affixed to the supply box. Internal validity was enhanced by the daily research assistant rounds to answer bedside nurse questions and the by the presence of the RDH for consultations.

Limiting variations in practice is desirable in efficacy studies and further supports the aspect of internal validity (MRC 2000). However, there may have some physician driven variations in practice during the RCT. One such confounding variable would have been the medication used for sedation. Data was not collected on type of agent used, but the two most common sedation agents were propofol and midazolam. Propofol decreases the gag and cough response making stimulation with oral care potentially less disturbing for patients and inflated the score for swallow on the OAG. If used, propofol may have also impacted the immune system thereby possibly altering oral and sputum culture results. The critical care physicians charged with management of the respiratory system may have had individual practice patterns guiding the prescribing antibiotics. However, these same physicians are charged with the respiratory management of all NICU patients. The strength of the RCT minimizes the impact of confounding variables through the consistent execution of the intervention, and the inclusion and exclusion criteria.

Construct Validity

Construct validity refers to how well the instrument measures what it is intended to measure. As such, construct validity involves the measurement and the construct itself, providing inferences about detected causal relationships (Shadish et al. 2002). The GCS was used as the construct for overall neurological impairment for all samples in this research. Despite it's drawbacks towards heavily weighted motor response and the original development for head injury, it remains a staple in all emergency and neurocritical care units and continues to be used in clinical trials as a baseline measure of neurological assessment (Schirmer-Mikalsen et al. 2007).

The outcome measure of intracranial safety was measured by ICP via intraventricular monitoring (Papers I and II) and CPP via intravascular monitoring (Paper II). The adult intracranial content is constant under normal circumstances containing brain, blood, and cerebrospinal fluid. Since these three elements are constant, when intracranial mass occurs, there is a necessary decrease in the volume of venous blood and cerebrospinal fluid, otherwise known as the Monro-Kellie-Burrows doctrine (Weed & Hughson 1921). When the compensatory mechanisms of cerebrospinal fluid displacement or alterations in venous flow are exhausted, increased ICP may result (Kanter & Robertson 1990). The CPP is obtained by the difference of mean arterial

blood pressure and the mean ICP representing the vascular pressure gradient across cerebral vascular beds and should be maintained greater than 60 mm Hg (White & Venkatesh 2008). The ICP monitor and the arterial line were attached to a bedside computer monitoring system which yielded digital and analog values. Nursing staff undergo yearly competency evaluations in the maintenance of these devices and demonstrate proficiency in the setup, calibration, and maintenance. During each shift, staff are required to calibrate the lines and troubleshoot if inconsistent or questionable readings appear. Such data provide the cornerstone to intracranial management for patients in an NICU and are commonly used for patients with central nervous system dysfunction and mass effect or the potential to result in brain compression. Routine recordings of ICP every 15 minutes and CPP every 30 minutes was the standard in the NICU during the cohort and RCT; although increased frequency may be required depending on the patient's condition (March 2000; Kirkness et al. 2009). No changes to routine documentation were made during the cohort or RCT and transient elevations in ICP or decreased CPP may not have been captured. However, the nursing staff had the opportunity to document aborted oral care measures if pathological, sustained changes occurred.

The outcome variable of oral health was evaluated by the OAG and reported in Papers I and III. When an index is introduced for measuring a clinical state, it should be fundamentally easy to learn with an accurate recording of the findings (Bearn et al. 1996). The OAG been used in hospitals and revisions have been used in a variety of settings including out-patient settings and residential care facilities (Andersson et al. 1999; Andersson et al. 2002b; Andersson et al. 2004; Miller et al. 2007). In the original OAG (Eilers et al. 1988), the total OAG incorporated the item of 'voice'. For the purpose of this study with intubated patients, voice was deleted from the OAG since intubation renders such an assessment meaningless. Therefore the total OAG score ranged from 7-21 for the cohort study, making comparisons to other published results troublesome. During the RCT, voice was replaced with odor since halitosis is associated with oropharyngeal bacteria (Rosenberg 1996; Outhouse et al. 2006). Furthermore, inclusion of odor as part of the OAG has previously been reported as a valid indicator of poor oral health (Sjogren & Nordstrom 2000). Odor assessment demonstrated good concordance between raters and when used with an RDH as the gold standard. Assessments of tongue and saliva were marked by lower concordance in both Papers I and III, 0.66 and 0.63, respectively. Tongue assessment has proved troublesome in previous reports of non-intubated patients (Eilers & Berger 1988; Kayser-Jones et al. 1995). The lowered percentage of agreement may reflect the difficulties in assessments accentuated by the ETT's presence. Saliva has also proved problematic for inter-rater agreement and has been noted to display similar difficulties between nurses and RDH evaluations and should therefore be taken into consideration in interpretation of results (Andersson et al. 2002b). The category of swallow was automatically rated as a '2' upon intubation, or a '3' with sedation which may have led to an artificially high swallow score compared to the original intent of the OAG. This scoring was applied consistently by OAG raters throughout the trial. Finally, the item of teeth in the cohort and RCT (Papers I and III) demonstrated high concordance, 0.82 and 0.91, respectively. This is in contrast to previously reported difficulty as evidenced

by a 0.46 Kappa coefficient (Andersson et al. 2002b). The construct validity of scores obtained for teeth in this research may have been supported by the use of a disclosing solution, which has not previously been described in the critical care literature.

The variables of oral and respiratory nosocomial flora reported in Papers I and IV are broad indicators of potential respiratory pathogens. Laboratory technicians undergo yearly competencies in agar plate analyses. If bacterial growth patterns are questionable, the lead microbiologist consults on the interpretation. Reporting of bacteria was pared to the most commonly occurring pathogenic organisms and other pathogens were broadly classified into gram positive and gram negative classifications. This classification system may have omitted identification of some organisms and therefore underrepresented the specificity of the bacterial load. Due to cost restraints, genetic testing of pathogens from the oral cavity and respiratory tract was not possible.

The outcome variable of VAP (Papers I and IV), was defined based on commonly accepted diagnostic findings, i.e., fever, leukocytosis, purulent sputum, and identification of a new infiltrate on a CXR (Tablan et al. 2003). VAP has also been defined based on the Clinical Pulmonary Infection Score which incorporates the above markers in addition to tracheal cultures, and oxygenation (Cook et al. 1998). Temperature recordings were obtained with core measurements six times daily, more often if temperature extremes were noted. The WBC counts were drawn by licensed staff from arterial lines and submitted to the hospital hematology department with results electronically sent to the patient record. Machines used for WBC analysis undergo routine calibration. The presence of leukopenia or leukocytosis was monitored and recorded daily. Documentation of sputum color was based on assessment by licensed respiratory therapists. During the period of intubation, respiratory therapists are required to perform necessary ETT suctioning and document findings. Their assessment of sputum color was used in the determination of VAP although written description of sputum purulence is variable. While the microbiology lab was capable of confirming neutrophilic or squamous epithelial cell counts, due to cost constraints this was not an option and description by the respiratory therapist was used instead. Board certified pulmonary critical care physicians, blinded to group assignment, evaluated all CXRs. The diagnosis of a new or worsening infiltrate was the threshold for VAP criteria. When there was disagreement between raters, comparison with previous or subsequent CXRs was performed. Atelectasis or pulmonary effusions were not included as a measurement of VAP. Overall estimate of VAP rates may have been overestimated due to combining probable and possible VAP diagnosis as reported in Paper I and IV due to reduced number of subjects over time.

Statistical Conclusion Validity

Statistical conclusion validity refers to the extent that a statistical relationship between the theorized cause and effect can be detected (Shadish et al. 2002). When testing a null hypothesis, the investigator may undermine the validity of the research by making a Type I or Type II error. Type I error results when a true null hypothesis is rejected and conclusions are made in the belief that there was a genuine effect in the population

when in fact, there was none (Field 2005). The probability of making a Type I error, alpha, can be controlled by altering the alpha level. In this thesis the alpha was set at 0.05, i.e., there was a 5% chance that a significant result was obtained by chance alone. A Type I error may occur with repeated analyses of data; consequently, a reduced p value was calculated using the Bonferroni method to reduce the risk of mass significance (Bland & Altman 1995). A reduced p value ($p < 0.01$) was used for multiple OAG comparisons (Papers I and III) to control for the risk of mass significance. A Type II error is the risk of accepting a false null hypothesis and the conclusion there is no effect in the population when, in reality, a difference does exist (Field 2005). To reduce the possibility of a Type II error, consideration of the power needed to detect actual differences in the population is required (Shadish et al. 2002).

A power analysis was performed prior to the RCT for Papers III-IV. The effect size is an additional measure of statistical conclusion validity and is calculated as the mean of the experimental group minus the mean of the control group divided by the pooled standard deviation (Melnyk & Fineout-Overholt 2010). Accordingly, the effect size is the magnitude of the effect of the independent variable on the dependent variable and the widely accepted nomenclature of .10, indicating small, .50 for medium, and .80 for large, was used for ICP, CPP, and OAG investigations (Cohen 1988). In Paper IV, a projected sample size of 100 patients in each oral care protocol wasestimated. The results, although suggestive of a trend, did not achieve statistical significance.

External Validity

External validity refers to the extent that causal relationships apply to patients within the experiment and for those not in the experiment (Shadish et al. 2002). A key element to external validity is how well the sample represents the populations from which it was drawn and questions if there are other possible causal relationships (Melnyk & Fineout-Overholt 2010). When findings are able to be generalized to and across populations, broader applications of the study may be made based on the findings supported by the research results (Ferguson 2004). Random sampling is an efficient method to decrease threats to external validity (Hulley et al. 2007) and was the study design used in Papers II, III, and IV. Since random samples are likely to target the population studied based on the premise that each person in the population has an equal chance of being chosen, in this thesis intubated NICU patients, results can be unbiased and lessens the threat to external validity (Munro 2005). The majority of patients enrolled in these studies had the admission diagnosis of stroke and therefore findings need to be interpreted with caution for other NICU populations.

Studies need to be designed to facilitate retention of subjects and carefully assess dropouts to determine if those no longer participating had specific characteristics which may have influenced the study (Shadish et al. 2002). There were patients, largely due to death or extubation, whereby the duration of the intervention did not extend through the first week making analyses of nosocomial oral and respiratory cultures difficult. Due to the study being underpowered, no firm conclusions can be drawn from results.

Results from this research may not translate to other NICUs whose populations are not drawn from tertiary referral patterns, academic centers, or both. Additionally, there may be differences between NICU patient populations and those that exist in other critical care settings such as cardiac, medical, or surgical ICUs that may result in different findings. Furthermore, young adults and geriatric patients were under-represented in the analyses and therefore results should be interpreted accordingly.

Reliability

The reliability of quantitative instruments is a prime factor in the strength of the results and implies that results are repeatable (Polit & Beck 2008). The instrument must consistently and accurately measure the constructs represented as demonstrated by reliability coefficients of at least 0.70 (Melnyk & Fineout-Overholt 2010). Studies of interobserver variability help to answer the question of instrument reproducibility. Therefore, Kendall's W for the OAG (Papers I, III) and the Kappa statistic for CXR interpretation were used (Paper IV) in pilot studies as a measure of reliability. No reliability testing was performed on ICP or CPP measurements. However, the bedside monitors and invasive lines are recalibrated several times a shift and the nursing staff completes annual competency assessments in the care of patients with such devices.

The OAG, an ordinal scale used to measure oral health (Papers I and III), consists of ordered categories with intervals which are not quantifiable. The content validity of the OAG was originally expressed in the first publication detailing the OAG (Eilers et al. 1988), and has since been found to be a valid measure in a variety of settings (Andersson et al., 1999; Andersson et al., 2002b; Eilers & Epstein 2004). Holmes and Mountain (1993) evaluated the OAG and variations of the tool among oncology patients for reliability, validity, and the overall clinical usefulness. Although issues were reported with full descriptions of patient's oral health status, the Eilers OAG was deemed better than other assessment scales with a reported correlation coefficient of 0.73 between nurses. Their recommendation was continued use of the OAG until a better tool was verified (Holmes and Mountain 1993).

Kendall's statistic, a measure of association among raters is used when data are ordinal with three or more possible levels with natural ordering, e.g. normal, moderate, severe (Field 2005). The range for Kendall's W is zero, indicating no agreement, to one, indicating complete agreement between raters (Norman & Streiner 2000). In this thesis, the total OAG score demonstrated an acceptable coefficient of concordance of 0.76. However, there was some variability in item scores. Observer agreement for individual items of saliva and tongue were less than 0.70, thus showing decreased confidence in the reliability of these measurements. The items of swallowing, mucus membranes, and teeth demonstrated higher levels of concordance indicating a greater reproducibility of measurement.

To evaluate interobserver agreement for the presence of a new infiltrate on CXRs between two physicians, the Kappa statistic was used. Kappa, used for nominal data, is the proportion of agreement after chance agreement has been removed (Munro 2005). The Kappa score may range from -1, indicating perfect disagreement, to 0, indicating

the same as expected by chance, to 1, indicating perfect agreement (Hulley et al. 2007). The stronger the agreement, the higher value of Kappa and consequently the greater reliability of interobserver agreement (Hulley et al. 2007). A Kappa of 0.84 indicating good reliability of the physician interpretations of CXR findings was obtained (Paper IV).

General discussion of the findings

This research was conducted to investigate and compare effects of oral care protocols with respect to safety, effectiveness, and reduction of nosocomial oral bacteria that contributes to the development of VAP. Given the relationship of oral health to systemic health and the projected increased general population of ICU patients (Halpern & Pastores 2010), this study contributes findings that relate to best oral care practices for an increasing ICU population.

Safety of oral care

To provide critical care for critically ill patients, safe oral care practice must be performed prior to implementation of effective oral care. If the proposed oral care procedure resulted in harm to the patient, regardless of the clinical oral efficacy, the hygienic results would be overshadowed by the injury. Safety in this study was assessed by changes in ICP, CPP, and notations of adverse patient responses made by the nursing staff during the time of oral care. Results from the cohort and the RCT studies did not demonstrate clinically significant changes resulting in increased ICP or reduced CPP during or 30 minutes following oral care among patients with ICP <20 mm Hg prior to oral care. In the absence of increased ICP, oral care appeared to be safely tolerated, regardless of the protocol assignment. In those patients whose ICP > 20 mm Hg prior to oral care, there was no documented, sustained rise in ICP, decline in CPP, or notation of clinical worsening was noted. Interpretation of such results must be made with caution since the numbers of patients that underwent oral care with increased ICP are too small to make any generalization with regard to safety. Monitoring aspects such as length of time ICP was observed by the caregiver, the rate of change in the ICP, a subtle change in the clinical condition of the patient, or inattention by the bedside nurse resulting in missed or transient elevations may not have been captured. Indeed, as some researchers have proposed, closer examination of physiologic parameters should be investigated when making determination of intracranial safety (Hickey et al. 2009).

The majority of patients in these studies had stroke as the admission diagnosis and therefore may not adequately reflected intracranial responses as may be seen among those with traumatic brain injury. Management of blood pressure is a cornerstone of ICU management as hypotension may lead to cerebral ischemia and hypertension may result in hyperemia or increased volume of an intracerebral hematoma (Nakagawa et al. 2011). Monitoring of the CPP appeared stable throughout the oral care protocols, regardless of group assignments. While cerebral autoregulation is poorly understood in patients with intracerebral hemorrhage, there is the suggestion

that CPP is preserved during the initial 72 hours following hemorrhage before deteriorating (Reinhard et al. 2010). Conversely, CPP has been reported to be altered immediately following intracerebral hemorrhage as measured by middle cerebral artery blood flow via transcranial doppler flow studies (Nakagawa et al. 2011). No such additional monitoring was used during the RCT. Recording of the systolic blood pressure was not noted and may have demonstrated episodic fluctuations not captured by the mean arterial blood pressure.

Patients appeared to tolerate the provision of oral care, regardless of intervention, without untoward reactions. While concerns of nursing have been previously expressed, such as extubation, etc, such complications were not observed. Moreover, 60% of patients were receiving intravenous sedation during the initial 72 hours, and 77% received narcotics during the same time frame. Standard practice within the NICU is to maintain patients sedated to a Riker Sedation Agitation Scale of 3 which is defined as sedated - difficult to arouse but awakens to verbal stimuli or gentle shaking; or a Riker score of 2 signifying the patient to be very sedated, arousing to physical stimuli only (Riker et al. 1999). Such sedation may have blunted responses to stimulation by such activities as oral care. Although biting the ETT was observed more often during oral care among those in the comprehensive protocol, generalized responses such as agitation, biting the ETT and coughing are frequent manifestations among intubated patients (Bader & Littlejohns 2010) and not necessarily due to the specifics of the protocol. Such responses may have, however, been attributed to the stimulation of the oral care. Interventions such as position changes, premedication, and sedation as used by the bedside nurse in anticipation of the oral care intervention are common practice and frequently recommended as safe practices (Bader & Littlejohns 2010). Irritation of the gums or poor oral hygiene may result in a bleeding tendency of the gums (Jenkins 1989). While bleeding was noted more often in the standard oral care protocol, it is unclear if this was due to pre-existing poor oral hygiene, trauma caused by the tooth brushing, or a combination of both. No episode of oral care was terminated due to bleeding.

Oral Health

Intubated patients are unable to independently perform self care activities such as oral care making the oral hygiene by nursing staff essential. Progressive deterioration in oral health, to varying degrees, was noted during the time of intubation in the cohort and RCT. This finding supports the notion that oral health is difficult to maintain in light of exogenous and endogenous threats. However, the stable oral health scores in key areas of the OAG assessment, namely teeth, tongue, gingiva and mucous membrane among those enrolled in the comprehensive oral care protocol support the efficacy of a multi-faceted approach to oral hygiene.

The gingival margins and teeth have been well-documented as harborages of increasing dental plaque and the reservoir of pathogenic oral bacteria leading to oral malodor which can be reduced by brushing (Tashiro et al. 2011). The electric toothbrush has proven superior in debridement of dental plaque and development of plaque induced gingival inflammation (Goyal et al. 2007, Moritis et al. 2008) and the

disruption of soft plaque and oral debris most likely contributed to the improved scores in the categories of teeth and gingiva. Although few studies have explored the introduction of a powered toothbrush in the ICU, results have demonstrated superior removal of dental plaque (Needleman et al. 2011).

Overall tongue health was attributed to the twice daily tongue scraping and use of oral care products specifically formulated for xerostomia. Tongue scraping appeared effective in minimizing deterioration during intubation with stable OAG scores in the comprehensive care protocol. This was supported by the scores obtained in the category of odor where the only significant difference was between the last day of intubation and 48 hours post-extubation. Tongue coating has been found to support growth of VSC responsible for malodor (Yaegaki & Sanada 1992; Miyazaki et al. 1995). Although reliability of the tongue was suboptimal with Kendall W of 0.66/0.63 for Papers I and III respectively, significant differences between protocols were noted. Among those receiving the comprehensive protocol, tongue scores reflected small effect sizes during and after the time of intubation. These results can be interpreted with some degree of confidence since odor reflected only modest deterioration between admission and the last day of intubation, and no change in the item score when the admission and 48 hour post extubation scores were compared.

With non-foaming agents used in oral care, there was less debris and dryness noted in the mucous membranes. With decreased residue from traditional oral care products containing SLS, removal of toothpaste was easier and resulted in an overall improved mucous membrane health. It is not possible to identify which aspect of the comprehensive protocol was superior, but the combination of products resulted in stable or improved scores as one would expect. Since components of the mouth consist of soft and hard structures, it follows that a combination of products would yield superior results. As such it is surmised the toothbrush was related to the scores for teeth and gingiva, the moisturizers and non-foaming products for the mucous membranes, and the tongue scraper for the tongue integrity.

Fidelity to the oral care protocols exceeded 91% signifying that patients in both groups underwent the intervention of two minute tooth brushing twice daily. This frequency has been purported to be the standard for critical care yet effectiveness as measured by oral assessments has previously been lacking. Despite protocol compliance, among those enrolled in the standard protocol, deterioration occurred in all item scores of the OAG and none returned to baseline signifying the current standard may be substandard. Yet the Nursing Interventions Classification characterizes oral health maintenance as one of the nursing interventions needed by those unable to perform or complete oral hygiene activities for themselves (Dochterman & Bulechek 2004).

Two item scores of the OAG, swallow and lips, were not expected to differ over time in either protocol. Since all patients were intubated from admission thru the last day of intubation with concurrent administration of sedation affecting the gag reflex, swallow would have been moderately to maximally impaired with expected improvement following extubation. The lips underwent moisturizing in both arms of the group and

reflected similar deterioration and effect sizes in item scores over time were similar. This finding underscores the difficulty in maintaining moist lips while accommodating placement and securing the ETT.

Microbial flora and VAP

Dental plaque has been identified as a source in respiratory colonization of pathogenic organisms found among mechanically intubated patients diagnosed with VAP (El-Solh et al. 2004; Heo et al. 2008). With no specified oral care intervention, as in cohort study, progressive deterioration in oral health as measured by pathogenic oral flora was noted and exceeded results seen in both groups within the RCT. *S. aureus*, a common offending gram positive organism detected in dental plaque, is a main pathogen in VAP (Scannapieco et al. 1992; Fourrier et al. 1998). As reported in the cohort study, oral specimens with *S. aureus* reached a peak incidence of 36% by day four of intubation. This is in sharp contrast to a 5% occurrence among non-colonized patients enrolled in both protocols during the RCT on day four, and 30% and 0% in the standard and comprehensive protocol of those colonized during the RCT. *S. aureus* and has been found to be sensitive to applications of CHX (Koeman et al. 2006). The efficacy of CHX on *S. aureus* among 115 trauma ICU ventilated patients that received CHX compared to a placebo, was demonstrated by a significant reduction in dental plaque concentration of *S. aureus* in the treatment group (Scannapieco et al. 2009). Mouth care described only as four times daily topical application of 1% CHX gel was used as part of a VAP reduction strategy in a mixed medical-surgical ICU. Decreased VAP rates and incidence of *S. aureus* were reported but no information was provided on other aspects of oral care nor was there a reduction in ICU length of stay or duration of mechanical ventilation (Morris et al. 2011). Patients in the RCT that were colonized on admission and randomized to the comprehensive protocol had no oral colonization of *S. aureus* after the day of admission. This may be due to the fact that both groups within the RCT underwent a specified intervention resulting in less colonization over time yet comparisons are only speculative.

Accumulation of dental plaque begins with attachment of bacteria which bind to tooth enamel and results in cell aggregation of various bacteria (Addy et al. 1992). If left undisturbed, the initial plaque serves as a base for further colonization over three to four days and may contain upwards of 600 different bacterial species (Moore 1987; Dewhirst et al. 2010). Since the surface of the tooth provides a non-shedding host for bacteria and both groups of patients in the RCT underwent mechanical disruption of dental plaque, this may have accounted for the lower incidence of nosocomial bacteria reported during the RCT. Under normal circumstances, antibacterial properties of saliva together with the mechanical washing action of salivary flow contribute to bacterial clearance of pathogenic bacteria from the mouth (Mandel 1987). Intubation predisposes a patient to xerostomia and combined with the absence of oral intake and restricted tongue movements, can predispose a patient to xerostomia and accumulation of bacteria. However, the aggressive hydration protocol in the comprehensive protocol may have contributed to the stable scores in mucous membranes and tongue further adding to the lowered prevalence of oral pathogenic bacteria.

Furthermore, patients in both arms of the RCT that were not colonized on admission had colonization rates of 11% and 5% rates on days two and four of the study. This finding may support the notion that disruption of dental plaque biofilms may be effective as a strategy in decreasing *S. aureus* without the use of chemical rinses.

Twenty-five percent of patients were colonized on admission in both the cohort and RCT study (Paper IV). While it is unclear as to why patients would have been colonized on admission, aspiration from the time of insult or pre-existing poor oral health may have been a contributing factor. No exam for caries or loose teeth was made and conclusions drawn regarding such pathology on baseline oral health are lacking. The small sample size for both groups was a limiting factor in achieving any firm conclusions regarding the pathogenic flora or incidence of VAP. Yet results from the RCT suggest a trend of less colonization by nosocomial bacteria among patients randomized to the comprehensive oral care protocol.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Oral care should be performed in patients with ICP and CPP values within the clinically acceptable range. Provision of safe oral care for neuroscience patients was supported as demonstrated by intracranial monitoring. Minor fluctuations of ICP, with little clinical relevance, were demonstrated during and after recorded episodes of oral care.

Sustained CPP pressures of > 60 mm Hg were noted during and after oral care further supporting the safety of providing oral care in critically ill neuroscience patients.

The comprehensive oral care protocol demonstrated superiority to current published standards for ICU oral care protocols as measured by the OAG. The tongue scraper, electric toothbrush, non-foaming tooth paste, and oral moisturizers were most effective for oral hygiene during the time of intubation as evidenced by OAG item scores of tongue, teeth, gingiva, and mucous membranes and should be considered part of standard oral care for NICU patients.

The use of a tongue scraper as a part of comprehensive oral care, previously unreported in critical care oral protocols, was effective in preserving tongue hygiene as noted by the OAG item scores and supported by the reduction in odor compared to the standard protocol.

Among patients receiving comprehensive oral care, there was a trend of a decreased rate of conversion to oral nosocomial colonization. The incidence of VAP, however, was equivalent amongst the comprehensive and standard treatment group.

This thesis, while limited in scope to providing oral hygiene among intubated NICU patients, provides empirical support for oral assessments and safety in performing comprehensive oral care to maintain oral health during periods of intubation and mechanical ventilatory support.

FURTHER RESEARCH

The information gained from the research conducted as part of this thesis provides a platform for additional studies for clinicians, researchers, and policy makers. Given the medically critical and costly nature of infections caused by nosocomial organisms, the importance of comprehensive care as a route to reduce VAP and other infections cannot be under-stressed. Continued research regarding safety and efficacy of oral care protocols remain an important task in an era where level of care is assessed by its quality and cost to society.

The issue of safety requires further exploration to guide the oral care practices of critically ill patients with intracranial pathologies resulting in elevated and labile ICP, poor intracranial compliance, or both. Measures of ICP fluctuations, the rate of change of ICP during oral care or possible changes in clinical exam warrants further investigation. In patients with impaired autoregulation, as seen following hemorrhagic stroke, traumatic brain injury, or shock, the CPP may demonstrate alterations in flow not captured during this investigation and requires additional investigation.

Oral assessments need to be incorporated as part of routine care in all hospitalized patients. Assessments need to be sensitive to changes in oral health and reproducible over time. Psychometric testing of the OAG should be conducted to further discriminate measures of oral health and identify individuals that may require more intensive hygiene. As such, the OAG could be used to guide tailored, effective oral care.

Incorporation of oral hygiene products novel to the ICU setting, such as the electric toothbrush and tongue scraper, should be incorporated as part of the clinical armamentarium for preventive and maintenance care for intubated ICU patients. Use of a comprehensive protocol with therapeutically justified products should be explored for other ICU populations as well as the non-intubated patient with self-care deficits.

Introduction of other health care team members such as registered dental hygienists or dentists into the hospital setting should be explored. These providers have a place at the bedside for those patients who are admitted with destructive bony loss due to periodontal disease, facial trauma, extensive caries, and/or loose teeth for modifications to oral care protocols and heightened surveillance for systemic problems related to oral bacteria.

Future intervention trials need to incorporate long-term outcomes in oral health and care costs to aid in refinement of oral care protocols. Health care consumption costs should also be calculated as indicators of efficacy in future intervention trials. The one time cost of an electric tooth brush which can be used throughout the patient's hospitalization is significantly less than pre-packed daily oral care products with manual toothbrushes. These systems mandate daily charges to the patients' heath care cost and evidence to support their superiority is lacking. An effective, comprehensive oral care protocol may result in reduced health care costs in the treatment of VAP or

complications of poor oral hygiene. As the incidence of VAP is deemed a quality of care measure related to preventable hospital acquired infections and is not a health care reimbursement by some insurers in the United States, interventions to reduce the development of VAP serves to impact health care costs. Additional research is needed to identify cost-effective, safe and robust oral care interventions that can be applied to the complex milieu of the critical care setting.

ACKNOWLEDGEMENTS

This thesis was carried out at the Department of Nursing, Lund University. I wish to express my sincere gratitude to those who have been a lamp, a ladder, or a lifeboat during these past years of study:

- *Ingalill Rahm Hallberg* - the lessons I've learned from you extend beyond the covers of this book. You have taught me the meaning of *ad utrumque* and have been a true inspiration personally and professionally.
- *Stefan Renvert, Ulf Jakobsson, Peter Hagell and Albert Westergren* - who provided insights, constructive feedback, and challenges to thinking along the way as co-supervisors.
- *Robert Spetzler* and *Julie Ward* - for their unwavering support and gentle acceptance during my trips across the pond.
- *Cindy Kleiman* - for your contagious enthusiasm in the world of dental hygiene and keeping me flush with enough oral care products to last a lifetime.
- *Rick Sue, Pam Goslar, Omar Gonzalez, Ana Moran, Greg Ahern* - a team of selfless colleagues who provided scientific support, constructive feedback, and encouragement every step of the way.
- *Mary King, Manny Mejia, Madona Plueger* - thanks to your stalwart efforts throughout the RCT the entire project went smoother than one could have hoped for! You three were absolute superstars and made the experience fun!
- *Steev Mallon, Ina Reynolds, Charlotte Schiestel, Heidi Jahnke, Kristen Deshmukh* - for all the weekends you spent enrolling patients or looking in and smelling their mouths.
- *BNI APN Team* - for working harder while I was away at school and tolerating boxes of oral care supplies everywhere!
- *Shelley Kick, Marie Clarkson, Dawn Mutchler, and Jamie Canales* - for teaching the syntax of scientific writing, dotting i's, crossing t's and making pictures of oral health far more interesting than one could imagine...
- *Tess, Cindy, Steve* - who have been lifeboats! This journey would have been dismal without your laughter, love, and your resolute belief in me.
- *Mia* - a gal pal of gal pals, the Light of Lund! I am indebted to you for all the acts of generosity and kindness you so graciously gave.
- *Neurosurgical colleagues* - special thanks to Volker, Nick, Steve, Andrew, Yashar, Jay, and residents along the way.
- *JD, Linda, Jan, Starr, and Michele* - for all of your professional wisdom and personal kindnesses.
- *Juanita* - for all the support you've given and never complaining when asked to print 'just one more document'.
- *Mike Eimer* - thanks for keeping me connected to my files and the internet no matter where on the planet I was standing!

- *Anna Blomgren* - you have a great eye for detail and manage to help each of us as we pass thru the landscape of doctoral students! Många tack!
- *Molly Harrington* and *Nicole Galvan* - for finding every reference known to man and always sending them along with kindness!
- *Anna C, Irén, and fellow PhD students* in the 'landscape' - continued success to each of you during your own personal journey!
- *Brian, Bobby, Joyce, and Trish* - thanks for your support and understanding through the years.
- *Katie, Clare, Michael* – your tolerance amid the chaos these past years is a tribute to your character. A mother couldn't love her children any more than I love you.
- In deep appreciation to my parents whose sacrifices for education and examples of love have been the best lessons I've learned.
- This work was generously supported by grants from the Barrow Neurologic Foundation.

REFERENCES

Abidia RF (2007). "Oral care in the intensive care unit: a review." J Contemp Dent Pract **8**(1): 76-82.

A'Court C, and Garrard CS, (1992). "Nosocomial pneumonia in the intensive care unit: mechanisms and significance." Thorax **47**(6): 465-73.

Adams R (1996). "Qualified nurses lack adequate knowledge related to oral health, resulting in inadequate oral care of patients on medical wards." J Adv Nurs **24**(3): 552-60.

Addy M., Slayne MA, et al. (1992). "The formation and control of dental plaque--an overview." J Appl Bacteriol **73**(4): 269-78.

Alexander M (1971). "Biochemical ecology of microorganisms." Annu Rev Microbiol **25**: 361-92.

Allen GS, Ahn HS, et al. (1983). "Cerebral arterial spasm--a controlled trial of nimodipine in patients with subarachnoid hemorrhage." N Engl J Med **308**(11): 619-24.

American Association of Critical-Care Nurses. (2006). "Oral Care in the Critically Ill " Practice Alerts Retrieved March 7, 2008, 2008, from http://www.aacn.org/AACN/practiceAlert.nsf/vwdoc/pa2Oral Care in the Critically Ill - Issued

Amerongen A V, and Veerman EC, (2002). "Saliva--the defender of the oral cavity." Oral Dis **8**(1): 12-22.

Ames NJ (2011). "Evidence to support tooth brushing in critically ill patients." Am J Crit Care **20**(3): 242-50.

Andersson P, Hallberg IR, et al. (2002b). "Inter-rater reliability of an oral assessment guide for elderly patients residing in a rehabilitation ward." Spec Care Dentist **22**(5): 181-6.

Andersson P, Hallberg IR, et al. (2004). "Oral health problems in elderly rehabilitation patients." Int J Dent Hyg **2**(2): 70-7.

Andersson P, Persson L, et al. (1999). "Testing an oral assessment guide during chemotherapy treatment in a Swedish care setting: a pilot study." J Clin Nurs **8**(2): 150-8.

Andersson P, Westergren A, et al. (2002a). "Oral health and nutritional status in a group of geriatric rehabilitation patients." Scand J Caring Sci **16**(3): 311-8.

Bader JD, Shugars DA, et al. (2001). "A systematic review of selected caries prevention and management methods." Community Dent Oral Epidemiol **29**(6): 399-411.

Bader MK, and Littlejohns LR, Eds. (2010). AANN Core Curriculum for Neuroscience Nursing. Glenview, IL, AANN.

Bagg J, MacFarlane T, et al. (2006). Essentials of Microbiology for Dental Student. New York, Oxford University Press.

Bagyi K, Haczku A, et al. (2009). "Role of pathogenic oral flora in postoperative pneumonia following brain surgery." BMC Infect Dis **9**: 104.

Barkauskas VH, Baumann LC, et al. (2001). Health and physical assessment. St. Louis, Mosby.

Bartlett JG, O'Keefe P, et al. (1986). "Bacteriology of hospital-acquired pneumonia." Arch Intern Med **146**(5): 868-71.

Bauer TT, Ferrer R, et al. (2000). "Ventilator-associated pneumonia: incidence, risk factors, and microbiology." Semin Respir Infect **15**(4): 272-9.

Bayliss R., Clarke C, et al. (1983). "The teeth and infective endocarditis." Br Heart J **50**(6): 506-12.

Bearn DR, Aird JC, et al. (1996). "Index of Oral Cleanliness (I.O.C.). A new oral hygiene index for use in clinical audit." Br J Orthod **23**(2): 145-51.

Beauchamp T, and Childress J, (2001). Principles of biomedical ethics. New York, Oxford University Press.

Beck S (1979). "Impact of a systematic oral care protocol on stomatitis after chemotherapy." Cancer Nurs **2**(3): 185-99.

Benbadis SR, Wolgamuth BR, et al. (1995). "Value of tongue biting in the diagnosis of seizures." Arch Intern Med **155**(21): 2346-9.

Berry AM, and Davidson PM, (2006). "Beyond comfort: oral hygiene as a critical nursing activity in the intensive care unit." Intensive Crit Care Nurs **22**(6): 318-28.

Berry AM, Davidson PM, et al. (2011). "Effects of three approaches to standardized oral hygiene to reduce bacterial colonization and ventilator associated pneumonia in mechanically ventilated patients: a randomised control trial." Int J Nurs Stud **48**(6): 681-8.

Binkley C, Furr LA, et al. (2004). "Survey of oral care practices in US intensive care units." Am J Infect Control **32**(3): 161-9.

Blair KA, and Lapinski P, (2007). "Dysphagia in older adults." Adv Nurse Pract **15**(1): 45-6, 48.

Bland JM, and Altman DG, (1995). "Multiple significance tests: the Bonferroni method." BMJ **310**(6973): 170.

Blumenfeld H (2002). Neuroanatomy through clinical cases. Sunderland, Massachusetts, Sinauer Associates, Inc.

Boortz-Marx R (1985). "Factors affecting intracranial pressure: a descriptive study." J Neurosurg Nurs **17**(2): 89-94.

Brailsford S, and Beighton D, Eds. (2005). Oral infections. Oral care in advanced disease. New York, Oxford University Press.

Bratton SL, Chestnut RM, et al. (2007). "Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds." J Neurotrauma **24 Suppl 1**: S55-8.

Braunschweiger P, and Goodman K, (2007). "The CITI Program: An International Online Resource for Education in Human Subjects Protection and the Responsible Conduct of Research." Academic Medicine **82**: 861-864.

Briar C, Lasserson B, et al. (2003). Crash Course: Nervous System. St Louis, Mosby.

Bruya MA, and Madeira NP, (1975). "Stomatitis after chemotherapy." Am J Nurs **75**(8): 1349-52.

Buglass E A (1995). "Oral hygiene." Br J Nurs **4**(9): 516-9.

CDC (2004). "Guidelines for preventing health-care-associated pneumonia, 2003 recommendations of the CDC and the Healthcare Infection Control Practices Advisory Committee." Respir Care **49**(8): 926-39.

Chalmers JM, King PL, et al. (2005). "The oral health assessment tool--validity and reliability." Aust Dent J **50**(3): 191-9.

Chan EY, Lee YK, et al. (2011). "Translating evidence into nursing practice: oral hygiene for care dependent adults." Int J Evid Based Healthc **9**(2): 172-83.

Chastre J, and Fagon JY, (2002). "Ventilator-associated pneumonia." Am J Respir Crit Care Med **165**(7): 867-903.

Cohen J (1977). Statistical power analysis for the behavioral sciences. New York, Academic Press.

Cohen J (1988). Statistical power analysis for the behavioral sciences. Hillsdale, NJ, Earlbaum.

Cohn JL, and Fulton JS, (2006). "Nursing staff perspectives on oral care for neuroscience patients." J Neurosci Nurs **38**(1): 22-30.

Concato J, Shah N, et al. (2000). "Randomized, controlled trials, observational studies, and the hierarchy of research designs." N Engl J Med **342**(25): 1887-92.

Cook DJ, Walter SD, et al. (1998). "Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients." Ann Intern Med **129**(6): 433-40.

Coulter ID, Marcus M, et al. (1994). "Measuring oral health status: theoretical and methodological challenges." Soc Sci Med **38**(11): 1531-41.

Craven DE (2000). "Epidemiology of ventilator-associated pneumonia." Chest **117**(4 Suppl 2): 186S-187S.

Craven DE, De Rosa FG, et al. (2002). "Nosocomial pneumonia: emerging concepts in diagnosis, management, and prophylaxis." Curr Opin Crit Care **8**(5): 421-9.

Cutler CJ, and Davis N, (2005). "Improving oral care in patients receiving mechanical ventilation." Am J Crit Care **14**(5): 389-94.

Crosby C (1989). "Method in mouth care." Nurs Times **85**(35): 38-41.

Daley ML, Narayanan N, et al. (2008). "Stroke with subarachnoid hemorrhage: assessment of cerebrovascular pressure regulation and simulated cerebrovascular resistance." Acta Neurochir Suppl **102**: 321-5.

Davies RM, Davies GM, et al. (2003). "Prevention. Part 4: Toothbrushing: what advice should be given to patients?" Br Dent J **195**(3): 135-41.

Davis L (1992). "Instrument review: Getting the most from a panel of experts." Applied Nursing Research **5**: 194-197.

Dawes C (1996). Factors influencing salivary flow rate and composition. Saliva and oral health. W. Edgar and D. O'Mullane. London, British Dental Association**:** 27-41.

Day R (1993). "Mouth care in an intensive care unit: a review." Intensive Crit Care Nurs **9**(4): 246-52.

De Angelis CD, Drazen JM, et al. (2006). "Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors." Haematologica **91**(3): 293-5.

DeKeyser Ganz F, Fink NF, et al. (2009). "ICU nurses' oral-care practices and the current best evidence." J Nurs Scholarsh **41**(2): 132-8.

De Palma P, Frithiof L, et al. (2005). "Oral health of homeless adults in Stockholm, Sweden." Acta Odontol Scand **63**(1): 50-5.

Demmer RT, and Desvarieux M, (2006). "Periodontal infections and cardiovascular disease: the heart of the matter." J Am Dent Assoc **137 Suppl**: 14S-20S; quiz 38S.

Dennesen P, van der Ven A, et al. (2003). "Inadequate salivary flow and poor oral mucosal status in intubated intensive care unit patients." Crit Care Med **31**(3): 781-6.

Deshmukh J, Vandana KL, et al. (2006). "Clinical evaluation of an ionic tooth brush on oral hygiene status, gingival status, and microbial parameter." Indian J Dent Res **17**(2): 74-7.

DeWalt EM (1975). "Effect of timed hygienic measures on oral mucosa in a group of elderly subjects." Nurs Res **24**(2): 104-8.

DeWalt EM, and Haines AK, (1969). "The effects of specified stressors on healthy oral mucosa." Nurs Res **18**(1): 22-7.

Dewhirst FE, Chen T, et al. (2010). "The human oral microbiome." J Bacteriol **192**(19): 5002-17.

Dochterman J, and Bulechek G, (2004). Nursing interventions classification (NIC). St. Louis, Mosby.

Dudjak LA (1987). "Mouth care for mucositis due to radiation therapy." Cancer Nurs **10**(3): 131-40.

Eadie DR, and Schou L, (1992). "An exploratory study of barriers to promoting oral hygiene through carers of elderly people." Community Dent Health 9(4): 343-8.

Eilers J (2004). "Nursing interventions and supportive care for the prevention and treatment of oral mucositis associated with cancer treatment." Oncol Nurs Forum 31(4 Suppl): 13-23.

Eilers J, and Epstein JB, (2004). "Assessment and measurement of oral mucositis." Semin Oncol Nurs **20**(1): 22-9.

Eilers J, and Million R, (2007). "Prevention and management of oral mucositis in patients with cancer." Semin Oncol Nurs **23**(3): 201-12.

Eilers J, Berger AM, et al. (1988). "Development, testing, and application of the oral assessment guide." Oncol Nurs Forum **15**(3): 325-30.

El-Solh AA, Pietrantoni C, et al. (2004). "Colonization of dental plaques: a reservoir of respiratory pathogens for hospital-acquired pneumonia in institutionalized elders." Chest **126**(5): 1575-82.

Ely EW, Shintani A, et al. (2004). "Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit." JAMA 291(14): 1753-62.

Epstein JB, Emerton S, et al. (1999). "A double-blind crossover trial of Oral Balance gel and Biotene toothpaste versus placebo in patients with xerostomia following radiation therapy." Oral Oncol **35**(2): 132-7.

Ersson U, Carlson H, et al. (1990). "Observations on intracranial dynamics during respiratory physiotherapy in unconscious neurosurgical patients." Acta Anaesthesiol Scand **34**(2): 99-103.

Ewald C, Kuhn S, et al. (2006). "Pyogenic infections of the central nervous system secondary to dental affections--a report of six cases." Neurosurg Rev **29**(2): 163-6; discussion 166-7.

Feider LL, Mitchell P, et al. (2010). "Oral care practices for orally intubated critically ill adults." Am J Crit Care **19**(2): 175-83.

Ferguson L (2004). "External validity, generalizability, and knowledge utilization." J Nurs Scholarsh **36**(1): 16-22.

Field A (2005). Discovering statistics using SPSS. London, Sage.

Fitch JA, Munro CL, et al. (1999). "Oral care in the adult intensive care unit." Am J Crit Care **8**(5): 314-8.

Forsell M, Kullberg E, et al. (2011). "An evidence-based oral hygiene education program for nursing staff." Nurse Education in Practice **11**(4): 256-259.

Fourrier F, Duvivier B, et al. (1998). "Colonization of dental plaque: a source of nosocomial infections in intensive care unit patients." Crit Care Med **26**(2): 301-8.

Fowler EB, Breault LG, et al. (2001). "Periodontal disease and its association with systemic disease." Mil Med **166**(1): 85-9.

Furr LA, Binkley CJ, et al. (2004). "Factors affecting quality of oral care in intensive care units." Journal of Advanced Nursing **48**(5): 454-462.

Furrow B, Greaney T, et al. (2008). Bioethics: health care law and ethics. St. Paul, MN, Thomson West.

Garcia R, Jendresky L, et al. (2009). "Reducing ventilator-associated pneumonia through advanced oral-dental care: a 48-month study." Am J Crit Care **18**(6): 523-32.

Garvey L, Kroigaard HM, et al. (2007). "IgE-mediated allergy to chlorhexidine." J Allergy Clin Immunol 120(2): 409-15.

Gendron R, Grenier D, et al. (2000). "The oral cavity as a reservoir of bacterial pathogens for focal infections." Microbes Infect **2**(8): 897-906.

Gift HC, Atchison KA, et al. (1997). "Conceptualizing oral health and oral health-related quality of life." Soc Sci Med **44**(5): 601-8.

Givens E Jr. (2006). "Update on xerostomia: current treatment modalities and future trends." Gen Dent **54**(2): 99-101.

Goyal CR, Qaqish JG, et al. (2007). "Efficacy and safety of a new power toothbrush in a population with mild to moderate gingivitis." J Clin Dent **18**(3): 65-9.

Grap MJ, Munro CL, et al. (2003). "Oral care interventions in critical care: frequency and documentation." Am J Crit Care **12**(2): 113-8; discussion 119.

Grap MJ, Munro CL, et al. (2004). "Duration of action of a single, early oral application of chlorhexidine on oral microbial flora in mechanically ventilated patients: a pilot study." Heart Lung **33**(2): 83-91.

Greene JC, and Vermillion JR, (1971). "Oral hygiene research and implications for periodontal care." J Dent Res **50**(2): 184-93.

Greenman J, Duffield J, et al. (2004). "Study on the organoleptic intensity scale for measuring oral malodor." J Dent Res **83**(1): 81-5.

Greenman J, El-Maaytah M, et al. (2005). "Assessing the relationship between concentrations of malodor compounds and odor scores from judges." J Am Dent Assoc **136**(6): 749-57.

Greenwood M, and Meechan JG, (2003). "General medicine and surgery for dental practitioners Part 4: Neurological disorders." Br Dent J **195**(1): 19-25.

Haden NK, Catalanotto FA, et al. (2003). "Improving the oral health status of all Americans: roles and responsibilities of academic dental institutions: the report of the ADEA President's Commission." J Dent Educ **67**(5): 563-83.

Haffajee AD, Thompson M, et al. (2001). "Efficacy of manual and powered toothbrushes (I). Effect on clinical parameters." J Clin Periodontol 28(10): 937-46.

Hallberg IR, and Andersson P, (2011). Oral health and oral assessment. International Handbook of Assessment Tools for Nursing and Health Care Research (Internationales Handbuch für Pflegeforschung und -praxis). B. Reuschenbach and C. Mahler. Bern, Verlag Hans Huber**:** 253-270.

Halpern NA, and Pastores SM, (2010). "Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs." Crit Care Med 38(1): 65-71.

Hamamoto DT, and Rhodus NL, (2009). "Methamphetamine abuse and dentistry." Oral Dis **15**(1): 27-37.

Harrell JS, and Damon JF, (1989). "Prediction of patients' need for mouth care." West J Nurs Res **11**(6): 748-56.

Harris DJ, Eilers J, et al. (2008). "Putting evidence into practice: evidence-based interventions for the management of oral mucositis." Clin J Oncol Nurs **12**(1): 141-52.

Hayes J, and Jones CJ, (1995). "A collaborative approach to oral care during critical illness." Dental Health **34**(3).

Heanue M, Deacon SA, et al. (2003). "Manual versus powered toothbrushing for oral health." Cochrane Database Syst Rev(1): CD002281.

Hennekens C, and Buring J, (1987). Analysis of epidemiologic studies: evaluating the role of bias. Epidemiology in medicine. S. Mayrent. Boston, Mass, Little, Brown**:** 272-286.

Heo SM, Haase EM, et al. (2008). "Genetic relationships between respiratory pathogens isolated from dental plaque and bronchoalveolar lavage fluid from patients in the intensive care unit undergoing mechanical ventilation." Clin Infect Dis **47**(12): 1562-70.

Herlofson BB, and Barkvoll P, (1993). "Desquamative effect of sodium lauryl sulfate on oral mucosa. A preliminary study." Acta Odontol Scand **51**(1): 39-43.

Herlofson BB, and Barkvoll P, (1996). "The effect of two toothpaste detergents on the frequency of recurrent aphthous ulcers." Acta Odontol Scand **54**(3): 150-3.

Hickey JV (2009). The Clinical Practice of Neurological and Neurosurgical Nursing. Philadelphia, Lippincott Williams & Wilkins.

Hickey JV, Olson DM, et al. (2009). "Intracranial pressure waveform analysis during rest and suctioning." Biol Res Nurs **11**(2): 174-86.

Hlatky R, Valadka AB, et al. (2005). "Intracranial pressure response to induced hypertension: role of dynamic pressure autoregulation." Neurosurgery **57**(5): 917-23; discussion 917-23.

Hohlrieder M, Hinterhoelzl J, et al. (2004). "Maxillofacial fractures masking traumatic intracranial hemorrhages." Int J Oral Maxillofac Surg **33**(4): 389-95.

Holmes S, and Mountain E, (1993). "Assessment of oral status: evaluation of three oral assessment guides." Journal of Clinical Nursing **2**(1): 35-40.

Howarth H (1977). "Mouth care procedures for the very ill." Nurs Times **73**(10): 354-5.

Hsiang JK, Chesnut RM, et al. (1994). "Early, routine paralysis for intracranial pressure control in severe head injury: is it necessary?" Crit Care Med **22**(9): 1471-6.

Hsu SP, Liao CS, et al. (2011). "The effects of different oral care protocols on mucosal change in orally intubated patients from an intensive care unit." J Clin Nurs **20**(7-8): 1044-53.

Hulley SB, Cummings SR, et al. (2007). Designing Clinical research. Philadelphia, PA, Lippincott.

ICMJE (2004). "International Committee of Medical Journal Editors (ICMJE): Uniform Requirements for Manuscripts Submitted to Biomedical Journals: writing and editing for biomedical publication." Haematologica **89**(3): 264.

Jacomo AD, Carmona F, et al. (2011). "Effect of oral hygiene with 0.12% chlorhexidine gluconate on the incidence of nosocomial pneumonia in children undergoing cardiac surgery." Infect Control Hosp Epidemiol **32**(6): 591-6.

Jenkins D (1989). "Oral care in the ICU: an important nursing role." Nurs Stand **4**(7): 24-8.

Jones H (2005). "Oral care in intensive care units: a literature review." Spec Care Dentist **25**(1): 6-11.

Jones DJ, Munro CL, et al. (2010). "Oral care and bacteremia risk in mechanically ventilated adults." Heart Lung **39**(6 Suppl): S57-65.

Kanter MJ, and Robertson CS, (1990). "Measurement of intracranial pressure." Intensive Care World **7**(1): 16-9.

Kaste LM, and Bolden AJ, (1995). "Dental caries in homeless adults in Boston." J Public Health Dent **55**(1): 34-6.

Kau AL, Ahern PP, et al. (2011). "Human nutrition, the gut microbiome and the immune system." Nature **474**(7351): 327-36.

Kayser-Jones J, Bird WF, et al. (1995). "An instrument to assess the oral health status of nursing home residents." Gerontologist **35**(6): 814-24.

King TB, and Gibson G, (2003). "Oral health needs and access to dental care of homeless adults in the United States: a review." Spec Care Dentist **23**(4): 143-7.

Kintscher U, Hartge M, et al. (2008). "T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance." Arterioscler Thromb Vasc Biol 28(7): 1304-10.

Kirkness CJ, Burr RL, et al. (2009). "Intracranial and blood pressure variability and long-term outcome after aneurysmal sub-arachnoid hemorrhage." Am J Crit Care **18**(3): 241-51.

Koch SM, Fogarty S, et al. (1996). "Effect of passive range of motion on intracranial pressure in neurosurgical patients." J Crit Care **11**(4): 176-9.

Koeman M, van der Ven AJ, et al. (2006). "Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia." Am J Respir Crit Care Med **173**(12): 1348-55.

Kolenbrander PE (2000). "Oral microbial communities: biofilms, interactions, and genetic systems." Annu Rev Microbiol **54**: 413-37.

Kshirsagar AV, Moss KL, et al. (2005). "Periodontal disease is associated with renal insufficiency in the Atherosclerosis Risk In Communities (ARIC) study." Am J Kidney Dis **45**(4): 650-7.

Labeau S, and Blot S, Eds. (2011). Research Priorities in Oral Care for Endotracheally-intubated Patients. Annual Update in Intensive Care and Emergency Medicine 2011. New York, Springer.

Landis JR, and Koch GG, (1977). "The measurement of observer agreement for categorical data." Biometrics **33**(1): 159-74.

Lewis-Beck M (1995). Data analysis: an introduction. Thousand Oaks, California, Sage

Li M, Wang B, et al. (2008). "Symbiotic gut microbes modulate human metabolic phenotypes." Proc Natl Acad Sci U S A 105(6): 2117-22.

Li X, Kolltveit KM, et al. (2000). "Systemic diseases caused by oral infection." Clin Microbiol Rev **13**(4): 547-58.

Little J, Falace D, et al. (2008). Dental management of the medically compromised patient. St. Louis, Mosby.

Loe H, Theilade E, et al. (1965). "Experimental Gingivitis in Man." J Periodontol **36**: 177-87.

Locker D (1997). Concepts of Oral Health, Disease and the Quality of Life. Measuring Oral Health and Quality of Life, Chapel Hill: University of North Carolina, Department of Dental Ecology.

Lundberg N, Troupp H, et al. (1965). "Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. A preliminary report." J Neurosurg **22**(6): 581-90.

MRC (2000) A Framework for development and evaluation of RCTs for Complex Interventions to Improve Health. **Volume**, DOI:

Mager DL, Haffajee AD, et al. (2005). "The salivary microbiota as a diagnostic indicator of oral cancer: a descriptive, non-randomized study of cancer-free and oral squamous cell carcinoma subjects." J Transl Med **3**: 27.

Malkin B (2009). "The importance of patients' oral health and nurses'role in assessing and maintaining it." Nurs Times **105**(17): 19-23.

Mandel ID (1987). "The functions of saliva." J Dent Res **66 Spec No**: 623-7.

March K (2000). "Intracranial pressure monitoring and assessing intracranial compliance in brain injury." Crit Care Nurs Clin North Am 12(4): 429-36.

Marsh PD, and Devine DA, (2011). "How is the development of dental biofilms influenced by the host?" J Clin Periodontol **38 Suppl 11**: 28-35.

McCauley H (1946). "Toothbrushes, toothbrush materials and design." J Am Dent Assoc **33**: 283-93.

McDowell I, and Newell C, (1996). Measuring health: a guide to rating scales and questionnaires. New York, Oxford University Press.

McNeill HE (2000). "Biting back at poor oral hygiene." Intensive Crit Care Nurs **16**(6): 367-72.

Mealey BL, and Rose LF, (2008). "Diabetes mellitus and inflammatory periodontal diseases." Compend Contin Educ Dent **29**(7): 402-8, 410, 412-3.

Melnyk B, and Fineout-Overholt E, (2010). Evidence-based practice in nursing & healthcare: a guide to best practice. Philadelphia, Lippincott Williams &Wilkins.

Miller M, and Kearney N, (2001). "Oral care for patients with cancer: a review of the literature." Cancer Nurs **24**(4): 241-54.

Miller M, Taylor A, et al. (2007). "Evaluation of the feasibility and acceptability of an oral care diary by patients during chemotherapy." Int J Nurs Stud **44**(5): 693-701.

Milligan S, McGill M, et al. (2001). "Oral care for people with advanced cancer: an evidence-based protocol." Int J Palliat Nurs **7**(9): 418-26.

Miltner CC (1948). The elements of ethics. New York, The Macmillan Company.

Mitchell PH (1986). "Decreased adaptive capacity, intracranial: a proposal for a nursing diagnosis." J Neurosci Nurs **18**(4): 170-5.

Mitchell PH, and Mauss NK, (1978). "Relationship of patient-nurse activity to intracranial pressure variations: a pilot study." Nurs Res **27**(1): 4-10.

Mitchell PH, Ozuna J, et al. (1981). "Moving the patient in bed: effects on intracranial pressure." Nurs Res **30**(4): 212-8.

Mitscherlich A, and Mielke F, (1949). Doctors of infamy: the story of the Nazi medical crimes. New York, Schuman.

Miyazaki H, Sakao S, et al. (1995). "Correlation between volatile sulphur compounds and certain oral health measurements in the general population." J Periodontol **66**(8): 679-84.

Moher D, Schulz KF, et al. (2001). "The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials." Lancet **357**(9263): 1191-4.

Moore WE (1987). "Microbiology of periodontal disease." J Periodontal Res **22**(5): 335-41.

Moore K, and Dalley A, (2006). Clinically oriented anatomy. Philadelphia, Lippincott Williams & Wilkins.

Moritis K, Jenkins W, et al. (2008). "A randomized, parallel design study to evaluate the effects of a Sonicare and a manual toothbrush on plaque and gingivitis." J Clin Dent **19**(2): 64-8.

Morris AC, Hay AW, et al. (2011). "Reducing ventilator-associated pneumonia in intensive care: impact of implementing a care bundle." Crit Care Med **39**(10): 2218-24.

Mueller AA, Saldamli B, et al. (2009). "Oral bacterial cultures in nontraumatic brain abscesses: results of a first-line study." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **107**(4): 469-76.

Munro BH (2005). Statistical methods for health care research. Philadelphia, Lippincott Williams & Wilkins.

Munro CL, and Grap MJ, (2004). "Oral health and care in the intensive care unit: state of the science." Am J Crit Care **13**(1): 25-33; discussion 34.

Munro CL, Grap MJ, et al. (2006)a. "Oral health measurement in nursing research: state of the science." Biol Res Nurs **8**(1): 35-42.

Munro CL, Grap MJ, et al. (2006)b. "Oral health status and development of ventilator-associated pneumonia: a descriptive study." Am J Crit Care **15**(5): 453-60.

Mylonas AI, Tzerbos FH, et al. (2007). "Cerebral abscess of odontogenic origin." J Craniomaxillofac Surg **35**(1): 63-7.

Nagendran V, Wicking J, et al. (2009). "IgE-mediated chlorhexidine allergy: a new occupational hazard?" Occup Med (Lond) 59(4): 270-2.

Nakagawa K, Serrador JM, et al. (2011). "Dynamic cerebral autoregulation after intracerebral hemorrhage: A case-control study." BMC Neurol **11**: 108.

NANDA (2005). Nanda nursing diagnoses: Definitions and classification 2005-2006 Philadelphia, North American Nursing Diagnosis.

Needleman IG, Hirsch NP, et al. (2011). "Randomized controlled trial of toothbrushing to reduce ventilator-associated pneumonia pathogens and dental plaque in a critical care unit." J Clin Periodontol **38**(3): 246-52.

Neuwelt EA, Kikuchi K, et al. (1983). "Immune responses in patients with brain tumors. Factors such as anti-convulsants that may contribute to impaired cell-mediated immunity." Cancer 51(2): 248-55.

Norman GR, and Streiner DL, (2000). Biostatistics the bare essentials. Hamilton, BC Decker Inc.

Novak V, Chowdhary A, et al. (2003). "Altered cerebral vasoregulation in hypertension and stroke." Neurology **60**(10): 1657-63.

Olson DM, Thoyre SM, et al. (2007). "Changes in intracranial pressure associated with chest physiotherapy." Neurocrit Care **6**(2): 100-3.

Outhouse TL, Al-Alawi R, et al. (2006). "Tongue scraping for treating halitosis." Cochrane Database Syst Rev(2): CD005519.

Pace CC, and McCullough GH, (2010). "The association between oral microorgansims and aspiration pneumonia in the institutionalized elderly: review and recommendations." Dysphagia **25**(4): 307-22.

Paju S, and Scannapieco FA, (2007). "Oral biofilms, periodontitis, and pulmonary infections." Oral Dis **13**(6): 508-12.

Panchabhai TS, Dangayach NS, et al. (2009). "Oropharyngeal cleansing with 0.2% chlorhexidine for prevention of nosocomial pneumonia in critically ill patients: an open-label randomized trial with 0.01% potassium permanganate as control." Chest **135**(5): 1150-6.

Parsons LC, Peard AL, et al. (1985). "The effects of hygiene interventions on the cerebrovascular status of severe closed head injured persons." Res Nurs Health **8**(2): 173-81.

Pesonen E, Kaprio E, et al. (1981). "Endothelial cell damage in piglet coronary artery after intravenous administration of E. coli endotoxin. A scanning and transmission electron-microscopic study." Atherosclerosis **40**(1): 65-73.

Polit DF, and Beck CT, (2008). Nursing research: generating and assessing evidence for nursing practice. Philadelphia, Lippincott Williams & Wilkins.

Porter SR, and Scully C, (2000). "Adverse drug reactions in the mouth." Clin Dermatol **18**(5): 525-32.

Prasad K (1996). "The Glasgow Coma Scale: a critical appraisal of its clinimetric properties." J Clin Epidemiol **49**(7): 755-63.

Puri KS, Suresh KR, et al. (2009). "Declaration of Helsinki, 2008: implications for stakeholders in research." J Postgrad Med **55**(2): 131-4.

Rahamat-Langendoen JC, van Vonderen MG, et al. (2011). "Brain abscess associated with Aggregatibacter actinomycetemcomitans: case report and review of literature." J Clin Periodontol **38**(8): 702-706.

Ralph WJ (1987). "Hygiene of the tongue." Gerodontics **3**(4): 169-70.

Rams T, and Slots J, Eds. (1992). Systemic manisfestations of oral infections. Contemporary oral microbiology and immunology. St. Louis, MO, Mosby.

Rangel-Castilla L, Gasco J, et al. (2008). "Cerebral pressure autoregulation in traumatic brain injury." Neurosurg Focus **25**(4): E7.

Reinhard M, Neunhoeffer F, et al. (2010). "Secondary decline of cerebral autoregulation is associated with worse outcome after intracerebral hemorrhage." Intensive Care Med **36**(2): 264-71.

Rello J, Koulenti D, et al. (2007). "Oral care practices in intensive care units: a survey of 59 European ICUs." Intensive Care Med **33**(6): 1066-70.

Renvert S (2003). "Destructive periodontal disease in relation to diabetes mellitus, cardiovascular diseases, osteoporosis and respiratory diseases." Oral Health Prev Dent **1 Suppl 1**: 341-57; discussison 358-9.

Restrepo MI, Anzueto A, et al. (2010). "Economic burden of ventilator-associated pneumonia based on total resource utilization." Infect Control Hosp Epidemiol **31**(5): 509-15.

Riker RR, Picard JT, et al. (1999). "Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients." Crit Care Med **27**(7): 1325-9.

Rising CJ (1993). "The relationship of selected nursing activities to ICP." J Neurosci Nurs **25**(5): 302-8.

Roldan S, Herrera D, et al. (2003). "Biofilms and the tongue: therapeutical approaches for the control of halitosis." Clin Oral Investig **7**(4): 189-97.

Robinson PG, Deacon SA, et al. (2005). "Manual versus powered toothbrushing for oral health." Cochrane Database Syst Rev(2): CD002281.

Rosenberg M (1996). "Clinical assessment of bad breath: current concepts." J Am Dent Assoc **127**(4): 475-82.

Rosenberg M, and McCulloch CA, (1992). "Measurement of oral malodor: current methods and future prospects." J Periodontol **63**(9): 776-82.

Roth PT, and Creason NS, (1986). "Nurse administered oral hygiene: is there a scientific basis?" J Adv Nurs **11**(3): 323-31.

Rowley G, and Fielding K, (1991). "Reliability and accuracy of the Glasgow Coma Scale with experienced and inexperienced users." Lancet **337**(8740): 535-8.

Sabbatani S, Manfredi R, et al. (2004). "Capnocytophaga spp. brain abscess in an immunocompetent host: problems in antimicrobial chemotherapy and literature review." J Chemother **16**(5): 497-501.

Saito T, Oobayashi K, et al. (2008). "Association of dry tongue to pyrexia in long-term hospitalized patients." Gerontology **54**(2): 87-91.

Scannapieco FA (1999). "Role of oral bacteria in respiratory infection." J Periodontol **70**(7): 793-802.

Scannapieco FA, and Mylotte JM, (1996). "Relationships between periodontal disease and bacterial pneumonia." J Periodontol **67**(10 Suppl): 1114-22.

Scannapieco FA, Wang B, et al. (2001). "Oral bacteria and respiratory infection: effects on respiratory pathogen adhesion and epithelial cell proinflammatory cytokine production." Ann Periodontol **6**(1): 78-86.

Scannapieco FA, Yu J, et al. (2009). "A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients." Crit Care **13**(4): R117.

Scannapieco FA, Bush RB, et al. (2003). "Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review." Ann Periodontol **8**(1): 54-69.

Scheutz F (1984). "Dental health in a group of drug addicts attending an addiction-clinic." Community Dent Oral Epidemiol **12**(1): 23-8.

Schirmer-Mikalsen K, Vik A, et al. (2007). "Severe head injury: control of physiological variables, organ failure and complications in the intensive care unit." Acta Anaesthesiol Scand **51**(9): 1194-201.

Schweiger J, and Lang JW, (1981). "Oral care and assessment in the critical care setting." Crit Care Update **8**(11): 26-34.

Seidel HM, Ball JW, et al. (2006). Mosby's guide to physical examination. St. Louis, Mosby Elsevier.

Shadish WR, Cook TD, et al. (2002). Experimental and quasi-experimental designs for generalized causal inference. Boston, Houghton Mifflin Company.

Shahdad SA., Taylor C, et al. (2005). "A double-blind, crossover study of Biotene Oralbalance and BioXtra systems as salivary substitutes in patients with post-radiotherapy xerostomia." Eur J Cancer Care (Engl) **14**(4): 319-26.

Shaner J (2002). "Caries associated with methamphetamine abuse." J Mich Dent Assoc. **84**(9): 42-7.

Shay K (2002). "Infectious complications of dental and periodontal diseases in the elderly population." Clin Infect Dis **34**(9): 1215-23.

Shay K, Scannapieco FA, et al. (2005). "Nosocomial pneumonia and oral health." Spec Care Dentist **25**(4): 179-87.

Shifman A, Orenbuch S, et al. (2002). "Bad breath--a major disability according to the Talmud." Isr Med Assoc J **4**(10): 843-5.

Sicilia A, Arregui I, et al. (2002). "A systematic review of powered vs manual toothbrushes in periodontal cause-related therapy." J Clin Periodontol **29 Suppl 3**: 39-54; discussion 90-1.

Silness J, and Loe H, (1964). "Periodontal Disease in Pregnancy. Ii. Correlation between Oral Hygiene and Periodontal Condtion." Acta Odontol Scand **22**: 121-35.

Sjogren R, and Nordstrom G, (2000). "Oral health status of psychiatric patients." J Clin Nurs **9**(4): 632-8.

Slade G (1997). Measuring Oral Health and Quality of Life. Chapel Hill: University of North Carolina, Department of Dental Ecology.

Smith M (2008). "Monitoring intracranial pressure in traumatic brain injury." Anesth Analg **106**(1): 240-8.

Sole ML, Poalillo FE, et al. (2002). "Bacterial growth in secretions and on suctioning equipment of orally intubated patients: a pilot study." Am J Crit Care **11**(2): 141-9.

Sona CS, Zack JE, et al. (2009). "The impact of a simple, low-cost oral care protocol on ventilator-associated pneumonia rates in a surgical intensive care unit." J Intensive Care Med **24**(1): 54-62.

Song HK, and Jeong DC, (2004). "The effect of propofol on cytotoxicity and apoptosis of lipopolysaccharide-treated mononuclear cells and lymphocytes." Anesth Analg **98**(6): 1724-8, table of contents.

Sonis ST, Eilers JP, et al. (1999). "Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group." Cancer **85**(10): 2103-13.

Stefanc SJ, and Nesbit SP, (2007). Treatment planning in dentistry. Philadelphia, Mosby.

Sterer N, Greenstein RB, et al. (2002). "Beta-galactosidase activity in saliva is associated with oral malodor." J Dent Res **81**(3): 182-5.

Stiefel KA, Damron S, et al. (2000). "Improving oral hygiene for the seriously ill patient: implementing research-based practice." Medsurg Nurs **9**(1): 40-3, 46.

Stonecypher K (2010). "Ventilator-associated pneumonia: the importance of oral care in intubated adults." Crit Care Nurs Q **33**(4): 339-47.

Sumi Y, Kagami H, et al. (2003). "High correlation between the bacterial species in denture plaque and pharyngeal microflora." Gerodontology **20**(2): 84-7.

Sweeney P, Ed. (2005). Oral hygiene. Oral care in advanced disease. New York, Oxford University Press.

Szklo M, and Nieto J, (2007). Epidemiology: beyond the basics. Sudbury, MA, Jones and Bartlett.

Tablan O (2003). "Guidelines for Preventing Health-Care--Associated Pneumonia." Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee, from http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5303a1.htm.

Talbot A, Brady M, et al. (2005). "Oral care and stroke units." Gerodontology 22(2): 77-83.

Tantipong H, Morkchareonpong C, et al. (2008). "Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia." Infect Control Hosp Epidemiol **29**(2): 131-6.

Tashiro K, Katoh T, et al. (2011). "The short-term effects of various oral care methods in dependent elderly: comparison between toothbrushing, tongue cleaning with sponge brush and wiping on oral mucous membrane by chlorhexidine." Gerodontology.

Teasdale G, and Jennett B, (1974). "Assessment of coma and impaired consciousness. A practical scale." Lancet **2**(7872): 81-4.

Terezakis E, Needleman I, et al. (2011). "The impact of hospitalization on oral health: a systematic review." J Clin Periodontol **38**(7): 628-36.

Terezhalmy GT, Bartizek RD, et al. (2005). "Relative plaque removal of three toothbrushes in a nine-period crossover study." J Periodontol **76**(12): 2230-5.

Terpenning MS, Taylor GW, et al. (2001). "Aspiration pneumonia: dental and oral risk factors in an older veteran population." J Am Geriatr Soc **49**(5): 557-63.

Thompson IE (1987). "Fundamental ethical principles in health care." Br Med J (Clin Res Ed) **295**(6611): 1461-5.

Thurgood G (1994). "Nurse maintenance of oral hygiene." Br J Nurs **3**(7): 332-4, 351-3.

Tonzetich J (1977). "Production and origin of oral malodor: a review of mechanisms and methods of analysis." J Periodontol **48**(1): 13-20.

Tombes MB, and Gallucci B, (1993). "The effects of hydrogen peroxide rinses on the normal oral mucosa." Nurs Res **42**(6): 332-7.

Tortora G, Funke B, et al. (2006). Microbiology: An introduction. San Francisco, CA, Benjamin-Cummings.

Touger-Decker R, and Mobley CC, (2007). "Position of the American Dietetic Association: oral health and nutrition." J Am Diet Assoc **107**(8): 1418-28.

Treloar DM, and Stechmiller JK, (1995). "Use of a clinical assessment tool for orally intubated patients." Am J Crit Care **4**(5): 355-60.

Trieger N (2004). "Oral care in the intensive care unit." Am J Crit Care **13**(1): 24.

van der Weijden GA, Timmerman MF, et al. (1994). "The long-term effect of an oscillating/rotating electric toothbrush on gingivitis. An 8-month clinical study." J Clin Periodontol **21**(2): 139-45.

Viera AJ, and Garrett JM, (2005). "Understanding interobserver agreement: the kappa statistic." Fam Med **37**(5): 360-3.

Yewe-Dyer M (1993). "The definition of oral health." Br Dent J **174**(7): 224-5.

Warde P, Kroll B, et al. (2000). "A phase II study of Biotene in the treatment of postradiation xerostomia in patients with head and neck cancer." Support Care Cancer **8**(3): 203-8.

Wardh I, Hallberg LR, et al. (2000). "Oral health care--a low priority in nursing. In-depth interviews with nursing staff." Scand J Caring Sci **14**(2): 137-42.

Watt R (2002). "Emerging theories into the social determinants of health: implications for oral health promotion." Community Dent Oral Epidemiol **30**: 241-7.

Weed L, and Hughson W, (1921). "The Cerebrospinal Fluid in Relation to the Bony Encasement of the Central Nervous System as a Rigid Container." American Journal of Physiology **58**: 85-100.

Weinberger B (2005). An Introduction to the History of Dentistry: With Medical & Dental Chronology & Bibliographic Data. Eastford, CT, USA, Martino Publishing.

Westergren A, Hallberg IR, et al. (1999). "Nursing assessment of dysphagia among patients with stroke." Scand J Caring Sci 13(4): 274-82.

White H, and Venkatesh B, (2008). "Cerebral perfusion pressure in neurotrauma: a review." Anesth Analg **107**(3): 979-88.

Wilkin K (2002). "A critical analysis of the philosophy, knowledge and theory underpinning mouth care practice for the intensive care unit patient." Intensive Crit Care Nurs **18**(3): 181-8.

Wilson-Pauwels L, Akesson E, et al. (2002). Cranial Nerves. Hamilton, Ontario, BC Decker.

Wu HJ, Ivanov II, et al. (2010). "Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells." Immunity **32**(6): 815-27.

Xu J, Kochanek K, et al. (2010) Deaths: Final data for 2007. National Vital Statistics Reports **58**(18): 1-118.

Yaegaki K, and Sanada K, (1992). "Volatile sulfur compounds in mouth air from clinically healthy subjects and patients with periodontal disease." J Periodontal Res **27**(4 Pt 1): 233-8.

Yanko JR, and Mitcho K, (2001). "Acute care management of severe traumatic brain injuries." Crit Care Nurs Q **23**(4): 1-23.

Young JS, Blow O, et al. (2003). "Is there an upper limit of intracranial pressure in patients with severe head injury if cerebral perfusion pressure is maintained?" Neurosurg Focus **15**(6): E2.