

CLINICAL GUIDELINES

Evidence-Based Clinical Practice Guideline for the Prevention of Ventilator-Associated Pneumonia

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Background: Ventilator-associated pneumonia (VAP) is an important patient safety issue in critically ill patients.

Purpose: To develop an evidence-based guideline for the prevention of VAP.

Data Sources: MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews.

Study Selection: The authors systematically searched for relevant randomized, controlled trials and systematic reviews that involved mechanically ventilated adults and were published before 1 April 2003.

Data Extraction: Physical, positional, and pharmacologic interventions that may influence the development of VAP were considered. Independently and in duplicate, the authors scored the validity of trials; the effect size and confidence intervals; the homogeneity of results; and safety, feasibility, and economic issues.

Data Synthesis: **Recommended:** The orotracheal route of intubation, changes of ventilator circuits only for each new patient and if the circuits are soiled, use of closed endotracheal suction

systems that are changed for each new patient and as clinically indicated, heat and moisture exchangers in the absence of contraindications, weekly changes of heat and moisture exchangers, and semi-recumbent positioning in the absence of contraindications. Consider subglottic secretion drainage and kinetic beds. **Not recommended:** Sucralfate to prevent VAP in patients at high risk for gastrointestinal bleeding and topical antibiotics to prevent VAP. Because of insufficient or conflicting evidence, no recommendations were made about systematically searching for maxillary sinusitis, chest physiotherapy, the timing of tracheostomy, prone positioning, prophylactic intravenous antibiotics, or intravenous plus topical antibiotics.

Limitations: No formal economic analysis was performed, and patient perspectives were not considered.

Conclusion: If effectively implemented, this guideline may decrease the morbidity, mortality, and costs of VAP in mechanically ventilated patients.

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Critically ill patients in the intensive care unit (ICU) are at high risk for infections associated with increased morbidity, mortality, and health care costs (1-3). The overall infection rate in critically ill patients approaches 40% and may be as high as 50% or 60% in patients who remain in the ICU for more than 5 days (4, 5). Respiratory tract infections account for 30% to 60% of all such infections. The incidence of pneumonia acquired in the ICU ranges from 10% to 65% (6-11). Among patients at high risk for ventilator-associated pneumonia (VAP) are those who have chronic obstructive pulmonary disease, burns, neurosurgical conditions, the acute respiratory distress syndrome, and witnessed aspiration; those who are reintubated; and those who receive paralytic agents or enteral nutrition (12, 13).

The attributable morbidity and mortality of VAP are clinically important. In a prospective, matched cohort study, patients with VAP remained in the ICU 4.3 days (95% CI, 1.5 to 7.0 days) longer than patients who did not have VAP and had a trend toward an increased risk for death (absolute risk increase, 5.8% [CI, -2.4% to 14.0%]) (14). Six other studies using a matching strategy found a prolonged length of ICU stay associated with VAP (range, 5 to 13 days) and attributable mortality ranging from an absolute risk increase of 0% to 50% (15-20). Therefore, strategies to decrease the incidence of VAP could decrease morbidity, mortality, and health care costs and improve patient safety.

A survey of the use of VAP prevention strategies identified differences across countries (21). For example, changing the ventilator circuit for each new patient was reported more frequently by French ICU directors than those in Canada (21). This survey also showed that some effective strategies were used infrequently, suggesting inadequate translation of randomized trial results into practice. One potential catalyst for knowledge translation is an evidence-based clinical practice guideline. Therefore, a Joint Planning Group of the Canadian Critical Care Society and Canadian Critical Care Trials Group commissioned the development of an evidence-based clinical practice guideline for the prevention of VAP. In this paper, we describe the methods used to create the guideline and the recommendations generated.

METHODS

The Joint Planning Group selected an 11-member VAP Prevention Guideline Panel made up of 9 intensivists from university-affiliated and community hospitals, an ICU nurse, and an ICU respiratory therapist. Panel members were experts in critical care medicine ($n = 9$), VAP ($n = 4$), evidence-based medicine ($n = 4$), and guideline development ($n = 3$). The context was mechanically ventilated adult patients cared for in the ICU. The target au-

dience was ICU clinicians in university-affiliated and community hospitals.

To identify potentially relevant evidence, we searched 3 bibliographic databases (MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews) to 1 April 2003 for randomized trials that evaluated interventions influencing VAP (Appendix, available at www.annals.org). We had no language restrictions. We also reviewed personal files and practice guidelines on this subject previously published by the Centers for Disease Control and Prevention (22) and the American Thoracic Society (23).

We included randomized trials and systematic reviews of randomized trials that 1) studied adult critically ill patients; 2) had VAP as an outcome; and 3) evaluated any of the following interventions: physical strategies (route of endotracheal intubation, systematic search for maxillary sinusitis, frequency of ventilator circuit changes, type of airway humidification, frequency of humidifier changes, endotracheal suctioning system, subglottic secretion drainage, chest physiotherapy, and tracheostomy timing), positional strategies (kinetic beds, semi-recumbent positioning, and prone positioning), and pharmacologic strategies (stress ulcer prophylaxis and prophylactic antibiotics, including selective decontamination of the digestive tract). Since study authors used various definitions of VAP, we used the definitions they provided. The most common definition was a new or persistent radiographic infiltrate plus fever, leukocytosis, change in the volume or color of sputum, or isolation of a pathogen. If available, histologic evidence of pneumonia was also used. A priori, we decided to review only systematic reviews of randomized clinical trials for antibiotic prophylaxis and only randomized clinical trials for all other topics. We excluded crossover and before-after studies. We also excluded randomized trials of ventilator weaning, including noninvasive mechanical ventilation, and nutritional interventions evaluating VAP because guidelines addressing these topics have recently been published (24, 25).

In duplicate and independently, 3 pairs of panel members critically appraised each trial (26, 27) and systematic review (28). Each member of a pair compared his or her independent appraisal of a given trial or systematic review with that of the other member of the pair. For each randomized trial, we abstracted sample, allocation, intervention, co-interventions, exclusions after randomization, blinding of outcome assessment, definition of VAP, crude VAP events, relative risk for VAP, and other outcomes. For each intervention, we summarized the risk differences and calculated a pooled risk difference. For each systematic review, we abstracted number of trials, population, intervention, selection criteria, search strategy, validity assessment, method of pooling results, homogeneity assessment, VAP definition, pooled event rates, and other outcomes. Before the panel meeting, each pair of appraisers achieved consensus on the validity and results of the trials they reviewed. One month before the panel meeting, panel members re-

ceived the evidence tables for review prepared by the 3 pairs of appraisers. A priori, panel members agreed to read all circulated documents and evidence tables in advance, to use levels of evidence to generate a status statement for each item, and to abide by the group process and consensus methods. The Canadian Critical Care Society appointed a chair to ensure that the panel achieved its objectives through group process (29).

At the panel meeting, each member recorded any potential conflicts of interest (30). The pair of panel members responsible for critical appraisal of each intervention provided a structured written and oral presentation of the evidence. After the panel discussion, the initial evidence summary was revised if necessary. The panel members assigned levels of evidence, semi-quantitative scores to summarize the evidence and describe the intervention, and a status statement. We classified trials as level 1 if they had all of the following: concealed randomization, blinded outcome adjudication, an intention-to-treat analysis, and an explicit definition of VAP. Trials were classified as level 2 if any one of these characteristics was unfulfilled and as level 3 if allocation was not strictly randomized. We used a semi-quantitative score (0, 1, 2, or 3) to evaluate each intervention with respect to the validity of the randomized trials; the effect size of each intervention; the confidence intervals around the estimate of effect; the homogeneity of the trial results; and the safety, feasibility, and economic consequences of the intervention. The language of the status statement for each item was keyed to the levels of evidence and the semi-quantitative scores. We used the term *recommended* if there were no reservations about endorsing an intervention and the term *considered* if the evidence supported an intervention but there were minor uncertainties about the benefits, harms, or costs. No recommendation was made if evidence regarding an intervention was inadequate or if there were major uncertainties about the benefits, harms, or costs.

After the panel meeting, the chair compiled the summaries and status statements and sent them to all panel members to check accuracy and clarity. In addition, the pairs of evidence appraisers wrote background documents for the interventions they appraised, including the rationale for each intervention, appraisal of randomized trials and systematic reviews, and harms and costs of the interventions. The chair and the writing committee organized the background documents, the evidence summaries, a table of the semi-quantitative scores, and the status statement for each item. We formatted the document with a structured abstract (31), a summary of the evidentiary basis for each recommendation, and a status statement for each item. We also created a quick reference guide.

The draft guideline document was submitted for structured external review by the executives of the Canadian Critical Care Society and the Canadian Critical Care Trials Group and the respective executives of the Canadian Association of Critical Care Nurses, Canadian Society of Respi-

Table 1. Semi-quantitative Scores of Strategies To Prevent Ventilator-Associated Pneumonia*

Intervention	Trials, n	Semi-Quantitative Scores							Status	
		Effect Size	Confidence Interval	Validity	Homogeneity	Safety	Feasibility	Low Cost		
Physical strategies										
Oral endotracheal tube	5	2	1	2–3	NA	2	3	3	Recommended	
Search for sinusitis	1	1	1	1	NA	1	1	1	No recommendation	
Frequency of ventilator circuit changes	3	1	3	3	2	3	3	3	Recommended	
Heat and moisture exchanger	7	1	3	2	2	2	3	3	Recommended	
Frequency of humidifier changes	3	1	2	2	1	2	3	3	Recommended	
Closed suction system	4	1	1	2	2	3	3	3	Recommended	
Frequency of change in suction system	1	1	1	2	NA	2	3	3	Recommended	
Drainage of subglottic secretions	5	2	2	2	3	2	2	3	Consider	
Chest physiotherapy	1	2	1	1	NA	3	2	3	No recommendation	
Early tracheostomy	3	0	2	1	2	2	2	1	No recommendation	
Positional strategies										
Kinetic beds	8	2	2	2	2	2	1	1	Consider	
Semi-recumbent positioning	1	3	1	1	NA	2	3	3	Recommended	
Prone positioning	1	2	1	1	NA	1	2	3	No recommendation	
Pharmacologic strategies										
Sucralfate	2	0	1	2	2	2	2	1	Not recommended	
Intratracheal antibiotics	10†	3	1	1	NA	1	2	1	Not recommended	
Topical antibiotics	10†	3	3	2	2	1	3	1	Not recommended	
Intravenous antibiotics	10†	3	1	1	NA	1	2	1	No recommendation	
Intravenous and topical antibiotics	10†	3	3	2	2	1	3	1	No recommendation	

* The *effect size* is the magnitude of the absolute risk reduction attributable to the intervention listed. A higher score indicates a larger effect size. The *confidence interval* is the 95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if >1 trial). A higher score indicates a smaller confidence interval. *Validity* refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention-to-treat analysis, and an explicit definition of ventilator-associated pneumonia. A higher score indicates presence of more of these features in the trials appraised. *Homogeneity* indicates a similar direction of findings among trials. A higher score indicates more similarity of direction of findings among trials. *Safety* is the estimated probability of avoiding any significant harm that may be associated with the intervention listed. A higher score indicates a lower probability of harm. *Feasibility* is the ease of implementing the intervention listed. A higher score indicates greater ease of implementing the intervention in the intensive care unit. *Low cost* is the estimated cost of implementing the intervention listed. A higher score indicates a lower cost to implement the intervention in the intensive care unit. NA = not applicable.

† Meta-analyses.

ratory Therapists, Canadian Infectious Disease Society, and Canadian Thoracic Society. External reviewers were asked to critique whether the guideline was logical, clear, and practical and to critique the guideline development process. The panel revised the document on the basis of this feedback. The final guideline was returned to the external reviewers for further comments and official endorsement by their respective organizations. The final guideline was then piloted in 2 institutions.

To record the agreement of each panel member with the final status statement for each item, we sent the final document to all panel members. Independently, blinded to each other's ratings, panel members used a Likert scale from 1 to 9 that was anchored by "disagree completely" at the low end and "agree completely" at the high end. The panel will formally review and update this guideline every 2 years (32).

The funding source played no role in study selection for this guideline and had no role in its development, review, reporting, approval, or submission for publication.

RESULTS

The final summary statements, levels of evidence, and status statements for each of the interventions are reported. The semi-quantitative scores for each intervention are presented in Table 1, and the agreement scores for each panel

member are presented in Table 2.

Physical Strategies

Route of Endotracheal Intubation

On the basis of direct evidence from one level 2 trial (33), we conclude that orotracheal intubation is associated with a lower incidence of VAP compared with nasotracheal intubation. Furthermore, this trial and four other level 2 trials (34–37) have found that orotracheal intubation is associated with a decreased incidence of sinusitis and that incidence of VAP is lower in patients who do not develop sinusitis.

Status: We recommend that the orotracheal route of intubation should be used when intubation is necessary.

Systematic Search for Maxillary Sinusitis

On the basis of one randomized, controlled trial (38), we conclude that while a systematic search for maxillary sinusitis in patients who are intubated by the nasotracheal route may decrease the incidence of VAP, no evidence supports this practice in patients who are intubated by the orotracheal route.

Status: We make no recommendation because of insufficient evidence.

Frequency of Ventilator Circuit Changes

On the basis of evidence from one level 2 trial (39) and two level 3 trials (40, 41), we conclude that the frequency of ventilator circuit changes does not influence the incidence of VAP. Less frequent changes of ventilator circuits are not associated with harm, and more frequent changes are associated with increased cost.

Status: We recommend new circuits for each patient, and changes if the circuits become soiled, but no scheduled ventilator circuit changes.

Airway Humidification

Type of Humidifier. On the basis of evidence from seven level 2 trials (42–48), we conclude that the use of heat and moisture exchangers may be associated with a slightly decreased incidence of VAP compared with heated humidifiers. Concern about endotracheal tube obstruction associated with the use of heat and moisture exchangers has not been confirmed in recent studies that have evaluated newer heat and moisture exchangers. Cost considerations favor the use of heat and moisture exchangers.

Status: We recommend the use of heat and moisture exchangers in patients who have no contraindications (such as hemoptysis or requirement for high minute ventilation).

Frequency of Humidifier Changes. On the basis of evidence from three level 2 trials (49–51), infrequent changes to heat and moisture exchangers may be associated with a slightly decreased incidence of VAP. Reduction in the frequency of humidifier changes might be considered as a cost-reduction measure.

Status: We recommend weekly changes of heat and moisture exchangers.

Endotracheal Suctioning System

On the basis of evidence from two level 2 trials (52, 53) and two level 3 trials (54, 55), we conclude that type of

suctioning systems (open or closed) has no effect on the incidence of VAP. On the basis of evidence from one level 2 trial (56), we conclude that scheduled daily changes and unscheduled changes of closed suctioning systems have no effect on the incidence of VAP. Cost considerations favor the use of closed suctioning systems that are changed only as clinically indicated.

Status: We recommend the use of closed endotracheal suction systems that are changed for each new patient and as clinically indicated.

Subglottic Secretion Drainage

On the basis of evidence from five level 2 trials (57–61), we conclude that subglottic secretion drainage is associated with decreased incidence of VAP, especially early-onset VAP.

Status: We recommend that clinicians consider the use of subglottic secretion drainage.

Chest Physiotherapy

On the basis of evidence from one level 3 trial (62), we conclude that chest physiotherapy may be associated with decreased incidence of VAP. However, methodologic limitations of this level 3 trial and the lack of feasibility of universal application preclude widespread use of this intervention.

Status: We make no recommendation.

Timing of Tracheostomy

On the basis of evidence from one level 2 trial (63) and two level 3 trials (64, 65), we conclude that there is no difference in incidence of VAP between early tracheostomy and late tracheostomy. However, serious methodologic flaws threaten the validity of these trials.

Table 2. Agreement Scores of Panel Members with the Final Status of Each Item

Item	Scores for Each Panel Member									
	Member A	Member B	Member C	Member D	Member E	Member F	Member G	Member H	Member I	Member J
Route of intubation	9	9	9	9	8	9	9	9	9	9
Search for sinusitis	9	8	9	9	6	7	8	9	8	9
Circuit changes	9	9	9	9	8	9	9	9	9	9
Humidifier	9	7	9	9	8	9	9	8	8	9
Humidifier changes	8	9	9	8	9	9	9	7	9	9
Endotracheal suctioning	9	9	9	5	8	8	8	7	7	9
Subglottic secretion drainage	9	9	7	7	7	5	7	7	7	7
Chest physiotherapy	9	8	9	7	8	9	9	9	9	9
Tracheostomy	9	9	9	9	8	9	9	8	9	9
Kinetic beds	9	9	9	7	7	8	7	8	8	8
Semi-recumbent position	9	9	7	9	8	9	9	9	8	8
Prone position	9	7	7	7	8	9	9	9	9	9
Stress ulcer prophylaxis	7	9	9	9	8	7	7	9	9	9
Prophylactic antibiotics	9	8	9	7	7	8	8	9	9	8

Status: We make no recommendation because of insufficient evidence.

Positional Strategies

Kinetic Bed Therapy

On the basis of evidence from seven level 2 trials (66–72) and one level 3 trial (73), we conclude that the use of kinetic beds is associated with decreased incidence of VAP. However, feasibility and cost concerns may be barriers to implementation.

Status: We recommend that clinicians consider the use of kinetic beds.

Semi-recumbent Positioning

On the basis of evidence from one level 2 trial (74), we conclude that semi-recumbent positioning (caring for patients positioned at 45 degrees from horizontal) is associated with decreased incidence of VAP. Semi-recumbent positioning may be unsafe for some patients but is a feasible and low-cost intervention.

Status: We recommend the use of semi-recumbent positioning, with a goal of 45 degrees, in patients without contraindications.

Prone Positioning

On the basis of evidence from one level 2 trial (75), we conclude that use of prone positioning may be associated with decreased incidence of VAP. However, methodologic concerns about this trial and the lack of feasibility of universal application preclude widespread use of this intervention.

Status: We make no recommendation.

Pharmacologic Strategies

Stress Ulcer Prophylaxis

In patients at very low risk for clinically important bleeding (for example, those spontaneously breathing without coagulopathy), the best option to minimize the risk for VAP is to avoid stress ulcer prophylaxis. In high-risk patients (those who require mechanical ventilation for >48 hours or have coagulopathy), the risk for bleeding should be balanced against the risk for VAP. On the basis of evidence from two level 2 trials (76, 77), we conclude that the use of sucralfate does not influence the incidence of VAP compared with placebo.

Status: We recommend that sucralfate not be used to minimize the risk for VAP in patients at high risk for stress ulcer bleeding.

Prophylactic Antibiotics, Including Selective Decontamination of the Digestive Tract

On the basis of evidence from 10 meta-analyses (78–87), we conclude that selective digestive decontamination using topical antibiotics (intratracheal or oral) or intrave-

nous and topical antibiotics is associated with a decreased incidence of VAP. Cost-effectiveness of selective digestive decontamination is of unknown magnitude. The long-term risk for emergence of antibiotic-resistant bacteria when topical antibiotics are administered in the digestive tract or the trachea is unclear and is potentially harmful. Furthermore, only the combination of intravenous and topical antibiotics is associated with a decrease in mortality.

Status: We recommend that topical antibiotics alone not be used. We make no recommendations regarding selective digestive decontamination using intravenous and topical antibiotics because of insufficient data about antibiotic resistance and cost-effectiveness. We make no recommendation regarding intravenous antibiotics alone because of insufficient evidence.

DISCUSSION

The VAP prevention guidelines published in 1994 by the Centers for Disease Control and Prevention (23) and in 1995 by the American Thoracic Society (24) provided a strong foundation for our work. However, these documents did not explicitly outline how evidence was identified, interpreted, or integrated into recommendations. Our guideline is based on interventions tested in randomized trials that were in turn critically appraised with respect to study validity; the magnitude, precision, and homogeneity of the intervention's effect on VAP; and the safety, feasibility, and cost of the intervention. We used structured evidence reviews (88) to generate evidence-based practice guidelines (89).

Other strengths of this guideline include the detailed, explicit processes used to search for, select, and appraise the evidence (90); the multidisciplinary panel; and the panel's balance of university-based and community-based clinicians. In addition, the external reviewers represented nursing, respiratory therapy, respirology, infectious diseases, and critical care. To translate the findings into status statements, we used a semi-quantitative score to evaluate 7 domains for each intervention, integrating evidence and judgment about safety, feasibility, and cost. These judgments were based on qualitative and relative comparisons with other interventions in Canadian ICUs. For example, the feasibility and cost concerns related to kinetic beds reflected increased nursing workload and significant rental or retail costs, respectively. We used a transparent method to grade the evidence and a final score to reflect the panelists' confidential agreement with each status statement (91). The panel also highlighted areas that were unsuitable for evidence-based recommendations but suitable for future research (92). These include the systematic search for maxillary sinusitis among mechanically ventilated patients, chest physiotherapy, prone positioning, the timing of tracheostomy, and intravenous or intravenous plus topical antibiotic prophylaxis as interventions to prevent VAP. Further randomized trials of VAP prevention strategies are necessary since practice guidelines, like systematic reviews

(93), need to be updated as new evidence emerges and as values and health resources change (32).

This document meets the 3 quality criteria for a guideline from a specialty society as proposed by Grilli and colleagues (94); it describes the developers, the data sources, and the methods used to grade the status statements. This document also meets all 10 methodologic criteria on guideline development and 8 of 10 criteria on evidence identification and summary proposed by Shaneyfelt and colleagues (95). We did not specify the health care costs of implementing each intervention in specific practice settings because of the sparse reporting of economic outcomes in these trials, the absence of guideline implementation costs in the ICU, and the limited validity and generalizability of cost-effectiveness statements for these interventions within and among different health care systems (96). Finally, this document meets 20 of 20 criteria on the rigor of guideline development and 12 of 12 criteria on context and content proposed by Cluzeau and colleagues (97).

One aspect of guideline appraisal as proposed by Cluzeau and colleagues (97) focuses on 5 criteria addressing applicability in practice, including whether monitoring criteria, acceptable thresholds, and outcome measures for guideline adherence are specified; whether key considerations for local guideline groups are identified; and whether methods for dissemination and implementation are indicated. We believe that these criteria should be developed by guideline consumers regionally. While no evidence informs these issues, a strong body of evidence exists on effective dissemination and implementation methods, including academic detailing, opinion leaders, audit and feedback, interactive education, computer decision support systems, and multifaceted approaches (98). Prevention strategies for VAP that are behavioral instead of pharmacologic or technological may require different implementation techniques in the complex, dynamic setting of the ICU. Qualitative studies (99) and observational studies (100) can identify attitudinal and clinical barriers to implementing specific VAP prevention guidelines. We propose that the next steps for implementation of this guideline should be review by local clinician groups and adaptation to individual practice settings and health care systems.

Although there are several methods for development of practice guidelines (29, 90, 91, 101), critical appraisal of many guidelines reveals room for improvement. In an analysis of 279 guidelines from several sources, Shaneyfelt and colleagues found that only 40% adhered to methodologic standards (95). A study of 217 guidelines for drug therapy (102) found that 15% met at least half of the criteria for rigorous development, 62% met at least half of the criteria for context and content, and none met at least half of the criteria for guideline application. In a critique of guidelines developed by specialty societies, Grilli and colleagues (94) found that 67% did not describe the stakeholders, 88% did not describe the literature searches, and

82% did not explicitly grade the strength of recommendations. Since endorsement by professional organizations influences physicians' confidence in guidelines (103, 104), it is crucial that guidelines developed by specialty societies are valid.

This guideline has several limitations. First, we did not elicit patient perspectives during the guideline development process. Second, we did not conduct formal economic evaluations for each intervention appraised. Third, we did not formally incorporate published economic analyses into the guideline development. During the latter phases of external review and final agreement measures, an economic evaluation was published (105), estimating that \$1900 U.S. could be saved per case of VAP prevented by subglottic secretion drainage. Our statement to consider subglottic secretion drainage is thus supported.

Rigorous guideline development efforts are easily dwarfed by the skills and time of the experienced individuals needed to implement them (106). Evidence-based implementation of evidence-based medicine requires knowledge of the most successful strategies for behavior change (107). Rather than making recommendations about guideline implementation in the current document (101), we endorsed a programmatic approach. Thus, we separated the development of the guideline from its implementation and evaluation. Phase 1 of this program is development of this evidence-based VAP prevention guideline. Phase 2 is being led by a Guideline Implementation and Evaluation Panel, which is testing the clinical outcomes associated with different guideline implementation strategies in a multicenter trial. Only with effective implementation will guidelines have the potential to decrease the risk for VAP and its attendant morbidity and mortality in critically ill, mechanically ventilated patients.

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