

A Low-Sodium Solution for Airway Care: Results of a Multicenter Trial

Robert D Christensen MD, Erick Henry MPH, Vickie L Baer RN, Nhan Hoang PharmD,
Gregory L Snow PhD, Gorgi Rigby RRT, Jill Burnett RN, Susan E Wiedmeier MD,
Roger G Faix MD, and Larry D Eggert MD

BACKGROUND: Normal saline is sometimes instilled into the endotracheal tube preparatory to airway suctioning, to assist in removing thick secretions. However, saline can damage the antimicrobial properties of airway secretions. We previously described a low-sodium physiologically based solution for airway care and reported a small ($n = 60$) randomized trial in neonates, which showed trends toward less ventilator-associated pneumonia (VAP) and less chronic lung disease with the new solution. We now report a multicenter trial of that solution. **METHODS:** We conducted a before-and-after study with a parallel control group, in 4 level-3 neonatal intensive care units (NICUs). During year 1, all 4 NICUs used saline for airway care. During year 2, one NICU used the test solution exclusively while the other NICUs used saline exclusively. The 2 study outcomes were VAP (cases/1,000 ventilator days) and chronic lung disease, defined 3 ways: supplemental oxygen at 28 days; supplemental oxygen at 36 weeks gestation; and supplemental oxygen on hospital discharge. **RESULTS:** During the study period 1,116 neonates had endotracheal intubation for respiratory management. Of those, 1,029 received the standard saline for airway suctioning, and the 87 in NICU 4 received the test solution. NICU 4 had a decrease in VAP rate, from 4.2 VAPs/1,000 ventilator days with saline, to 1.6 VAPs/1,000 ventilator days with the test solution ($P = .04$), and also had the lowest prevalence of chronic lung disease ($P < .001$ for each definition). **CONCLUSIONS:** The test solution significantly reduced the VAP and chronic lung disease rates. *Key words:* nosocomial infection; saline; airway care; endotracheal tube; ventilator-associated pneumonia; sepsis; chronic lung disease. [Respir Care 2010;55(12):1680–1685. © 2010 Daedalus Enterprises]

Introduction

If liquid is instilled into the endotracheal tube (ETT) of a neonate, preparatory to ETT suctioning, sterile normal

(0.9%) saline is generally selected as that liquid.¹⁻⁵ Instilling saline before ETT suctioning is intended to enhance removal of thick secretions that can restrict gas flow through the tube.

One problem with using saline for airway care is the adverse affects of saline on the antimicrobial properties of airway secretions. Tracheal and nasal secretions and saliva contain natural antimicrobial substances that are damaged by high concentrations of sodium and chloride.⁶⁻¹⁵ One such substance is LL-37, a 37-amino-acid peptide with broad antimicrobial properties.^{6,16-18} We speculated that a solution patterned after unstimulated secretions would be

Robert D Christensen MD, Vickie L Baer RN, Nhan Hoang PharmD, Gorgi Rigby RRT, Jill Burnett RN, Susan E Wiedmeier MD, Roger G Faix MD, and Larry D Eggert MD are affiliated with the Women and Newborns Clinical Program, Intermountain Healthcare, Salt Lake City, Utah. Erick Henry MPH is affiliated with Intermountain Healthcare and the Institute for Healthcare Delivery Research, Salt Lake City, Utah. Gregory L Snow PhD is affiliated with the Statistical Data Center, LDS Hospital, Salt Lake City, Utah.

This research was partly supported by a grant from the Deseret Foundation, Salt Lake City, Utah.

The authors have disclosed no conflicts of interest.

Correspondence: Robert D Christensen MD, Neonatal Intensive Care, McKay-Dee Hospital Center, Intermountain Healthcare, 4403 Harrison Boulevard, Ogden UT 84403. E-mail: rdchris4@ihc.com.

better than saline. We devised a prototype solution and conducted 2 previous studies^{19,20} that suggested that the test solution was feasible to administer with no more patient intolerance than saline. In a 60-patient 2-center randomized double-masked trial, the recipients of the test solution had trends toward less VAP and less chronic lung disease (CLD).²⁰ The present study was intended to expand that work in a multicenter trial. We hypothesized that the test solution would lower the VAP and CLD rates.

Methods

Study Design

We selected a before-and-after study design with a parallel control group. All 4 intensive care units (NICUs) used standard saline for all airway care during a 12-month period (Period 1), then, during the subsequent 12 months (Period 2), one of the NICUs used the test solution exclusively, while the other 3 NICUs continued using saline. At the end of each month, a designated infection-control nurse at each NICU used a standardized VAP definition to determine the number of VAPs that month, and used a uniform reporting mechanism to report the VAP rate to the Intermountain Healthcare Women and Newborns Clinical Program.

Standard Saline and Test Solution

The standard liquid for airway care was normal saline (Cardinal Health, San Diego, California), which is dispensed in 5-mL plastic tubes. The test solution was produced in the hospital pharmacy of NICU 4. The composition of the test solution is: Na 7.8 mEq/L, K 24.5 mEq/L, Ca 3.67 mEq/L, Mg 1.2 mEq/L, Cl 36.3 mEq/L, PO₄ 3 mEq/L, SO₄ 1.2 mEq/L, albumin 1,940 mg/L. The test solution was sterilely compounded with the hospital's parenteral nutrition equipment, and was sent to NICU 4 in sterile, pyrogen-free syringes labeled "AIRWAY CARE STUDY SOLUTION." When a NICU patient no longer required any liquid for airway care (because he or she was extubated, had no nasal cannula, and needed no liquid for nasal care), the pharmacist did not send any additional airway care study solution to the bedside.

During Period 1, only saline was used for airway care (ie, suctioning of the ETT or nares). During Period 2, NICUs 1, 2, and 3 used only saline, whereas NICU 4 used only the test solution. No other liquids were used for airway care.

The Intermountain Healthcare Institutional Review Board approved the study. The informed-consent requirement was waived because the patient data was de-identified data and the study was part of standard quality-assurance activities.

Participating NICUs

Intermountain Healthcare is a not-for-profit organization that owns and manages 20 hospitals with labor and delivery services. The 4 NICUs in this study are the 4 largest NICUs in the Intermountain Healthcare system. Three are in large perinatal centers: McKay-Dee Hospital Center, Ogden, Utah (32-bed NICU); Intermountain Medical Center, Murray, Utah (48-bed NICU); and Utah Valley Regional Medical Center, Provo, Utah (39-bed NICU). The other is in Primary Children's Medical Center, Salt Lake City, Utah, which is the regional children's hospital (50-bed NICU). The 4 NICUs are all located within a 40-mile radius of Salt Lake City. The 3 perinatal centers care for neonates with a similar range of conditions, whereas the NICU at Primary Children's is the regional extracorporeal membrane oxygenation (ECMO) center and provides exclusive service for neonates requiring surgical and cardiac care.

Standardization of Respiratory Care Across the 4 NICUs

Guidelines for NICU respiratory care were developed to standardize and improve consistency of respiratory care across the Intermountain Healthcare NICUs. The respiratory therapy managers and medical directors of each NICU participated in developing these guidelines, and then instructed each NICU's staff on implementation. Guidelines were developed for: use of airway-care solutions in the trachea, nose, or mouth; closed suctioning of ETTs; obtaining tracheal aspirate for Gram stain and culture; reducing nosocomial infections; ventilator weaning and extubation; and diagnosing VAP. The 4 NICUs developed: a consistent approach to reducing line-associated infections; intubation/extubation guidelines; and oxygen saturation ranges. A consistent definition of VAP was in place in the 4 participating NICUs.

Calculation and Reporting of VAP and CLD

A designated infection-control nurse at each NICU used the standardized VAP definition to determine the number of VAPs each month. Based on the number of VAP cases and ventilator days for the month, the Women and Newborns Clinical Program staff calculated and archived each center's VAP rate each month. The CLD rate was calculated for each CLD definition: supplemental oxygen at 28 days; supplemental oxygen at 36 weeks gestation; and supplemental oxygen on hospital discharge. The individuals who collected the data and provided the monthly reports were not otherwise involved in the study.

Table 1. Admissions, Birth Weight, Gestational Age, and Sex of the Patients

NICU	Admissions (n) [*]		Birth Weight (mean g)			Gestational Age (mean wk)			Male (%)		
	Period 1	Period 2	Period 1	Period 2	P	Period 1	Period 2	P	Period 1	Period 2	P
1	460	506	2,536	2,436	.09	35.3	35.0	.23	58.6	56.8	.59
2	493	533	2,566	2,545	.73	34.9	34.9	.76	55.2	58.0	.38
3	659	624	2,390	2,440	.36	35.7	35.6	.98	61.6	58.0	.18
4	621	646	2,194	2,295	.06	33.8	34.2	.055	55.9	59.0	.27

* Admissions to the 4 Intermountain Healthcare neonatal intensive care units (NICUs).

Statistical Analysis

The de-identified data were entered into a spreadsheet (Excel 2003, Microsoft, Redmond, Washington) and analyzed with statistics software (SPSS 14.0, SPSS, Chicago, Illinois). No individual patient data were available for analysis, because the data were aggregated. Descriptive statistics were calculated with standard methods. The comparisons were via independent-samples *t* tests for continuous variables, chi-square for dichotomous variables, and the Mann-Whitney U test for non-parametrically distributed groups. The results were stratified based on birth weight, because the outcomes of interest (VAP and CLD rates) are generally more prevalent in infants with lower birth weight. We graphed the VAP data as an interrupted time series, which shows measurements taken over regular intervals, as described by Wagner et al.²¹ All tests were 2-sided, and an α of .05 was considered significant.

Results

There were no significant differences in birth weight, gestational age at birth, sex, or number of patients admitted to the NICUs between Period 1 (February 1, 2007, through January 31, 2008) and Period 2 (February 1, 2008, through January 31, 2009) (Table 1). The mean \pm SD numbers of patients admitted per month were: 42 \pm 8 in NICU 1, 42 \pm 8 in NICU 2, 53 \pm 12 in NICU 3, and 53 \pm 10 in NICU 4. There were no significant differences between the 2 periods in the percent of patients who received antenatal steroids, duration of hospital stay, or mortality rate. In Period 1, 2,233 neonates were admitted to the 4 NICUs, and of those 598 received endotracheal intubation and airway suctioning with saline. In Period 2, 2,309 neonates were admitted to the 4 NICUs, and of those 518 received endotracheal intubation and airway suctioning, 431 with saline and 87 with the test solution.

Table 2 shows the overall VAP rates. In the 4 NICUs combined, the VAP rate did not change between Period 1 (2.6 VAPs/1,000 ventilator days) and Period 2 (2.4 VAPs/

Table 2. Overall VAP Rates

NICU	VAP Rate [*] (mean and 95% CI)		P
	Period 1	Period 2	
1	2.0 (0.81–2.75)	3.1 (1.80–4.34)	.88
2	2.0 (1.01–3.09)	2.6 (1.41–3.74)	.79
3	2.2 (1.57–3.99)	2.6 (1.41–3.75)	.92
4	4.2 (2.74–5.72)	1.6 (0.70–2.55)	.04
Total	2.6 (1.48–3.85)	2.4 (1.35–3.65)	.93

* Cases per 1,000 ventilator days.

VAP = ventilator-associated pneumonia

NICU = neonatal intensive care unit

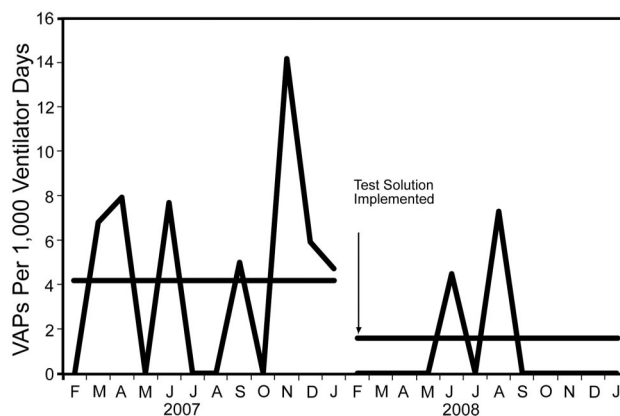


Fig. 1. Ventilator-associated pneumonia (VAP) cases per 1,000 ventilator days each month in neonatal intensive care unit 4, February 1, 2007, through January 31, 2009.

1,000 ventilator days). However, the VAP rate in NICU 4 (which used the test solution in Period 2) changed significantly, falling from the highest rate in the system in Period 1 (4.2 VAPs/1,000 ventilator days) to the lowest in the system in Period 2 (1.6 VAPs/1,000 ventilator days, *P* = .04). Figure 1 shows the monthly VAP rates at NICU 4. Table 3 shows the VAP rates according to birth weight and study group.

Tables 4, 5, and 6 show the proportions of NICU patients who developed CLD, under the 3 CLD definitions. The patients who received saline for airway care had a

Table 3. VAP Rate Relative to Birth Weight and Study Group

Birth Weight (g)	VAP Rate*		P
	Saline	Test Solution	
< 1,000	6.3	2.7	.04
1,000–1,500	1.1	0	.68
> 1,500	1.1	0	.41
Total	2.7	1.6	.72

* Cases per 1,000 ventilator days.
VAP = ventilator-associated pneumonia

Table 4. Chronic Lung Disease, Defined as Supplemental Oxygen at 28 Days After Birth, Relative to Birth Weight and Study Group

Birth Weight (g)	Saline		Test Solution		P
	(n)*	(%)	(n)	(%)	
< 1,000	169/399	42	20/63	32	.07
1,000–1,500	110/324	34	22/73	30	.32
> 1,500	183/3,171	6	5/510	1	< .001
Total	462/3,894	12	47/646	7	< .001

* Number of patients who developed chronic lung disease over number of patients admitted to the neonatal intensive care unit.
VAP = ventilator-associated pneumonia

Table 5. Chronic Lung Disease, Defined as Supplemental Oxygen at 36 Weeks Gestation, Relative to Birth Weight and Study Group

Birth Weight (g)	Saline		Test Solution		P
	(n)*	(%)	(n)	(%)	
< 1,000	147/399	37	18/63	29	.002
1,000–1,500	96/324	30	14/73	19	.046
> 1,500	332/3,171	10	14/510	3	< .001
Total	575/3,894	15	46/646	7	< .001

* Number of patients who developed chronic lung disease over number of patients admitted to the neonatal intensive care unit.
VAP = ventilator-associated pneumonia

Table 6. Chronic Lung Disease, Defined as Supplemental Oxygen After Discharge From the Hospital, Relative to Birth Weight and Study Group

Birth Weight (g)	Saline		Test Solution		P
	(n)*	(%)	(n)	(%)	
< 1,000	135/399	34	10/63	16	< .001
1,000–1,500	80/324	25	7/73	10	.002
> 1,500	330/3,171	10	10/510	2	< .001
Total	545/3,894	14	27/646	4	< .001

* Number of patients who developed chronic lung disease over number of patients admitted to the neonatal intensive care unit.
VAP = ventilator-associated pneumonia

higher prevalence of CLD than did those who received the test solution. The patients who weighed > 1,500 g at birth had the greatest test-solution-associated improvement in CLD prevalence.

The number of days mechanical ventilation did not significantly differ between the saline and test-solution groups. The patients who weighed < 1,000 g at birth and were treated with saline had a median of 22 days (range 1–127 d) of mechanical ventilation, versus 12 days (range 2–65 d) in those treated with the test solution ($P = .31$). The patients who weighed > 1,500 g at birth treated and were treated with saline received mechanical ventilation for a median of 3 days (range 1–105 d), versus 3 days (range 1–10 d) in those treated with the test solution ($P = .46$).

Discussion

Consistent with our previous findings in a small ($n = 60$), 2-center, randomized trial,²⁰ the recipients of the test solution appeared to benefit, with lower rates of VAP and CLD than those treated with the standard normal saline.

More investigation is needed to determine the benefits and the risks of instilling this or other solutions into the airways of NICU patients, as a means of facilitating airway suctioning.^{6–15} Many NICU nosocomial infections are with organisms considered to be of low virulence in healthy adults, such as *Candida albicans* and coagulase-negative staphylococcus.²² Low concentrations of immunoglobulin A and immunoglobulin G, and other developmental immunodeficiencies probably predispose preterm neonates to such infections.²³ Irritation of the airway endothelium by tubes in the trachea, nose, or mouth probably also contribute. In addition, instilled saline weakens the patient's microbial defenses.

The type and quantity of liquid instilled before ETT suctioning are matters of ongoing discussion and study.^{1–4} Kinloch suggested not instilling any liquid,³ but the studies by Caruso et al in adult patients suggested that saline instillation is better than dry suctioning.²⁴ It seems to us that most neonates intubated for several days will have at least occasional liquid instillation, and that liquid is always saline.²⁰ Based on our present and previous trials, we speculate that a physiologically based low-sodium solution is better than saline.^{19,20}

Limitations

Our study design was less rigorous and less informative than a randomized, double-masked trial,²⁵ but we selected this design for what we considered a sound reason. We learned from our previous randomized trial²⁰ that all study subjects received saline for airway care during their first

day following birth, because it required about one day to give parents the study information, for them to make a decision about study entry, and to bring the study solution to the bed-side for use. We speculate that this confounding aspect limited the value of the test solution, since it was never used as the initial and sole treatment. The present study design removed that confounder, in that all airway care was always with only one solution or the other. An additional design criticism is that the available grant funding to produce the test solution limited its use to only one NICU; the study would have benefited from using the test solution in more than one NICU.

Another limitation in our study is that changes in our clinical practices, other than the airway solution, might have affected respiratory outcomes in NICU 4 during Period 2. Prior to Period 1, we attempted to minimize that possibility by standardizing our respiratory care practices to reduce nosocomial infections in all the NICUs (the latter effort was headed by RGF). But we realize that unknown factors might be responsible for the improved respiratory outcomes in NICU 4, which we tentatively ascribe to the test solution.

Another limitation is that the VAP data were de-identified, which was required by privacy concerns. The numbers of VAP cases and ventilator days were tabulated by infection-control nurses who were not involved as study investigators, and we collected the overall patient demographics in each hospital each month but were unable to link each VAP case back to the clinical information. Consequently, we have meaningful data about the VAP and CLD rates, but we could not engage in multivariate analysis.

Another limitation is that we restricted our testing to only the pre-suctioning liquid, but we recognize that other approaches to VAP reduction might produce equal or greater benefit. Other new VAP-reduction approaches include silver-coated ETTs²⁶ and means of reducing aspiration around the ETT.²⁷

Conclusions

Despite the deficiencies in our study, we interpret the findings as an advance in knowledge over our previous phase I and II studies,^{19,20} and encouraging toward our overall efforts to reduce the prevalence of VAP and CLD in neonatal patients.

ACKNOWLEDGMENTS

We thank Diane K Lambert RN, Daniel Woodhead RT, Scott Scofield PharmD, Tracy Karp MSc NNP-BC, Robert Muelleck RPh MBA, and Karla Snow PharmD, all of Intermountain Healthcare, Salt Lake City, Utah, for valuable assistance.

REFERENCES

1. Pedersen CM, Rosendahl-Nielsen M, Hjermand J, Egerod I. Endotracheal suctioning of the adult intubated patient—what is the evidence? *Intensive Crit Care Nurs* 2009;25(1):21-30.
2. Trawogger R, Kolobow T, Cereda M, Giacomini M, Usuki J, Horiba K, Ferrans VJ. Clearance of mucus from endotracheal tubes during intratracheal pulmonary ventilation. *Anesthesiology* 1997;86(6):1367-1374.
3. Kinloch D. Instillation of normal saline during endotracheal suctioning: effects on mixed venous oxygen saturation. *Am J Crit Care* 1999;8(4):231-240.
4. Lindgren S, Almgren B, Hogman M, Lethvall S, Houtz E, Lundin S, Stenqvist O. Effectiveness and side effects of closed and open suctioning: an experimental evaluation. *Intensive Care Med* 2004;30(8):1630-1637.
5. Cunha-Goncalves D, Perez-de-Sa V, Ingimarsson J, Werner O, Larsson A. Inflation lung mechanics deteriorates markedly after saline instillation and open endotracheal suctioning in mechanically ventilated healthy piglets. *Pediatr Pulmonol* 2007;42(1):10-14.
6. Doss M, White MR, Teale T, Hartshorn KL. Human defensins and LL-37 in mucosal immunity. *J Leukocyte Biol* 2010;87(1):79-92.
7. Goldman MJ, Anderson GM, Stolzenberg ED, Kari UP, Zasloff M, Wilson JM. Human-defensin-1 is a salt-sensitive antibiotic in lung that is inactivated in cystic fibrosis. *Cell* 1997;88(4):553-560.
8. Smith JJ, Travis SM, Greenberg EP, Welsh MJ. Cystic fibrosis airway epithelia fail to kill bacteria because of abnormal airway surface fluid. *Cell* 1996;85(2):229-236.
9. Zabner J, Sieler MP, Launspach JL, Karp PH, Kearney WR, Look DC, et al. The osmolyte xylitol reduces the salt concentration of airway surface liquid and may enhance bacterial killing. *Proc Natl Acad Sci USA* 2000;10:97(21):11614-11619.
10. Zabner J, Smith JJ, Karp PH, Widdicombe JH, Welsh MJ. Loss of CFTR chloride channels alters salt absorption by cystic fibrosis airway epithelia in vitro. *Mol Cell* 1998;2(3):397-403.
11. Singh PK, Tack BF, McCray PB, Welsh M. Synergistic and additive killing by antimicrobial factors found in human airway surface liquid. *Am J Physiol Lung Cell Mol Physiol* 2000;279(5):L799-L805.
12. Travis SM, Conway BA, Zaabner J, Smith JJ, Anderson NN, Singh PK, et al. Activity of abundant antimicrobials of the human airway. *Am J Respir Cell Mol Biol* 1999;20(5):872-879.
13. Herr C, Shaykhev R, Bals R. The role of cathelicidin and defensins in pulmonary inflammatory diseases. *Expert Opin Biol Ther* 2007;7(9):1449-1461.
14. Ganz T. Antimicrobial polypeptides in host defense of the respiratory tract *J Clin Invest* 2002;109(6):693-697.
15. Bals R, Wilson JM. Cathelicidins: a family of multifunctional antimicrobial peptides. *Cell Mol Life Sci* 2003;60(4):711-720.
16. Wang Y, Walter G, Herting E, Agerberth B, Johansson J. Antibacterial activities of the cathelicidins prophenin (residues 62 to 79) and LL-37 in the presence of a lung surfactant preparation. *Antimicrob Agents Chemother* 2004;48(6):2097-2100.
17. Putsep K, Carlsson G, Boman HG, Anderson M. Deficiency of antibacterial peptides in patients with morbus Kostmann: an observational study. *Lancet* 2002;360(3940):1144-1149.
18. Cirioni O, Ghiselli R, Tomasinsig L, Orlando F, Silvestri C, Skerlavaj B, et al. Efficacy of LL-37 and granulocyte colony-stimulating factor in a neutropenic murine sepsis due to *Pseudomonas aeruginosa*. *Shock* 2008;30(4):443-448.
19. Woodhead DD, Lambert DK, Scofield S, Snow G, Baer V, Christensen RD. Feasibility and preliminary safety study of a new physiologically based solution for upper airway care in the neonatal intensive care unit. *Neo Int Care* 2006;19:29-33.

20. Christensen RD, Rigby G, Schmutz N, Lambert DK, Wiedmeier SE, Burnett J, et al. ETCare: a randomized, controlled, masked trial comparing two solutions for upper airway care in the NICU. *J Perinatol* 2007;27(8):479-484.
21. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Therapeut* 2002;27(4):299-309.
22. Carey AJ, Saiman L, Polin RA. Hospital-acquired infections in the NICU: epidemiology for the new millennium. *Clin Perinatol* 2008;35(1):223-249.
23. Strunk T, Richmond P, Simmer K, Currie A, Levy O, Burgner D. Neonatal immune responses to coagulase-negative staphylococci. *Curr Opin Infect Dis* 2007;20(4):370-375.
24. Caruso P, Denari S, Ruiz SA, Demarzo SE, Dehinzelin D. Saline instillation before tracheal suctioning decreases the incidence of ventilator-associated pneumonia. *Crit Care Med* 2009;37(1):32-38.
25. Murray DM, Varnell SP, Blitstein JL. Design and analysis of group-randomized trials: a review of recent methodological developments. *Am J Public Health* 2004;94(3):423-432.
26. Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, et al. on behalf of the NASCENT Investigation Group. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia. *JAMA* 2008;300(7):805-813.
27. Fletcher AJW, Ruffell AJ, Young PJ. The LoTrach™ system: its role in the prevention of ventilator-associated pneumonia. *Nurs Crit Care* 2008;13(5):260-268.