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Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: Diagnosis and treatment

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Treatment;
Antibiotics

Abstract

Background: Ventilator-associated pneumonia (VAP) is an important cause of morbidity and mortality in ventilated critically ill patients. Despite a large amount of research evidence, the optimal diagnostic and treatment strategies for VAP remain controversial.

Purpose: The aim of this study was to develop evidence-based clinical practice guidelines for the diagnosis and treatment of VAP. Data sources include Medline, EMBASE, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Database of Systematic Reviews and Register of Controlled Trials.

Study Selection: The authors systematically searched for all relevant randomized controlled trials and systematic reviews on the diagnosis and treatment of VAP in mechanically ventilated adults that were published from 1980 to October 1, 2006.

Data Extraction: Independently and in duplicate, the panel critically appraised each published trial. The effect size, confidence intervals, and homogeneity of the results were scored using predefined definitions. The full guideline development panel arrived at a consensus for scores on safety, feasibility, and economic issues.

Levels of Evidence: Based on the scores for each topic, the following statements of recommendation were used: recommend, consider, do not recommend, and no recommendation because of insufficient or conflicting evidence.

Data Synthesis: For the diagnosis of VAP in immunocompetent patients, we recommend that endotracheal aspirates with nonquantitative cultures be used as the initial diagnostic strategy. When there is a suspicion of VAP, we recommend empiric antimicrobial therapy (in contrast to delayed or culture directed therapy) and appropriate single agent antimicrobial therapy for each potential pathogen as

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[1] Ventilator-associated pneumonia guidelines committee was composed of Martin Albert, Clarence Chant, Sue Elliott, Richard Hall, Lori Hand, Rick Hodder, Carolyn Hoffman, Mike Jacka, Lynn Johnston, Jim Kutsogiannis, David Leasa, Kevin Laupland, Martin Legare, Claudio Martin, Mike Miletin, Brenda Morgan, Linda Nusdorfer, Juan Ronco, Kevin Saunders, Taz Sinuff, Derek Townsend, Louis Valiquette, Christine Weir, Karl Weiss, Dan Zuege.

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empiric therapy for VAP. Choice of antibiotics should be based on patient factors and local resistance patterns. We recommend that an antibiotic discontinuation strategy be used in patients who are treated of suspected VAP. For patients who receive adequate initial antibiotic therapy, we recommend 8 days of antibiotic therapy. We do not recommend nebulized endotracheal tobramycin or intratracheal instillation of tobramycin for the treatment of VAP.

Conclusion: We present evidence-based recommendations for the diagnosis and treatment of VAP. Implementation of these recommendations into clinical practice may lessen the morbidity and mortality of patients who develop VAP.

1. Introduction

Despite efforts to prevent ventilator-associated pneumonia (VAP), this disease continues to occur frequently in critically ill patients and is associated with significant morbidity and mortality [1-5]. Although prevention is paramount, when VAP does occur, optimal management is important to reduce further morbidity, mortality, and health care costs. The 2 main facets of VAP management are its diagnosis and treatment.

The diagnosis of VAP is challenging [6,7]. Bedside evaluation using clinical and radiographic criteria for the presence of VAP is neither specific nor sensitive [8]. The reference standard for the diagnosis of VAP remains the histopathologic examination and culture of lung tissue [9,10]. However, this technique is invasive, has associated risks, and thus has not been adopted for the routine clinical diagnosis of VAP. Both invasive (bronchoscopic) and noninvasive (endotracheal aspirates) techniques to obtain samples for microbiological cultures are used in clinical practice, without consensus as to which technique is superior [11]. A recently published meta-analysis suggested that bronchoscopic techniques as compared to endotracheal aspirates have no effect on mortality but are superior for the management of antibiotic therapy for VAP [12]. In the American Thoracic Society guidelines, invasive quantitative cultures are favored over endotracheal aspirates [13]. However, these findings were not confirmed by a large recently published trial, which compared bronchoscopy and bronchoalveolar lavage to endotracheal aspirates, and found no difference in mortality, antibiotic management, or other clinical outcomes in patients without suspected or documented multidrug-resistant organisms [14].

The optimal antimicrobial agents and duration of treatment of VAP is also unclear [15]. Delays in appropriate therapy are associated with increased morbidity and mortality [16-18]. Recent trials have demonstrated that treatment duration can be safely shortened from traditional 2-week courses, that antibiotic management protocols improve outcomes, and that antibiotic discontinuation based on objective criteria reduces antibiotic use without adversely affecting clinical outcomes [19-21].

Given the volume and complexity of the published trials about VAP, comprehensive clinical practice guidelines are needed to distill and translate this knowledge on VAP prevention, diagnosis, and treatment into recommendations for action. Therefore, the Canadian Critical Care Trials Group undertook the development of an updated evidence-based clinical practice guideline for the prevention, diagnosis, and treatment of VAP. Herein, we report our guidelines for the diagnosis and treatment of VAP. The guidelines for the prevention of VAP are also reported in this issue [22].

2. Methods

The detailed methods for creating these guidelines are reported in the companion article of guidelines for VAP prevention in this issue [22]. In brief, a multispecialty panel (N = 29) of intensivists, infectious disease physicians, respiratory therapists, pharmacists, and nurses was convened. We considered all relevant literature in the clinical context of Canadian intensive care units (ICUs), and the target audience was ICU clinicians.

To identify potentially relevant evidence, we searched 4 bibliographic databases (Medline, EMBASE, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Database of Systematic Reviews/Registry of controlled trials) from 1980 to October 1, 2006, for randomized controlled trials and systematic reviews or meta-analyses that evaluated interventions for the diagnosis and treatment of VAP (see Appendix A for search strategy). There were no language restrictions. We also reviewed personal files and the practice guidelines on this subject previously published by the American Thoracic Society [13].

We only included randomized trials and systematic reviews of randomized trials of adult critically ill patients that evaluated the diagnosis and treatment of VAP. Trials of diagnostic approaches were required to evaluate specific diagnostic modalities and report on the clinical end points of mortality, length of stay (ICU and/or hospital), ventilator days, antibiotic use, or antibiotic resistance. For trials of VAP treatment, all interventions used to treat VAP, including initial empiric therapy were included. Required outcomes in these studies were mortality, length of stay (hospital or ICU), duration of mechanical ventilation, antibiotic use, relapse of pneumonia, superinfection, or antibiotic resistance. For trials that included both hospital acquired pneumonia and VAP, VAP had to account for 75% of all the cases of pneumonia for the trial to be included.

Trials that did not report on the outcomes of interest listed above were excluded.

We did not set a standard definition of VAP; definitions used in each of the appraised studies were accepted. The most common definition used was a new or persistent radiographic infiltrate plus fever, leukocytosis, change in the volume or color of sputum, or isolation of a new pathogen. If available, histologic evidence of pneumonia was also used to define VAP. We excluded studies that used the following experimental designs: intervention crossover, before and after, and interrupted time series. We graded trials as level 1 if they demonstrated concealed randomization, blinded outcome adjudication, an intention-to-treat analysis (ITT), and an explicit definition of VAP. Trials were graded as level 2 if any one of these characteristics was unfulfilled and as level 3 if allocation was not strictly randomized. Level 3 trials were excluded from inclusion into these guidelines.

The explicit process used to arrive at recommendations is the same as that reported for the prevention guidelines in this issue [22]. To summarize, each primary article was critically appraised in duplicate, and for each, intervention risk differences were calculated. Because of the large size of the panel (N = 29) and the vast amount of literature to consider, the evidence was first reviewed by 2 small working groups (chaired by SK and JM) and then by the whole panel (chaired by JM). Using a specified group process that included a structured summary of specific descriptors for each article, a draft recommendation was generated for each intervention reviewed [23]. These recommendations were then discussed by the whole panel until consensus was reached.

For each intervention, we used a predefined semiquantitative scoring system for the effect size, confidence intervals around the estimate of effect, validity, and homogeneity of trial results (Table 2). Similar scores for safety, feasibility, and cost consequences of the interventions were determined by consensus of the panel. The language of the draft recommendation for each item was keyed to the level of evidence and the scores generated. We used the term *recommend* if there were no reservations about endorsing an intervention and the term *consider*, if the evidence supported an intervention, but there were minor uncertainties about the benefits, harms, or costs. *No recommendation* was used if the evidence regarding an intervention was inadequate or if there were major uncertainties about the benefits, harms, and costs. *Do not recommend* was used if there was harm from an intervention or there was no benefit and there were concerns with regard to the safety or cost of the intervention. Recommendations were only made if there was randomized controlled trial (RCT) evidence regarding the use or futility of specific diagnostic or treatment interventions.

The draft guideline document was submitted for external review to the Board of the Canadian Critical Care Society, the Canadian Critical Care Trials Group, the Canadian Association of Critical Care Nurses, the Canadian Society of Respiratory Therapists, the Canadian Association of Medical Microbiology and Infectious Disease, and the Canadian Thoracic Society. In addition, expert external (international) reviewers (Drs Andrew Shorr and Christian Bruin-Bruisson) were asked to critique the guideline. External societies and reviewers were asked to assess the guideline for logic, clarity, and practicality and to critique the guideline development process. The panel revised the document based on this feedback.

To record the agreement of each panel member with the final recommendation 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

Table 1 Summary of diagnosis and treatment recommendations

Diagnosis		
1.0	Invasive vs noninvasive techniques	We recommend that, if empiric antibiotic therapy is being initiated at the time VAP is suspected, endotracheal aspirates with nonquantitative cultures be used as the initial diagnostic strategy
Treatment		
2.0 Initial treatment of VAP		
2.1	Empiric vs delayed culture directed therapy	We recommend empiric therapy when there is a clinical suspicion of VAP
2.2	Monotherapy vs combined empiric antibiotic therapy	We recommend appropriate spectrum monotherapy for empiric therapy for VAP
3.0 Duration of treatment for VAP		
3.1	Duration of antibiotic use	In patients who receive adequate initial antibiotic therapy, we recommend a maximum of 8 d of antibiotic therapy for the treatment of VAP
3.2	Antibiotic discontinuation strategy based on clinical criteria	We recommend that an antibiotic discontinuation strategy be used for the treatment of suspected VAP
4.0 Choice of antibiotic		
4.1	Antibiotic "A" vs "B"	We recommend that the antibiotic treatment of VAP be based on local resistance patterns and patient factors
5.0 Administration of antibiotics via endotracheal tube		
5.1	Nebulized tobramycin via endotracheal tube	We do not recommend the use of nebulized endotracheal tobramycin for the treatment of VAP
5.2	Instillation of tobramycin via endotracheal tube	We do not recommend the intratracheal instillation of tobramycin for the treatment of suspected VAP

from 1 to 9 that was anchored by "disagree completely" at the low end and "agree completely" at the high end.

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

3. Results

The final summary statements and levels of evidence for each of the interventions are reported. The results are divided into diagnosis and treatment strategies. Treatment strategies are divided into initial treatment, duration of treatment, choice of antibiotic, and route of antibiotic administration. The summary of the recommendations is reported in Table 1. The semiquantitative scores for each intervention are presented in Table 2, and the agreement scores for each panel member are presented in Table 3.

3.1. Ventilator-associated pneumonia: Diagnosis

3.1.1. Invasive vs noninvasive techniques

On the basis of 5 level 2 trials [14,24-27], a diagnostic approach for suspected VAP using quantitative cultures derived from bronchoscopically obtained bronchoalveolar lavage and/or protected specimen brush samples compared to nonquantitative cultures of endotracheal aspirates does not lead to differences in hospital mortality, length of stay, or duration of mechanical ventilation. Cost, feasibility, and safety considerations favor endotracheal aspirates. All of the 5 trials evaluated immunocompetent patients, and 4 of the 5 trials used empiric antibiotic therapy initiated at the time of suspected VAP.

3.1.2. Recommendation

We recommend that, if empiric antibiotic therapy is being initiated at the time VAP is suspected in immunocompetent patients, endotracheal aspirates with nonquantitative cultures be used as the initial diagnostic strategy.

3.2. Ventilator-associated pneumonia: Treatment

3.2.1. Initial treatment of VAP

3.2.1.1. Empiric vs delayed culture-directed therapy. For this discussion, *empiric therapy* is defined as the initiation of antibiotic therapy at the time of VAP suspicion and delayed culture-directed therapy is defined as the initiation of antibiotic therapy for VAP when culture reports are available. On the basis of one level 2 study [17] that showed no benefit in mortality and a trend toward increased costs and increased

Table 2 Semiquantitative scores for each intervention

Recommendations	Effect size [a]	Confidence intervals [b]	Validity [c]	Homogeneity [d]	Safety [e]	Feasibility [f]	Cost [g]
1.0 Diagnosis of VAP—invasive vs noninvasive techniques	0	2	2	2	3	3	3
2.1 Initial treatment of VAP—empiric vs culture-directed therapy	0	0	2	0	1	2	1
2.2 Initial treatment of VAP—monotherapy vs combined empiric antibiotic therapy	0	0	2	2	2	3	3
3.1 Duration of treatment of VAP—duration of antibiotic use	3	2	3	0	2	3	3
3.2 Duration of treatment for VAP—antibiotic discontinuation strategy based on clinical criteria	2	3	3	0	2	2	2
4.1 Treatment of VAP—choice of antibiotic "A" vs "B"	0	0	1	0	3	3	0
5.1 Administration of antibiotics via endotracheal tube—nebulized endotracheal tobramycin	0	0	2	0	1	3	1
5.2 Administration of antibiotics via endotracheal tube—instilled endotracheal tobramycin	0	0	1	0	1	2	3

[a] Effect size indicates the magnitude of absolute risk reduction (higher score = larger effect size).
[b] Confidence interval around estimate of effect, 95% confidence interval of absolute risk reduction (higher score = smaller confidence intervals).
[c] Validity indicates the internal validity of study—concealed randomization, blinded outcome, an intention to treat analysis, and explicit definition of VAP (higher score = more features).
[d] Homogeneity of trial results indicates similar direction among trials scored (higher score = similar results between trials).
[e] Safety indicates the probability of harm resulting from intervention (higher score = lower chance of harm).
[f] Feasibility indicates the ease of implementation of the intervention (higher score = greater ease of implementation).
[g] Cost consequences of intervention indicates cost of implementation of the intervention (higher score = lower cost).

Table 3 Agreement scores [a]

Recommendations	Mean (N = 29)	Median (N = 29)	Range of scores
1.1 Diagnosis of VAP—invasive vs noninvasive techniques	8.6	9	7-9
2.1 Initial treatment of VAP—empiric vs culture-directed therapy	8.8	9	5-9
2.2 Initial treatment of VAP—monotherapy vs combined empiric antibiotic therapy	8.4	9	5-9
3.1 Duration of treatment of VAP—duration of antibiotic use	8.3	9	4-9
3.2 Duration of treatment for VAP—antibiotic discontinuation strategy based on clinical criteria	8.7	9	7-9
4.1 Treatment of VAP—choice of antibiotic "A" vs "B"	8.9	9	8-9
5.1 Administration of antibiotics via endotracheal tube—nebulized endotracheal tobramycin	8.6	9	5-9
5.2 Administration of antibiotics via endotracheal tube—instilled endotracheal tobramycin	8.7	9	5-9

[a] Agreement scores based on a Likert scale of 1 to 9 with anchored by "disagree completely" at the low end and "agree completely" at the high end.

length of stay from delayed culture-directed therapy, we conclude that there is no advantage to delayed therapy. The committee also considered multiple observational studies that suggest harm from delayed therapy in arriving at a recommendation [28-33].

3.2.1.2. Recommendation. We recommend empiric therapy when there is a clinical suspicion of VAP.

3.2.1.3. Monotherapy vs combination empiric antibiotic therapy. On the basis of 5 level 2 trials [34-38] that compared empiric broad-spectrum monotherapy to combination therapy in patients with VAP, we conclude that there is no advantage to combination therapy. These trials did not demonstrate any differences in mortality or clinical response rates. However, the benefit of a reduction in antibiotic use and costs favors monotherapy. Empiric therapy should be based on local resistance patterns and patient risk factors. In settings where high rates of resistance are present, 2 or more agents may be warranted to ensure that each potential pathogen is covered by at least one agent. All of the 5 level 2 studies used antipseudomonal agents, but the decision to use such an agent as empiric therapy is dependent on patient and environmental factors.

3.2.1.4. Recommendation. We recommend appropriate single agent therapy for each potential pathogen as empiric therapy for VAP, when appropriate for local resistance patterns.

3.2.2. Duration of treatment of VAP

3.2.2.1. Duration of antibiotic use. On the basis of 1 level 2 trial [39], we conclude that antibiotics for the treatment of VAP can be stopped safely after 8 days of therapy in patients who have received adequate initial therapy. In this study, early discontinuation of antibiotics at 8 days compared to 15 days was not associated with significant differences in mortality, length of stay, or duration of ventilation. The shorter course was associated with a reduction in antibiotic use and a reduction in the emergence of resistance. A higher percentage of patients treated with 8 days of antibiotic therapy developed recurrence of pulmonary infection secondary to nonfermenting gram-negative bacteria, but this was not associated with worsened clinical outcomes. Among patients who developed a recurrent VAP, multiresistant organisms emerged significantly less often in the group who received 8 days of therapy. The decision to discontinue therapy for nonfermenting gram-negative bacteria (eg, *Pseudomonas* or *Acinetobacter* species) at 8 days should be based on clinical factors. For patients in whom initial therapy is inadequate and who subsequently require revision of their antibiotics, there are insufficient data to recommend the duration of treatment.

3.2.2.2. Recommendation. In patients who receive adequate initial antibiotic therapy, we recommend a total of 8 days of antibiotic therapy for the treatment of VAP.

3.2.2.3. Antibiotic discontinuation strategy based on clinical criteria. On the basis of 1 level 2 trial [40], we conclude that an antibiotic discontinuation strategy based on clinical criteria shortens the duration of antibiotic therapy with no adverse effects on clinical outcome. The antibiotic discontinuation strategy used in this trial was to stop empiric antibiotics when the signs and symptoms of infection resolved or were determined to be because of noninfectious causes.

3.2.2.4. Recommendation. We recommend that an antibiotic discontinuation strategy be used for the treatment of a clinical suspicion of VAP.

3.2.3. Choice of antibiotic

3.2.3.1. Antibiotic selection (A vs B). On the basis of a meta-analysis of 16 level 2 trials [36,41-55] that evaluated 11 antibiotic regimens for the treatment of VAP, we conclude that no regimen is superior. Methodological limitations of the trials that compared vancomycin to linezolid preclude a recommendation of one drug over the other for the empiric treatment of gram-positive VAP. Linezolid may be considered as a therapeutic option, but further studies are required. Consideration should be given to local resistance patterns and patient factors in deciding on a VAP treatment regimen.

3.2.3.2. Recommendation. We recommend that the antibiotic treatment of VAP be based on local resistance patterns and patient factors.

3.2.4. Route of antibiotic administration

3.2.4.1. Nebulized endotracheal tobramycin. On the basis of 1 level 2 trial [56], we conclude that there is no evidence that the use of nebulized endotracheal tobramycin results in improved outcomes as compared to intravenous administration alone. In addition, the panel had concerns regarding the theoretical potential for the development of resistance.

3.2.4.2. Recommendation. We do not recommend the routine use of nebulized endotracheal tobramycin for the treatment of VAP.

3.2.4.3. Endotracheal instillation of tobramycin. On the basis of 1 level 2 trial [57], we conclude that there is no evidence that the installation of endotracheal tobramycin results in improved outcome as compared to intravenous administration alone. Serious methodological concerns threaten the validity of this trial and the panel had concerns regarding the development of resistance.

3.2.4.4. Recommendation. We do not recommend routine endotracheal instillation of tobramycin for the treatment of suspected VAP.

4. Discussion

We have developed evidence-based clinical practice guidelines for the diagnosis and treatment of VAP. However, clinical challenges remain for critical care practitioners in spite of the extensive amount of research evidence that is available. These guidelines only incorporate high-level RCT evidence and illustrate the state of current knowledge on the diagnosis and treatment of VAP.

There is continued controversy over the optimal diagnostic strategy for the diagnosis of VAP. Approaches range from clinical criteria alone to the sampling of secretions from the lower respiratory tract using invasive diagnostic methods [58-61]. The major obstacle to achieving consensus on the optimal approach is the lack of a practical reference standard. Although studies have been conducted comparing diagnostic strategies to biopsy results or postmortem pathologic findings, these small studies enrolled highly selected populations, demonstrate a range of values for specificity and sensitivity, and are challenging to interpret because of variable prior antibiotic exposure and poor correlation with premortem clinical findings [9,62,63]. To address this, we adopted a pragmatic approach to the development of a guideline for the diagnosis of VAP.

Although a "clinically suspected" VAP can be defined relatively easily using clinical criteria including temperature, white cell count, purulence of sputum, and chest radiograph findings, in the absence of a reference standard, it is difficult to be certain that pneumonia is truly present. In this context, what is paramount to the clinician faced with a patient with clinically suspected pneumonia is how to ensure the best outcome for their patient. For this guideline, we decided *a priori*, to only include RCTs of diagnostic strategies that evaluated clinically important outcomes such as mortality, length of stay, and antibiotic use. Although there is extensive literature on the diagnosis of VAP, many diagnostic strategies, such as clinical criteria and biomarkers, have not been rigorously tested with respect to their impact on patient-important outcomes [64,65]. Studies that do evaluate these outcomes are restricted to those comparing invasive techniques such as bronchoscopy with bronchoalveolar lavage and/or protected specimen brush and quantitative cultures to noninvasive techniques such as endotracheal aspirates. On review of the available evidence, the panel did not find that use of invasive techniques with quantitative cultures in the populations studied was associated with improved clinical outcomes. In addition, as invasive diagnostic techniques with quantitative cultures are more intrusive, expensive, and less universally available, we did not recommend their routine use.

The following caveats apply to his recommendation. First, it is not possible to distinguish between the various invasive methods available to obtain respiratory samples for quantitative cultures as these have not been studied individually with regard to their ability to influence clinical outcomes. Second, this recommendation applies only to immunocompetent patients. Third, this recommendation is based on the assumption that a decision has already been made to treat with appropriate-spectrum antibiotics until culture results are available. This is the general practice in Canada and in many centers throughout the world. Lastly, one study demonstrated potential benefit to reducing antibiotic use by incorporating the findings from immediate Gram stain of bronchoscopic samples into their decision of whether to initiate antibiotics [26]. However, the validity and clinical reproducibility of these data are challenged by subsequent publications demonstrating a high error rate if decisions to withhold antibiotics are made on the basis of Gram stain findings [66-69].

For VAP treatment, the recommendation that antibiotics be initiated at the time that VAP is suspected is supported by one randomized clinical trial [17]. Although this trial demonstrated only a trend toward improved outcomes with empiric therapy at the time of VAP suspicion, there is a large amount of corroborating evidence in the form of observational data that associates delays in instituting adequate therapy with worse outcomes [28-32]. Similarly, an RCT, in which a large proportion of the patients had VAP, showed that the institution of empiric antibiotic therapy at the time of suspicion of infection resulted in improved outcomes as compared to culture-directed therapy [70]. We took these into consideration at arriving at a final recommendation although these trials were not incorporated into the tables of evidence. For empiric therapy, we considered combination therapy vs monotherapy. The rationale for the use of combination therapy over monotherapy is one or more of the following: to expand the spectrum of coverage, to reduce the acquisition of resistance, or to provide synergy between 2 antibiotics.

All trials reviewed assessed broad-spectrum antipseudomonal antibiotics as empiric therapy, either in combination or alone. In the combination groups, the antibiotics chosen were either the same antibiotic as in the monotherapy group with the addition of a second agent or 2 completely different antibiotics [34-37]. The panel could not find convincing evidence of clinical benefit of combination therapy. Cost considerations and the desirability of minimizing antibiotic use led to a recommendation in favor of monotherapy. However, for ICUs and patients where microbiology and resistance patterns do not permit appropriate spectrum empiric coverage with a single agent, combination therapy to ensure that at least one antibiotic has activity against the infecting organisms is clearly appropriate because inadequate empiric therapy has been associated with worsened outcomes [30,32,71,72].

Our search did not identify any specific antibiotic agent or agents to recommend over others for the treatment of VAP. The literature consisted of large and varied numbers of antibiotic regimens, populations, and local antibiotic resistance patterns. For these reasons, no one regimen was found to be superior over another. Therefore, we believe that antibiotic selection should be made on the basis of patient factors, local bacterial ecology, resistance patterns, and clinician judgment [13].

Strengths and limitations of this guideline are similar to those outlined in the companion guideline in this issue on the prevention of VAP [22]. To summarize, the major strengths are the explicit process used to select and appraise the evidence [73], the use of only high quality RCTs, the large multidisciplinary and multispecialty panel with a balance of university-based and community-based clinicians, and a wide range of external reviewers. We used a transparent method to grade the evidence and a final score to reflect the panelists' confidential agreement with each status statement [74]. Importantly, there was a high level of final agreement among the panel members with the diagnosis and treatment recommendations (Table 2). We only made recommendations when RCT evidence pertaining to VAP was available. For example, although the clinical pulmonary infection score is commonly used, only observational data describe its use in patients with VAP [59,75,76], and the only RCT that examined its usefulness included a large number of nonventilated patients [77]. Until there are RCTs on these topics, clinicians will need to rely upon judgment, observational evidence, and expert opinion to guide clinical practice.

The context of this guideline was Canadian critical care, and the members of this panel were mostly Canadian critical care practitioners. Although this guideline is applicable to the environments in which these individuals practice, it may not be broadly generalizable. For example, the lower prevalence of multidrug-resistant bacteria in Canada compared to that in the United States [78] may have influenced propensity to recommend noninvasive sampling of pulmonary specimens and abbreviated courses of appropriate monotherapy treatment. However, all recommendations were based upon a rigorous and transparent evaluation of the international literature.

In summary, this guideline incorporates recent evidence on the diagnosis and treatment of VAP into recommendations for clinicians who care for critically ill patients. These guidelines have examined evidence published up to October 1, 2006, but will require updating as new evidence is published [79,80]. The uncertainty that remains in many areas of diagnosis and treatment of VAP mandates further research to improve patient outcomes. Specific areas in great need of further work include the use of techniques or biomarkers to improve the specificity of VAP diagnosis; examination of invasive vs noninvasive diagnostic strategies for patients previously infected or colonized with resistant pathogens; antibiotic discontinuation strategies; and optimal duration of antibiotic therapy.

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Appendix A. Search strategies for the databases

Search strategy for Cumulative Index to Nursing and Allied Health Literature (CINAHL) database
Database: CINAHL (1982 to October Week 1 2006)
Search strategy
1. exp Pneumonia/
2. Cross Infection/
3. exp Ventilation, Mechanical/
4. Ventilators, Mechanical/
5. 1 and 2 and (3 or 4)
6. (vap and pneumonia$).mp. [mp=title, cinahl subject headings, abstract, instrumentation]
7. "ventilator associated pneumonia$".mp. [mp=title, cinahl subject headings, abstract, instrumentation]
8. "ventilator acquired pneumonia$".mp. [mp=title, cinahl subject headings, abstract, instrumentation]
9. 5 or 6 or 7 or 8
10. limit 9 to (yr=1980 - 2005 and journal article

Appendix B (continued)

Search Strategy for Medline database
1. exp PNEUMONIA/
2. Cross Infection/
3. Respiration, Artificial/
4. exp Ventilators, Mechanical/
5. 1 and 2 and (3 or 4)
6. (vap and pneumonia$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7. "ventilator associated pneumonia$".mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8. "ventilator acquired pneumonia$".mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
9. 5 or 6 or 7 or 8
10. limit 9 to (human and yr=1980 - 2006 and journal article)

Search strategy for Cochrane database
Cochrane Register of Controlled Trials
1. vap.ti.
2. (ventilat$ and associat$ and pneumonia$).ti.
3. (ventilat$ and acquire$ and pneumonia$).ti.
4. 1 or 2 or 3
5. from 4 keep 1-52

Database: evidence based medicine reviews—Cochrane database of systematic reviews (3rd Quarter 2006) search strategy
1. (vap and pneumonia$).mp.
2. "ventilator associated pneumonia$".mp
3. "ventilator acquired pneumonia$".mp.
4. 1 or 2
5. from 4 keep 1-9

Search strategy for EMBASE database
Database: EMBASE (1980 to 2006 Week 41) search strategy
1. exp PNEUMONIA/
2. Hospital Infection/
3. exp artificial ventilation/
4. ventilator/
5. 1 and 2 and (3 or 4)
6. (vap and pneumonia$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7. "ventilator associated pneumonia$".mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
8. "ventilator acquired pneumonia$".mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
9. 5 or 6 or 7 or 8
10. limit 9 to (human and yr=1980 - 2006)
11. limit 10 to (book or editorial or erratum or letter or note)
12. 10 not 11

Appendix B: Definitions of semiquantitative scores

Range of values for score: assign 0, 1, 2, and 3 according to rules below

Treatment effect

For treatment effect need to have relative risk (RR) from meta-analysis graph or can be calculated. Relative risk ratio (RRR) = RR (Relative risk) − 1.

Appendix B (continued)

If RR is	then RRR is	score should be
0.9-1.0	<10%	0
0.8-0.9	10%-20%	1
0.7-0.8	21%-30%	2
<0.7>	30%	3

Example: If RR is 0.95, then RRR = (RR − 1) = 0.95-1.0 = −0.05 = 5% = score 0.

Example: If RR is 0.45, then RRR = (RR − 1) = 0.45-1 = −0.55 = 55% = score 3.

Confidence intervals

Rate according to the *P* value of the treatment effect

If the *P* value is	score CI as
>0.1	0
0.1-0.051	1
0.05-0.01	2
<0.01	3

Validity

If 10-12 (none of ITT, concealed randomization, blinded missing), then 3+

If 6-9 (one is missing), then 2+

If <6 (more than one missing), then 1+

Homogeneity

Based on the interclass correlation (I^2) score derived from the meta-analysis plots. For single studies, homogeneity scored as 0.

If I^2 score is	score homogeneity as
<10%	3
10%-30%	2
31%-50%	1
>50%	0

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