Ventilator-Associated Pneumonia: Insights From Recent Clinical Trials

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Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in the ICU and contributes disproportionately to both poor outcomes and the high cost of care in critically ill patients. While VAP has been the focus of extensive research, little consensus exists about methods for diagnosis, treatment, or prevention. Delays in initiating appropriate therapy, antibiotic resistance due to indiscriminate and prolonged use of broad-spectrum antibiotics, and treatment of patients with a low risk of VAP (based on clinical pulmonary infection scores) represent a sample of VAP-related issues that have been addressed in recent clinical trials. Educational programs for VAP prevention and other nonpharmacologic strategies aimed at eliminating VAP have also been explored in clinical investigations. This review highlights selected areas of new clinical research on VAP treatment and prevention in order to place their significance in context.

Key words: antibiotic resistance; antibiotic therapy; ventilator-associated pneumonia

Abbreviations: CPIS = clinical pulmonary infection score; MRSA = methicillin-resistant Staphylococcus aureus; NIV = noninvasive mechanical ventilation; VAP = ventilator-associated pneumonia

Learning Objectives: 1. To provide an update on the incidence of and potential consequences associated with ventilator-associated pneumonia. 2. To review current research on the topic of ventilator-associated pneumonia, including strategies for its treatment and prevention in critically ill patients.

Ventilator-associated pneumonia (VAP) remains an area of active clinical investigation. Despite an improved understanding of this disease, multiple controversies remain about strategies for diagnosis, prevention, and management. There is, however, general agreement about the burden of VAP and its high cost. According to the National Nosocomial Infection Surveillance system, one third of all nosocomial infections in US ICUs are pneumonia; of these, 83% are associated with mechanical ventilation. Financially, several estimates suggest that the attributable costs of VAP approach $12,000 per case. The impact of VAP is also felt by society. Patients acquiring VAP have poorer outcomes, longer lengths of hospital and ICU stay, and higher mortality rates. Changes in pathogen distribution and patterns of antibiotic resistance have complicated care. Specifically, increased use of all classes of antibiotics over the past 10 years has correlated with alarming declines in susceptibilities. This has simultaneously heightened the need to adopt multidrug regimens for the initial treatment of nosocomial infections. In turn, this creates additional selection pressure and, concomitantly, more resistance.

Several investigators have identified the initial antibiotic regimen as a key determinant of patient outcome, and local microbiologic patterns are critical to guide the choice of a suitable initial treatment regimen. Observational studies suggest that clinicians’ primary antibiotic selections for VAP are inadequate (eg, the antibiotic administered does not cover the pathogen or the pathogen is resistant to that antibiotic) in over one third of cases. The price of making an incorrect anti-infective decision is high.
As with other infections encountered in the ICU, delayed treatment with appropriate antibiotics independently increases the risk for death from VAP. In an effort to improve outcomes, trials have examined mechanisms for ensuring adequate antimicrobial coverage. One approach, the creation of VAP management guidelines, has proven highly successful. Because of costs and the concern about overuse and abuse of antibiotics, nonpharmacologic strategies for the prevention of VAP have also attracted considerable attention. Health-care worker hygiene (e.g., hand washing), patient positioning techniques, ventilator device care, and noninvasive ventilation are some examples of these strategies. Although prevention can play a key role in reducing VAP incidence, these methods may require significant educational commitments and high rates of compliance in order to achieve success.

Whether attempting to treat or prevent this costly complication of ICU care, intensivists are constantly challenged to evaluate results from clinical trials and to keep abreast of current issues and trends in the management of VAP. The purpose of this manuscript is, therefore, to review key findings from selected recent studies regarding VAP treatment and prevention.

**TREATMENT ISSUES IN VAP**

**Antibiotic Use and Rising Resistance**

Few topics in intensive care medicine are as heavily discussed and debated as antibiotic use. Prior antibiotic exposure together with duration of mechanical ventilation represent important risk factors for development of VAP with resistant organisms. Antibiotic selection has the potential to influence the spectrum of bacteria endogenous to the hospital and community, and health-care providers need to appreciate that their antibiotic choices have downstream consequences. Although prompt identification of infection and isolation of the infecting organism can pose considerable challenges in the ICU, choosing the appropriate antibiotic that will treat the culprit pathogen and that simultaneously possesses the narrowest spectrum of activity can be equally challenging. A recent review of appropriate antibacterial utilization with examples of successful de-escalation approaches underscores the importance of these strategies to contain costs, reduce morbidity, and control the spread of resistance.

Prolonged and indiscriminate use of antibiotics has affected antibiotic resistance patterns and the sensitivities of organisms frequently encountered in the ICU. Recent susceptibility data for Gram-negative isolates from ICUs in 43 states show that resistance of *Pseudomonas aeruginosa* to ciprofloxacin has risen from 17 to 32% between 1994 and 2000 and has doubled for other Gram-negative bacilli as well. This trend was coincident with a 2.5-fold increase in fluoroquinolone utilization nationally (Fig 1). Moreover, Neuhauser and colleagues observed cross-resistance to cephalosporins and aminoglycosides with selected strains of bacteria, including *P. aeruginosa*, *Enterobacter* species, and *Klebsiella pneumoniae*. They and others have hypothesized that this has transpired because of the tendency for fluoroquinolones to select for bacteria with increased efflux capacity for antibiotics. Although Gram-negative pathogens have been implicated in > 60% of VAP cases, Gram-positive pathogens are increasingly prevalent in the ICU. The incidence of VAP due to *Staphylococcus aureus* now rivals that caused by *P. aeruginosa*. Additionally, methicillin-resistant *S. aureus* (MRSA) presently account for 50 to 70% of *S. aureus* encountered in the ICU. This fact further complicates antibiotic prescribing since broader use of vancomycin, as the prevalence of MRSA dictates, creates selection pressure for the development of vancomycin-resistant enterococci.

**Duration of Therapy**

The duration of antibiotic therapy for VAP presents another conundrum. Until recently, antibiotic treatment durations were based on expert opinion rather than randomized trials. Selecting a treatment duration requires one to balance the risk of either failure or relapse with short treatment courses against the threat of antibiotic overuse with more extended regimens. The belief that longer antibiotic regimens pose no risk to the patient as long as the specific agents used are effective against the infecting organisms is false. For example, despite initial resolution of clinical parameters of infection within 6 days of instituting appropriate antibiotic therapy, Dennesen and co-workers noted that Gram-negative pathogens reemerged to colonize the trachea during the second week of therapy. This led to recurrence of VAP but now with strains that were resistant to the original anti-infectives employed.

To discourage such colonization pressure, shorter 7-day courses of antibiotic therapy have been proposed for VAP. In a randomized 51-center trial, Chastre and colleagues tested the hypothesis that short courses (8 days) of initially appropriate antibiotic therapy for VAP are as effective as traditional courses (15 days). The study included 401 patients and was double blinded in the initial phase, through day 8. Antibiotic selections were not protocolized and were made at the physician's discretion based on cultures obtained following bronchoscopy (day 1).
Empiric therapy was initiated on day 1, incorporated local antibiogram information, and continued until susceptibility results were obtained (48 to 72 h after bronchoscopy). At that point, investigators randomized patients to receive either the 8- or 15-day therapies. The primary outcome measures, assessed at day 28, were death from any cause, antibiotic-free days, and recurrence of documented pulmonary infection. There were no differences in the rate of death or in the incidence of pulmonary infection between the two groups. More importantly, patients randomized to the 8-day cohort had significantly more antibiotic-free days (13.1 ± 7.4) than those in the 15-day cohort (8.7 ± 5.2 [mean ± SD]; p < 0.001). Overall, among those with recurrences of pulmonary infections (28.9% in the 8-day cohort vs 26.0% in the 15-day cohort), fewer resistant strains were detected in patients assigned to the short course. Secondary outcomes measures, including the number of mechanical ventilation-free days, organ failure-free days, physiologic parameters, and ICU length of stay, were similar. Thus, the authors determined that longer courses of treatment offer no clinical advantage. Readers should note that a crucial aspect of the trial design required patients to be receiving appropriate antibiotics, based on the results of cultures obtained from bronchoscopy, in order to continue in the study after initial evaluation. If subsequent invasive testing revealed that a patient had been treated with antibiotics that were not active against the responsible pathogen, the patient was excluded from further participation. If clinicians wish to shorten the length of therapy for VAP, therefore, they must ensure that their original antibiotic choices are correct. In other words, in order for the VAP treatment paradigm to shift from longer to shorter durations, it is imperative that the antibiotic regimen chosen provides adequate coverage from the start and is initiated promptly.

**Appropriate and Prompt Prescribing**

Intensivists should not underestimate the frequency at which the antibiotics they choose are inappropriate or are not given in a timely manner. For example, Iregui et al reported that delays in therapy of at least 24 h occur in almost one third of VAP cases after diagnosis, with the writing of antibiotic orders being the most common cause of delay. Furthermore, the consequence of inappropriate an-

![Figure 1](https://www.chestjournal.org/chestjournals.org/CHEST/128/5/NOVEMBER,2005SUPPLEMENT/585S.png)

**Figure 1.** Impact of fluoroquinolone use on resistance of *P. aeruginosa* and Gram-negative bacilli. The increasing rates of ciprofloxacin resistance correlate with the steadily increasing fluoroquinolone use (r = 0.976, p < 0.001 for *P. aeruginosa*; r = 0.891, p = 0.007 for Gram-negative bacilli; r = 0.958, p < 0.001 for years of observation). The data points from 1990 to 1993 represent composite susceptibility and fluoroquinolone use for those 4 years. Data used with permission from Neuhauser et al.
tibiotic prescribing was significant in this study in that it independently increased the risk for death nearly sevenfold.

One strategy for improving appropriate and timely prescribing of anti-infectives for VAP is to adopt clinical guidelines to assist in antibiotic management decisions. Before and after implementation of a VAP treatment guideline in one ICU, Ibrahim and colleagues demonstrated that initial administration of appropriate therapy increased from 48.0 to 94.2% (p < 0.001). The achievement of high rates of initially appropriate coverage necessitated that their guideline suggest starting with a broad-spectrum multidrug combination. Specifically, it included coverage not only for resistant Gram-negative pathogens but also for MRSA. Although this approach might raise concern about contributing further to selection pressure for resistance, Ibrahim et al concomitantly hypothesized that by guaranteeing correct coverage initially they would be able to shorten the duration of therapy. In fact, as a tradeoff for using multiple agents at the outset, they curtailed therapy at 8 days if the patient was improving clinically. With implementation of their practice guideline they found that actual treatment durations decreased from 14.8 ± 8.1 days to 8.6 ± 5.1 days (p < 0.001). This was also associated with a substantial reduction in VAP recurrence from 24.0 to 7.7% (p = 0.03).

Pressure on physicians to ensure initially appropriate antibiotic therapy leads them to quickly initiate therapy even in patients with a low likelihood of infection. Again, one can see the cost of this type of practice in the rising rates of resistance in the ICU. Singh et al explored if it were possible to “wean” intensivists from the overuse of antibiotics and to guide them to be better antibiotic stewards. Using a modified version of the clinical pulmonary infection score (CPIS) proposed by Pugin and colleagues to objectively stratify patients by likelihood of pneumonia, Singh and coworkers randomized subjects less likely to have an infection (CPIS ≤ 6) to either standard care (10 to 21 days, at the discretion of the health-care provider) or to a short course of empiric therapy (ciprofloxacin for 3 days followed by reevaluation, with discontinuation of treatment if the CPIS remained ≤ 6). Outcomes for patients treated with the short course were comparable to those receiving standard therapy. Thus, in patients with an initial CPIS ≤ 6, longer antibiotic regimens of 10 to 21 days may not be necessary. It is important to note that given the low CPIS coupled with the rapid improvement in the patients studied, it is likely that few actually had pneumonia. Additionally, the trial should not be viewed as an investigation of the diagnostic value of the CPIS. Rather, these researchers explored if the CPIS could effectively serve as a tool to limit antibiotic abuse. The authors were cautious to point out the limitations of their pilot, unblinded, single-center study. They recommended that each institution undertake its own assessment of antibiotic utilization practices before implementing ultrashort empiric therapy. Nevertheless, these researchers provide a provocative solution for reducing antibiotic use in the setting of suspected VAP. Taken as a whole, the results from all of these trials demonstrate that the responsibility for improvement rests with clinicians. Controlling the duration of therapy to limit the spread of resistance is indeed possible, if and when therapy is appropriate, initiated promptly, and administered to the appropriate patients.

### Prevention Strategies for VAP

Given cost-containment pressure and shrinking health-care resources, efforts aimed at preventing VAP are of paramount importance. For the reasons discussed above, namely, the emergence of multiresistant bacteria, strategies employing prophylactic antibiotics such as selective decontamination of the

### Table 1—CPIS Calculation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature, °C</td>
<td></td>
</tr>
<tr>
<td>≥ 36.5 and ≤ 38.4</td>
<td>0</td>
</tr>
<tr>
<td>≥ 38.5 and ≤ 38.9</td>
<td>1</td>
</tr>
<tr>
<td>≥ 39.0 and ≤ 36.0</td>
<td>2</td>
</tr>
<tr>
<td>Blood leukocytes, μL</td>
<td></td>
</tr>
<tr>
<td>≥ 4,000 and ≤ 11,000</td>
<td>0</td>
</tr>
<tr>
<td>&lt; 4,000 or &gt; 11,000 (with band forms &gt; 50%)</td>
<td>1 (+1)</td>
</tr>
<tr>
<td>Tracheal secretions</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Nonpurulent secretions present</td>
<td>1</td>
</tr>
<tr>
<td>Purulent secretions present</td>
<td>2</td>
</tr>
<tr>
<td>Oxygenation: PaO₂/fraction of inspired oxygen, mm Hg</td>
<td></td>
</tr>
<tr>
<td>&gt; 240 or ARDS†</td>
<td>0</td>
</tr>
<tr>
<td>≤ 240 and no ARDS</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary radiography</td>
<td></td>
</tr>
<tr>
<td>No infiltrate</td>
<td>0</td>
</tr>
<tr>
<td>Diffuse or patchy infiltrate</td>
<td>1</td>
</tr>
<tr>
<td>Localized infiltrate</td>
<td>2</td>
</tr>
<tr>
<td>Progression of pulmonary infiltrate</td>
<td></td>
</tr>
<tr>
<td>No radiographic evidence of progression</td>
<td>0</td>
</tr>
<tr>
<td>Radiographic progression (congestive heart failure and ARDS excluded)</td>
<td>2</td>
</tr>
<tr>
<td>Pathogenic bacteria cultured from tracheal aspirate</td>
<td></td>
</tr>
<tr>
<td>Rare or light quantity or no growth</td>
<td>0</td>
</tr>
<tr>
<td>Moderate or heavy quantity (with same growth on Gram stain)</td>
<td>1 (+1)</td>
</tr>
</tbody>
</table>

*Data are used with permission from Pugin et al as adapted by Singh et al.
†Defined as PaO₂/fraction of inspired oxygen ≤ 200, pulmonary arterial wedge pressure ≤ 18 mm Hg, and acute bilateral infiltrates
GI tract are controversial and not widely accepted in the United States. Fortunately, multiple less controversial nonpharmacologic strategies for VAP prevention exist. Most are well known but have not received the attention they merit.

**Semirecumbency**

One of the simplest and least expensive measures is maintaining the patient’s head of bed in an elevated position. Increasing the head-of-bed angle is effective because it decreases the risk of aspiration of both gastric contents and of secretions from the upper aerodigestive tract. These secretions are often colonized with potentially pathogenic bacteria, and generally colonization precedes infection. In a randomized prospective study conducted by Drakulovic and colleagues in patients receiving mechanical ventilation, semirecumbent positioning to ≥ 45° significantly reduced the risk of clinically suspected pneumonia by > 25% compared to the supine position. Although a well-recognized, simple, and inexpensive intervention, Helman et al. noted during informal observation that the majority of patients receiving mechanical ventilation in their ICU had head-of-bed angles maintained at < 30°, consistent with the findings of others. These authors attempted to change behavior and practice in their ICU by creating a standardized order set that required head-of-bed positioning at a ≥ 45° angle. With this tactic, investigators enhanced compliance, which climbed from 3% before intervention to 16% (p < 0.05). Supplemented with educational programs, head-of-bed positioning compliance further improved. In interviews with nurses, these researchers found that concerns about patients sliding in the bed, having reduced lateral movement, and patient discomfort were the most common reasons offered for noncompliance. Although Helman et al. were encouraged that head-of-bed angles increased an average of 11° over baseline, they emphasized that such interventions, simple as they may seem, require intense education, constant follow-up, and behavior modification on the part of physician, nursing, and respiratory therapy staff. Further research is needed to define whether head-of-bed positioning at ≥ 30° or ≥ 45° prevents VAP to a different extent, since lower angles were easier to achieve.

**Educational Initiatives and Guidelines**

The power of educational initiatives and their potential to lead to significant reductions in VAP is striking. Zack and coworkers described the impact of a self-study instructional module on VAP prevention strategies. A multidisciplinary task force comprised of two physician leaders and members of the hospital infection control team developed the program. Their educational module targeted respiratory care practitioners and critical care nurses. The intense but simple educational effort, involving before and after testing, facilitated the reduction of VAP by 57.6%. ICUs with the highest initial rates of VAP accounted for the largest decreases in VAP incidence (Fig 2). The authors estimated that their project yielded significant cost savings: up to $4 million annually. The success of the initiative was, in part, attributed to the participation of physician leaders and hospital administrators, as well as the general acceptance of the common goal, preventing VAP.

![Figure 2. Impact of educational efforts on reduction of VAP rates in individual ICUs. Data are from Zack et al. *Significant decrease in VAP rates before and after intervention (p < 0.001).*](image-url)
Not all guidelines or educational initiatives have achieved such success. Scarcity of resources, patient discomfort, disagreement with trial results, fear of potential adverse effects, and costs may impede adoption of comprehensive preventive strategies. In a survey conducted by Ricart and colleagues, nurses tended to cite patient discomfort and safety issues, whereas physicians were more likely to name costs or differences in interpretation of clinical trial results as reasons for nonadherence with evidence-based preventive strategies. Compliance with prevention recommendations also appears to vary between countries. Cook et al compared Canadian and French ICUs regarding the use of seven strategies to control secretions and care for ventilator circuits to prevent VAP and reduce overall healthcare costs. Adherence to specific prevention guidelines for VAP was statistically more common among French ICUs (64% vs 30%, \( p = 0.002 \)), although rates were low in both countries. These investigators also found that published recommendations did not appear to substantially affect whether prevention interventions were used within individual ICUs. Cook et al also surveyed clinicians to determine specifically the reasons for the lack of use of semirecumbency to prevent hospital-acquired pneumonia/VAP. Nurses perceived that the main determinant of semirecumbency was physicians’ orders, whereas intensivists perceived that the main determinant was nurses’ preferences. Participants identified barriers to semirecumbency related to useful alternative positions (eg, lateral position), contraindications (eg, hemodynamic instability), risk of harm (eg, decubitus ulcers), safety (eg, sliding out of the bed), and available resources (eg, insufficient beds facilitating semirecumbency). When made aware of the evidence, all participants endorsed the use of semirecumbency. Armed with this information, clinical guidelines and educational programs can be better designed to address these issues in an effort to improve compliance.

**Noninvasive Ventilation**

Several other nonpharmacologic strategies aimed at VAP prevention have been the subject of research. Noninvasive mechanical ventilation (NIV) has been shown to reduce the incidence of VAP and mortality in clinical trials of selected populations. By avoiding endotracheal intubation, NIV removes a major risk factor for the development of VAP. However, broader reliance on NIV has been limited. Girou and colleagues have documented the value of NIV. Over the course of an 8-year longitudinal study in patients with acute exacerbations of COPD or severe cardiogenic pulmonary edema, they observed that increased utilization of NIV was associated with decreased VAP rates and lower mortality (Fig 3). The relationships between NIV and improved survival remained statistically significant after adjusting for multiple potential confounding variables including severity of illness, bronchodilator use, and propensity scores (eg, probability of receiving treatment with NIV over the years). In their multivariate

![Figure 3](image-url)

**Figure 3.** Trends in NIV and associated outcomes: time-trend analysis of NIV use (\( p < 0.001 \)), nosocomial infections (\( p = 0.01 \)), and ICU mortality (\( p = 0.04 \)); \( p \) values are for 1994 vs 2001. Used with permission from Girou et al.
analysis, NIV independently appeared to exert its effect on improved outcomes mainly by preventing nosocomial infection. A meta-analysis completed by Burns et al.\textsuperscript{35} contains information about noninvasive positive pressure strategies for weaning from mechanical ventilation and its impact on VAP.

### Endotracheal Intubation

In addition to avoiding endotracheal intubation, redesigning the endotracheal tube has emerged as an intriguing option for VAP prevention. Frequently, the endotracheal tube becomes coated with a biofilm, which promotes upper airway and, in turn, lower airway colonization. Silver-coating urinary catheters as a means for limiting the emergence of colonized biofilm reduces urinary tract infections.\textsuperscript{36} A similar approach is currently being studied with endotracheal tubes. An animal model of mechanical ventilation and pneumonia revealed that silver-coated endotracheal tubes delay host colonization. This decreased propensity for colonization correlates with histologic evidence of delayed alveolar neutrophil infiltration and fewer cases of pneumonia.\textsuperscript{37} Continuous subglottic suctioning of endotracheal tubes represents another option for preventing VAP and is potentially attractive since it can be highly cost-effective.\textsuperscript{38} A recent study\textsuperscript{39} in which this technique was combined with semirecumbent positioning, however, showed no clinical benefit.

### Transfusion Practice

All efforts at preventing VAP initially require the identification of factors that increase the risk for this condition. Hand-washing programs, patient positioning, avoiding gastric overdistension and nasal intubation, maintenance of ventilator and suction devices, and other VAP prevention strategies all arose from observations that these variables both correlated with the diagnosis of VAP and were, at the same time, potentially modifiable. One issue that has received little attention, specifically as it relates to nosocomial infection, is transfusion practice. Several studies\textsuperscript{40–42} have suggested that in non-ICU patients, RBC transfusion heightens the risk for nosocomial infection. Similar data are emerging for VAP. In a secondary analysis\textsuperscript{43} of data from a large study (n = 4,892) of transfusion practices in critically ill patients,\textsuperscript{44} RBC transfusions were found to be an independent risk factor for VAP. Other factors associated with VAP included male gender, hospital admission following trauma, and treatment with heavy sedation (Table 2). Of these, RBC transfusions may represent an easily modifiable risk factor, especially since, in a recent study by Levy et al.\textsuperscript{45} patients receiving mechanical ventilation received transfusions at higher pretransfusion hemoglobin levels than patients not receiving mechanical ventilation (8.7 ± 1.7 g/dL vs 8.2 ± 1.7 g/dL, respectively; p < 0.0001). Strikingly, there seemed to be no one clear reason why patients needing mechanical ventilation received transfusions more often.

### Conclusions

VAP is a costly and common complication of intensive care. Despite multiple studies investigating the diagnosis, treatment, and prevention of VAP, disagreement and controversy remain. Education of practitioners about VAP prevention, timing of antibiotic treatment, appropriate selection and duration of antibiotic regimens, proper identification of patients requiring therapy, and counseling against the overuse of antibiotics represent several important strategies to reduce the burden of VAP.

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### Table 2—Risks of VAP Identified in a Secondary Analysis of Data from the CRIT Study*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.54 (1.15–2.07)</td>
<td>0.0042</td>
</tr>
<tr>
<td>Trauma admission</td>
<td>1.68 (1.15–2.47)</td>
<td>0.0079</td>
</tr>
<tr>
<td>Continuous sedation</td>
<td>1.43 (1.07–1.92)</td>
<td>0.0158</td>
</tr>
<tr>
<td>Enteral nutrition within 48 h of mechanical ventilation</td>
<td>2.65 (1.93–3.63)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>3.27 (2.24–4.75)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Transfusion with 1 to 2 U of RBCs</td>
<td>1.90 (1.28–2.92)</td>
<td>0.0027</td>
</tr>
<tr>
<td>Transfusion with &gt; 2 U of RBCs</td>
<td>1.87 (1.24–2.92)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Any transfusion†</td>
<td>1.89 (1.33–2.68)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, d</td>
<td>1.50 (1.33–1.70)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Data are used with permission from Shorr et al.\textsuperscript{41} CRIT = hematocrit and critical care study by Corwin et al.\textsuperscript{44} †Estimates from a separate model in which any transfusion replaces the categorical transfusion variables.
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