THERAPEUTICS

An antibiotic regimen for 8 days was as effective as one for 15 days in ventilator-associated pneumonia

Chastre J, Wolff M, Fagon JY, et al. **Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial.** JAMA. 2003;290:2588-98.

QUESTION
In patients with microbiologically proven ventilator-associated pneumonia (VAP), is an 8-day course of antibiotics as effective as (noninferior to) a 15-day course with respect to all-cause mortality, pulmonary infection recurrence, and antibiotic-free days?

METHODS
Design: Randomized controlled trial.

Allocation: Concealed.*

Blinding: Blinded for 8 days (clinicians, patients, and pharmacists).*

Follow-up period: 60 days.

Setting: 51 intensive care units (ICUs) in France.

Participants: 402 patients > 18 years of age who received mechanical ventilation for ≥ 48 hours and developed objectively documented (by quantitative culture results of broncho-scopic specimens) VAP. Exclusion criteria included early-onset pneumonia (within the first 5 d of mechanical ventilation) without antimicrobial therapy during the 15 days preceding infection, and enrollment in other studies.

Intervention: Patients were stratified by center and allocated to an antibiotic regimen (selected by the treating physician) for 8 days (n = 197) or 15 days (n = 204).

Outcomes: All-cause mortality, microbiologically documented pulmonary infection recurrence, and antibiotic-free days assessed 28 days after onset of VAP. The study had 90% power to exclude a 10% difference between the 2 groups for all-cause mortality and pulmonary infection recurrence.

Patient follow-up: 401 patients (99.8%) (mean age 61 y, 72% men) completed follow-up and were included in the intention-to-treat analysis.

MAIN RESULTS
The groups did not differ for rates of all-cause mortality or pulmonary infection recurrence (Table). However, the mean number of antibiotic-free days was greater in the 8-day regimen group than in the 15-day regimen group (Table).

CONCLUSIONS
In patients with microbiologically proven VAP, an 8-day antibiotic regimen did not differ from a 15-day regimen for all-cause mortality or recurrence of pulmonary infection. Patients also had more antibiotic-free days.

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*See Glossary.

8 vs 15 days of antibiotic therapy in ventilator-associated pneumonia at 28 days after bronchoscopy†

Outcomes	8-day regimen	15-day regimen	Difference (90% CI)
All-cause mortality	18.8%	17.2%	1.6% (−3.7 to 6.9)‡
Pulmonary infection recurrence	28.9%	26.0%	2.9% (−3.2 to 9.1)‡
Mean antibiotic-free d	13.1	8.7	4.4 (3.1 to 5.6)§

†CI defined in Glossary.
‡Criteria for noninferiority were met because upper limits of the 90% CIs were less than 10% (the prespecified clinically acceptable difference).
§Conventional 95% CI.

COMMENTARY
VAP is the scourge of the intensivist. Notoriously difficult to diagnose, VAP develops in 10% to 20% of patients in ICUs who are intubated for > 24 hours, contributes to a prolonged ICU stay, and increases ICU mortality. The causative organisms are typically resistant to first-line antibiotics, and persistence or recurrence despite therapy is common. As a result, clinicians often choose a prolonged course of broad-spectrum antibiotics, trading the potential risk for promoting antibiotic resistance or superinfection for the presumptive security that the patient is being adequately treated. Therapy is continued for a prolonged, but arbitrary, interval because validated and objective criteria to indicate that the infection has been successfully eradicated do not exist.

Chastre and colleagues have addressed this latter issue in a multi-center French study of the optimal duration of antibiotic therapy for culture-proven VAP. Their findings can be summarized as follows: 8 days of therapy does not differ appreciably from a longer course of 15 days, as mortality and recurrence rates are similar. A shorter course of therapy results in a higher recurrence rate of infection with nonfer-menting Gram-negative bacilli, such as *Pseudomonas*, but recurrence is less likely to be caused by multiresistant organisms. A shorter course of therapy results in more antibiotic-free days, although it is striking that patients in the 8-day treatment group still received antibiotics for 14.9 of the 28 study days, whereas those in the 15-day treatment group received antibiotics for a mean of 19.3 days.

Antibiotics are among the most widely used drugs in contemporary ICUs: Population-based surveys show that rates of use exceed 1100 drug-defined days per 1000 patient days. Although consensus exists that indiscriminate use of antibiotics has contributed to a serious problem of antibiotic resistance, few studies of strategies to minimize antibiotic exposure have been done. Showing that antibiotic exposure can be safely minimized in the ICU where patients are most vulnerable—and antibiotic use most intensive—makes an important contribution to responsible practice.

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