

A Randomized Clinical Trial of Intermittent Subglottic Secretion Drainage in Patients Receiving Mechanical Ventilation*

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Objective: To study the effect of subglottic secretions drainage on the incidence of ventilator-associated pneumonia (VAP) in patients receiving mechanical ventilation.

Design: A randomized clinical trial.

Setting: A 12-bed general ICU.

Patients: One hundred fifty patients with an expected duration of mechanical ventilation > 72 h were enrolled in the study.

Intervention: Patients were randomly assigned to receive either an endotracheal tube for intermittent subglottic secretions drainage or a standard endotracheal tube.

Outcome measurements: Incidence of VAP, duration of mechanical ventilation, length of ICU stay, length of hospital stay, and mortality.

Results: Seventy-five patients were randomized to subglottic secretion drainage, and 75 patients were randomized to the control group. The two groups were similar at the time of randomization with respect to demographic characteristics and severity of illness. VAP was seen in 3 patients (4%) receiving suction secretion drainage and in 12 patients (16%) in the control group (relative risk, 0.22; 95% confidence interval, 0.06 to 0.81; $p = 0.014$). The other outcome measures were not significantly different between the two groups.

Conclusion: Intermittent subglottic secretion drainage reduces the incidence of VAP in patients receiving mechanical ventilation. (*CHEST* 2002; 121:858–862)

Key words: aspiration; intubation; mechanical ventilation; subglottic secretion drainage; ventilator-associated pneumonia

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; RR = relative risk; VAP = ventilator-associated pneumonia

Nosocomial infections represent a major problem in hospitals because of the excess morbidity, mortality, and costs.^{1–3} Ventilator-associated pneumonia (VAP) in particular is associated with an increase in morbidity and mortality.^{4–6} The incidence of VAP ranges from 9 to 68% depending on the patient population.⁷ VAP that occurs within 48 h after tracheal intubation is termed *early-onset pneu-*

monia and often results from aspiration during intubation.⁸ VAP that occurs after 48 h is defined as *late-onset pneumonia*.^{9–11}

In the pathogenesis of VAP, two processes are considered essential for its development: bacterial colonization of the oropharynx and tracheobronchial

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tract, followed by aspiration of contaminated secretions into the lower airways.^{12–23} It has been shown that the presence of an endotracheal tube also facilitates bacterial colonization of the tracheobronchial tree.^{14–16}

Several studies^{14–18} have shown that pooled secretions above inflated endotracheal tube cuffs may be a source of aspiration and can be the cause of VAP. It has been suggested that chronic aspiration of subglottic secretions can be prevented by changing

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body position or by intermittent drainage of subglottic secretions.¹²⁻¹⁵ We performed a randomized trial to study the incidence of VAP in patients receiving mechanical ventilation for > 72 h, in which we compared an endotracheal tube with a dorsal lumen for intermittent drainage of subglottic secretions (Hi-Lo Evac; Mallinckrodt; Athlone, Ireland¹⁴) with a conventional endotracheal tube.

MATERIALS AND METHODS

Study Protocol

The study was performed in a 12-bed general ICU at the Bosch Medical Center, 's-Hertogenbosch, the Netherlands. The study protocol was reviewed and approved by the medical ethical committee of the hospital. Between May 1999 and June 2000, we studied 150 patients admitted to our ICU and expected to receive mechanical ventilation for > 72 h. Randomization was performed by drawing a card from a sealed envelope. The study group received an oral endotracheal tube with the possibility of intermittent subglottic secretions drainage. The control group received an oral conventional endotracheal tube. Informed consent was obtained from the nearest relative. We used intermittent instead of continuous subglottic drainage because continuous suction with 100 mg Hg may damage the tracheal wall. Intermittent suctioning was performed with a 20-s interval and duration of 8 s. All patients received stress ulcer prophylaxis with sucralfate.

Our standard protocol for infection prevention in patients receiving mechanical ventilation includes changes in body position from the left to the right decubitus position every 4 h, and routine endotracheal suction every 4 h or with an increase in airway resistance or audible or visible secretions in the endotracheal tube. Routine use of the semirecumbent position or selective decontamination of the digestive tract were not in place. Formal cuff pressures were not measured, but sealing of the endotracheal wall by the cuff was controlled every 4 h as a routine measure in our department. The cuff was inflated until no audible air leak occurred.

Data Collection

The following data were recorded: demographics, primary reason for ICU admission, APACHE (acute physiology and chronic health evaluation) II score,²⁴ presence of infection on hospital admission, antibiotic use, and risk factors for VAP (previous surgery, trauma, history of COPD, antibiotics at randomization, APACHE II score and stress ulcer prophylaxis). Outcome measures were incidence of VAP, duration of mechanical ventilation, length of ICU stay, length of hospital stay, and mortality on the ICU.

Microbiological Analysis and Monitoring

On admission to the ICU, surveillance cultures for aerobic microorganisms in the subglottic secretion were obtained from all patients in the study group. A tracheobronchial sample was obtained by tracheobronchial suction in the first 24 h in all patients using an aseptic catheter with a mucus collector. Throughout the ventilation period, tracheobronchial samples were obtained twice weekly.

The diagnostic criteria of VAP were adapted from criteria

established by the American College of Chest Physicians. We did not include BAL fluid cultures in the criteria because routine sampling of lower-airway secretions by bronchoscope is not performed in our unit.²⁵⁻²⁷ VAP was diagnosed when a new or progressive radiographic infiltrate developed in conjunction with either radiographic evidence for cavitation, histologic evidence of pneumonia, a positive blood culture finding without other source evidence of infection, a positive pleural fluid culture finding, or with any two of the following symptoms or signs: fever (increase in rectal temperature > 38.0°C), leukopenia, or leukocytosis or a purulent tracheal aspirate. Leukopenia and leukocytosis were defined as a leukocyte counts < 3 × 10⁶/L and > 10 × 10⁶/L, respectively. Tracheal secretions were considered purulent when the aspirate showed > 25 leukocytes per field. A radiologist blinded to the group assignment interpreted all chest radiographs.

Statistical Analysis

Analysis was performed with the statistical software (SPSS version 10.0 for Windows; SPSS; Chicago, IL). We used the Student's *t* test or Mann-Whitney test for continuous variables, and χ^2 test for categorical variables. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated.²⁸ The random-sample size was based on a power of 80% with a 15% reduction of the cumulative incidence of VAP. Survival analysis was used to calculate the probability of the development of nosocomial pneumonia during mechanical ventilation.²⁹

RESULTS

Total Study Population

Over a period of 13 months, 150 patients were enrolled in the study. The demographic data of the total study population are shown in Table 1. The two groups were similar in age, demographic character-

Table 1—Demographic Data of the Total Patient Population*

Characteristics	Subglottic Drainage (n = 75)	Control Group (n = 75)	p Value
Age, yr	63.7 ± 13.2	62.8 ± 15.6	NS
Gender			
Male	42 (56)	41 (55)	NS
Female	33 (44)	34 (45)	NS
APACHE II score	23.1 ± 7.6	22.3 ± 8.6	NS
Risk factors for VAP			
COPD	20 (27)	18 (24)	NS
Use of antibiotics at randomization	36 (48)	38 (51)	NS
Previous surgery	43 (57)	46 (61)	NS
Trauma	8 (11)	9 (12)	NS
Stress ulcer prophylaxis	62 (83)	65 (87)	NS
Reason for intubation			
Acute respiratory failure	51 (68)	49 (65)	NS
Neurologic disease	5 (6)	7 (9)	NS
Trauma	8 (11)	9 (12)	NS
Cardiac failure	11 (15)	10 (13)	NS

*Data are presented as mean ± SD or No. (%). NS = not significant.

istics, severity of illness on hospital admission, and underlying diseases. Fifteen patients (10%) had VAP develop, yielding a rate of 15.6 episodes of VAP per 1,000 ventilator-days. Three patients (4%) in the study group and 12 patients (16%) in the control group had VAP develop (RR, 0.22; 95% CI, 0.06 to 0.81; $p = 0.014$; Table 2). No significant differences were found in duration of mechanical ventilation, length of ICU stay, length of hospital stay, and mortality (Table 2). All patients with a diagnosis of VAP were treated with antibiotics.

Patients Receiving Mechanical Ventilation for > 72 h

Of the 150 patients, 42 patients (28%) were received mechanical ventilation < 72 h for the following reasons: early extubation (37 patients) or death (5 patients). Furthermore, three patients had pneumonia develop within 72 h. Of the 105 remaining patients receiving mechanical ventilation, 49 patients (46.7%) were randomized to the study group and 56 patients (53.3%) were randomized to the control group. Outcome measures are shown in Table 3. Five patients in the control group and two patients in the study group had pneumonia develop in the first week of hospital admission. The diagnosis of VAP in the other patients was made at a later time. Figure 1 provides the Kaplan-Meier curves comparing the onset of VAP in the two groups. Survival analysis and log-rank test indicated no significant differences ($p > 0.05$). Thirty-six patients (48%) in the study group and 38 patients (51%) in the control group received antibiotics at randomization. These antibiotics were usually administered for surgical prophylaxis.

Culture Data

In every case, the development of VAP was preceded by isolation of the infecting microorganism

Table 2—Clinical Outcome in All Randomized Patients*

Variables	Secretion Drainage (n = 75)	Control Group (n = 75)	p Value
VAP	3 (4)	12 (16)	0.014
Incidence rate†	9.2	22.5	< 0.001
Duration of mechanical ventilation, d	5.8 ± 4.4	7.1 ± 5.4	NS
Length of ICU stay, d	9.3 ± 7.4	12.3 ± 3.6	NS
Length of hospital stay, d	26.8 ± 23.3	28.3 ± 28.2	NS
Mortality	12 (16)	10 (13.3)	NS

*Data are presented as mean ± SD or No. (%) unless otherwise indicated. See Table 1 for expansion of abbreviation.

†Episodes of pneumonia per 1,000 ventilator days.

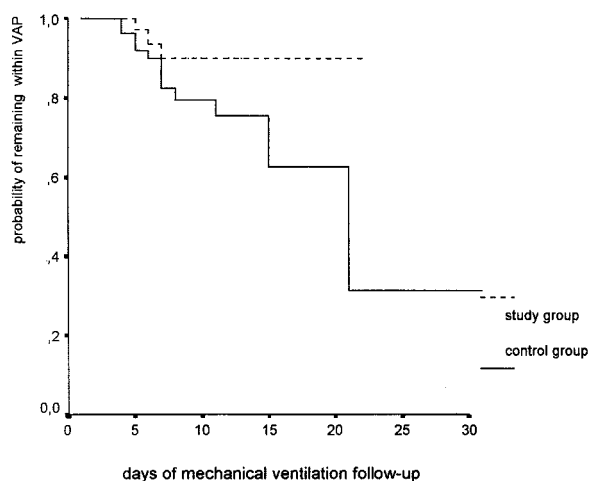
Table 3—Patient Characteristics and Clinical Outcome in Patients Receiving Mechanical Ventilation for > 72 h*

Variables	Secretion Drainage (n = 49)	Control Group (n = 56)	p Value
VAP	2 (4.1)	10 (17.9)	0.029
Incidence rate†	6.4	21.3	< 0.001
Duration of mechanical ventilation, d	7.9 ± 9.7	7.1 ± 3.4	NS
Length of ICU stay, d	11.9 ± 8.8	14.2 ± 11.1	NS
Length of hospital stay, d	32.1 ± 25.1	32.8 ± 31.6	NS
Mortality	9 (18)	10 (18)	NS

*Data are presented as mean ± SD or No. (%) unless otherwise indicated. See Table 1 for expansion of abbreviation.

†Episodes of pneumonia per 1,000 ventilator-days.

from the tracheal aspirate. Isolates had the same antibiotic susceptibilities, although phage typing or molecular typing was not performed. A total of 65% of all aspirates yielded polymicrobial cultures with several different pathogenic microorganisms (Table 4). Two patients with subglottic drainage had VAP develop. One patient had infection with *Pseudomonas aeruginosa* in combination with *Klebsiella pneumoniae*; the other patient had infection with *Staphylococcus aureus*. The following organisms were isolated from the 10 patients with VAP in the control group: *S aureus* (n = 3), *P aeruginosa* (n = 3), *Streptococcus pneumoniae* (n = 2), *Escherichia coli* with *Haemophilus influenzae* (n = 1), and yeast (n = 1).



Patients with subglottic secretion drainage

N = 49 34 16 5 2 0

Patients in control group

N = 56 44 24 10 7 4

FIGURE 1. Proportion of patients remaining without VAP in the two groups. Numbers at the bottom indicate intubated patients remaining without VAP.

Table 4—Bacterial Isolates in Tracheal Secretion From 150 Patients Receiving Mechanical Ventilation*

Microorganisms	Study Group (n = 75)	Patients With VAP in the Study Group (n = 2)	Control Group (n = 75)	Patients With VAP in the Control Group (n = 10)
<i>P aeruginosa</i>	14 (17)	1	13 (17)	3
<i>S aureus</i>	14 (17)	1	8 (11)	3
<i>S pneumoniae</i>	12 (16)		10 (13)	2
<i>K pneumoniae</i>	17 (23)	1	11 (15)	
Other Gram-negative microorganism/ <i>H influenza</i>	25 (33)		13 (17)	2
Yeast	12 (16)		8 (11)	1
Gram-positive cocccen	22 (29)		12 (16)	

*Data are presented as No. (%) or No.

DISCUSSION

In this randomized trial, 150 patients with an expected duration of mechanical ventilation > 72 h were randomized to intermittent subglottic secretion drainage or to a control group. VAP developed in 15 patients (10%), which translates to an incidence rate of 15.6 episodes per 1,000 ventilator-days. Patients randomized to intermittent subglottic secretion drainage had a statistically lower incidence of VAP than patients intubated with the conventional endotracheal tube. Three patients had VAP develop within 72 h (one patient with subglottic suctioning and two patients in the control group). As early-onset VAP is probably directly related to the intubation procedure, the use of subglottic suctioning is unlikely to change this incidence. No statistical differences were found in the duration of mechanical ventilation, length of ICU stay, length of hospital stay, and mortality. Several authors^{30–32} have stated that the attributable mortality from VAP is probably low, although it may be increased with *Pseudomonas* and *Acinetobacter* spp. Our study was not designed and probably too small to show a possible reduction in mortality.

Our results are in agreement with several earlier studies.^{14–16} Mahul et al¹⁵ studied a total of 145 patients intubated for > 3 days. In this study, nosocomial pneumonia was prevented by two additive measures: (1) prevention of aspiration by hourly subglottic secretion drainage, and (2) prevention of gastric colonization with either sucralfate or antacids. Subglottic secretion drainage treatment was associated with a decreased incidence of VAP (13% vs 29.1%) and a prolonged time until onset of VAP (8.3 ± 5 days vs 16.2 ± 11 days). Valles et al¹² studied 190 patients in a mixed medical-surgical ICU with an expected need for prolonged intubation (> 3 days). A total of 153 patients were randomized. Seventy-six patients had continuous aspiration of

subglottic secretions, and 77 patients received standard treatment. The incidence rate of VAP was 19.9 episodes per 1,000 ventilator-days in the patients receiving continuous aspiration of subglottic secretions and 39.6 episodes per 1,000 ventilator-days in the control patients (RR, 1.98; 95% CI, 1.03 to 3.82). Episodes of VAP occurred later in patients receiving continuous aspiration (12.0 ± 7.1 days) than in the control patients (5.9 ± 2.1 days; p = 0.003). No significant differences in outcome were found.

In contrast to these results, Kollef et al¹³ studied 343 patients undergoing cardiac surgery and requiring mechanical ventilation. One hundred sixty patients were assigned to continuous subglottic secretion drainage, and 183 patients were assigned to routine postoperative care. VAP was seen in 8 patients (5.0%) in the study group and in 15 patients (8.2%) in the control group. The difference was not statistically significant. Episodes of VAP occurred later in the patients in the study group. No statistically significant differences in other outcome measures were found. One explanation of the differences in outcome between this study and the other studies is the patient population studied (case mix). The number of patients in the study by Kollef et al¹³ may have been too low to detect a significant difference, as the incidence of VAP in the patients randomized to the control group was much lower in this study than in the other three studies. In our study, isolation of a pathogenic microorganism from the subglottic secretions preceded the development of VAP in every patient. *P aeruginosa* and *K pneumoniae* were cultured in 58% of the patients who had VAP develop, and *S aureus* was cultured in 33%.

Our study has some limitations. First, we used a clinical diagnosis of VAP without quantitative cultures of lower respiratory secretions obtained by bronchoscope. However, research has suggested that the use of clinical criteria to establish the diagnosis of

VAP is acceptable because of its greater diagnostic sensitivity compared with bronchoscopically obtained cultures and its good correlation with hospital mortality.²⁵⁻²⁷ Other authors³¹ have also suggested that diagnostic criteria for VAP, not based on bronchoscopically obtained specimens, are acceptable. Although the radiologist who interpreted the chest radiograph was blinded to the two study arms, bias cannot be excluded. A second limitation is that the sample size of the study is relatively small. All randomized patients were expected to receive mechanical ventilation for > 72 h. However, many patients were excluded because they were extubated within 72 h (28%). This did not influence the results of our study, as a decrease in VAP was also found when the analysis was done on an intention-to-treat basis. We conclude from our study that VAP can be prevented by subglottic secretion drainage in patients expected to receive mechanical ventilation > 3 days, and recommend that drainage of subglottic secretions be incorporated in the routine care of these patients.

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REFERENCES

- Dixon RE. Cost of nosocomial infections and benefits of infection control programs. In: Wenzel RP, ed. Prevention and control of nosocomial infections. 1st ed. Baltimore, MD: Williams and Wilkins, 1987; 19-25
- Freeman J, Mc Gowan JE Jr. Risk factors for nosocomial infection. *J infect Dis* 1978; 138:811-819
- Pennington JE. Hospital-acquired pneumonia. In: Wenzel RP, ed. Prevention and control of nosocomial infections. 1st ed. Baltimore, MD: Williams and Wilkins, 1987; 321-334
- Stevens RM, Teres D, Skillman JJ, et al. Pneumonia in an intensive care unit. *Ann Intern Med* 1974; 134:106-111
- Hemming VG, Overall JC Jr, Britt MR. Nosocomial infections in a newborn intensive care unit. *N Engl J Med* 1976; 294:1310-1316
- Fagon JY, Chastre J, Hance AJ, et al. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1994; 94:281-288
- Craven DE, Kunches LM, Kilinsky V, et al. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. *Am Rev Respir Dis* 1986; 133:792-796
- Torres A, Aznar R, Gatell JM, et al. Incidence, risk and prognosis factors of nosocomial pneumonia in ventilated patients. *Am Rev Respir Dis* 1990; 142:523-528
- Kollef MH, Silver P, Murphy DM, et al. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. *Chest* 1995; 108:1655-1662
- Crouch Brewers S, Wunderink RG, Jones CB, et al. Ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. *Chest* 1996; 109:1019-1029
- Craven DE, Steger KA. Epidemiology of nosocomial pneumonia: new perspectives on an old disease. *Chest* 1995; 108[Suppl]:1S-16S
- Valles J, Artigas A, Rello J, et al. Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. *Ann Intern Med* 1995; 122:179-186
- Kollef MH, Nikolaos J, Thoralf M. A randomized clinical trial of continuous aspiration of subglottic secretions in cardiac surgery patients. *Chest* 1999; 116:1339-1346
- Greene R, Thompson S, Jantsch H, et al. Detection of pooled secretions above endotracheal-tube cuffs: value of plain radiographs in sheep cadavers and patients. *AJR Am J Roentgenol* 1994; 163:1333-1337
- Mahul P, Auboyer C, Jospe R, et al. Prevention of nosocomial pneumonia in intubated patients: respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. *Intensive Care Med* 1992; 18:20-25
- Joshi N, Russell L, Bruce HH. A predictive risk index for nosocomial pneumonia in the intensive care unit. *Am J Med* 1992; 93:135-142
- Oikkonen M, Aromaa U. Leakage of fluid around low-pressure tracheal tube cuffs. *Anaesthesia* 1997; 52:567-569
- Du Moulin GC, Paterson DG, Hedley-White J, et al. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonization of the airway. *Lancet* 1982; 1:242-245
- Sottile FD, Marrie TJ, Prough DS, et al. Nosocomial pulmonary infection: possible etiologic significance of bacterial adhesion to endotracheal tubes. *Crit Care Med* 1986; 14: 265-270
- Inglis TJ, Millar MR, Jones G, et al. Tracheal tube biofilm as a source of bacterial colonization of the lung. *J Clin Microbiol* 1989; 27:2014-2018
- Inglis TJ, Jones JG, Paxton S. Penetration of an aerosol, produced by film atomization, through the carinal bifurcation. *Br J Anaesth* 1993; 70:527-531
- Inglis TJ. New insights into the pathogenesis of ventilator-associated pneumonia. *J Hosp Infect* 1995; 30[suppl]: 409-413
- Kollef MH. Avoidance of tracheal intubation as a strategy to prevent ventilator-associated pneumonia. *Intensive Care Med* 1999; 25:553-555
- Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 3:818-829
- Pingleton SK, Fagon JY, Leeper KV Jr. Patient selection for clinical investigation of ventilator-associated pneumonia: criteria for evaluating diagnostic techniques. *Chest* 1992; 102[Suppl 1]:553S-556S
- Joliet P, Chevreton J. Bronchoscopy in the intensive care unit. *Intensive Care Med* 1992; 18:160-169
- Niedrman MS, Torres A, Sumner W. Invasive diagnostic testing is not needed routinely to manage suspected ventilator associated pneumonia. *Am J Respir Crit Care Med* 1994; 150:565-569
- Rothman KJ. Analysis of crude data: In: Rotman KJ, ed. *Modern epidemiology*. Boston, MA: Little, Brown, 1986; 153-176
- Lee ET. Nonparametric methods of estimating survival functions. In: Lee ET, ed. *Statistical methods for survival data analysis*. New York, NY: Wiley, 1992; 66-130
- Timsit JF, Chevreton S, Valcke J, et al. Mortality of nosocomial pneumonia in ventilated patients: influence of diagnostic tools. *Am J Respir Crit Care Med* 1996; 154:116-123
- Bregeon F, Papazian L, Visconti A, et al. Relationship of microbiologic diagnostic criteria to morbidity and mortality in patients with ventilator-associated pneumonia. *JAMA* 1997; 277:655-662
- Heyland DK, Cook DJ, Griffith L, et al. The attributable morbidity and mortality of VAP in the critically ill patient. *Am J Respir Crit Care Med* 1999; 159:1249-1256