

Ontario Antimicrobial Stewardship Project
Evidence-Based Summary for
Appropriate Duration of Antimicrobial Therapy:

Ventilator-Associated Pneumonia

*For patients with proven ventilator-associated pneumonia (VAP) who have received adequate initial antimicrobial therapy, an overall duration of antibiotic treatment of 8 days is appropriate. Because of higher rates of recurrent infections caused by *Pseudomonas aeruginosa* or multidrug-resistant (MDR) *Acinetobacter* spp., consideration should be given to extending the duration of therapy to 15 days for patients with these infections.*

A randomized controlled trial of 197 patients with VAP compared durations of antibiotic treatment of 8 and 15 days.¹ Patients were included if they had undergone intubation followed by mechanical ventilation for more than 48 hours, had positive results on culture of respiratory samples, had a clinical diagnosis of VAP, and had been started on appropriate empiric antibiotic therapy. The selection of the empiric antibiotics was left to the discretion of the treating physician, but the preferred regimen was initial treatment with an aminoglycoside or fluoroquinolone plus a broad-spectrum beta-lactam, followed by targeted therapy after 48–72 hours. Overall, at follow-up on day 28, the 8-day course of therapy was non-inferior to the 15-day course of therapy for all-cause mortality and microbiologically documented recurrence of infection. There were no significant differences in the secondary end points of 60-day mortality, length of stay in the intensive care unit (ICU) or hospital, or number of days of mechanical ventilation. For primary infections caused by nonfermenting gram-negative bacilli (*P. aeruginosa* or *Acinetobacter* spp.), the percentage of patients with recurrence of pulmonary infection was greater for the 8-day treatment group, but mortality rate and length of hospital stay were no greater in this group. When such organisms were isolated and the initial antibiotic therapy is inadequate (i.e., culture-determined organism is not sensitive to initial therapy), it may be appropriate to continue therapy for 15 days, according to clinical response and requirement for continued intubation.

Formalized discontinuation strategies should be implemented to effectively shorten the duration of antibiotic therapy for patients with suspected VAP.

Evidence-based clinical practice guidelines for VAP recommend the use of an antibiotic discontinuation strategy based on clinical criteria, because such an approach shortens the duration of antibiotic therapy with no adverse effects on clinical outcome.²

A formal discontinuation policy for patients receiving empiric antibiotic therapy was compared with discontinuation based on the clinical judgement of the treating physician in a prospective, randomized study of 290 patients with presumed VAP.³ There were no statistically significant differences between the groups in terms of hospital mortality, length of stay in the ICU or the hospital, duration of mechanical ventilation, or total number of subsequent hospital-acquired infections, despite the difference in duration of antibiotic therapy. The discontinuation policy recommended that therapy be stopped if a noninfectious cause for pulmonary infiltrates was identified (e.g., atelectasis, pulmonary edema) or if all of the signs and symptoms suggesting active infection had resolved (i.e., temperature, leukocyte count, improvement or lack of progression as indicated by chest radiography, absence of purulent sputum, and ratio of

arterial oxygen pressure to fraction of inspired oxygen > 250). Use of the clinical pulmonary infection score (CPIS; see Appendix) as part of an antibiotic discontinuation strategy has also been found to shorten the duration of antibiotic therapy.⁴ The CPIS specifies criteria for temperature, blood leukocyte count, tracheal secretions, oxygenation, pulmonary radiography, progression of pulmonary infiltrate, and culture of tracheal aspirate. A randomized controlled trial assigned a total of 81 patients to an intervention or control group. The intervention group received intravenous ciprofloxacin, and the CPIS was evaluated at 3 days; if the CPIS was 6 or below, the antibiotic was stopped. For the control group, selection of antibiotics and duration of therapy were directed by the physician. There was no significant difference between the groups with respect to mortality. Patients in the intervention group had a significantly shorter duration of antibiotic therapy, shorter ICU stays, and lower incidence of antimicrobial resistance or super-infections. Other studies have demonstrated the safety of de-escalation and targeted antibiotic strategies in the management of VAP.^{5, 6}

Appropriate single-agent therapy for each potential pathogen is recommended as empiric therapy for VAP, tailored to local resistance patterns. The exception to this recommendation is patients who are at high risk for infections with Pseudomonas or MDR pathogens and patients who are receiving treatment in units where Pseudomonas or MDR pathogens are endemic who should be initiated on empiric combination therapy for VAP based local resistance patterns.

Recent evidence-based guidelines have recommended appropriate single-agent therapy for each potential pathogen as empiric therapy for VAP.^{1]} Using data from 5 trials, the authors of these guidelines concluded that empiric broad-spectrum combination therapy had no advantage over monotherapy with respect to mortality and clinical response rates. This use of “as-recommended monotherapy” is another strategy for efficient use of antimicrobial therapy.

In a study of 740 patients treated for more than 96 hours in the ICU similar outcomes were achieved with combination therapy and monotherapy with broad-spectrum antibiotics for suspected late-onset VAP.⁷ A subgroup analysis of 56 patients with at least one of *P. aeruginosa*, *Acinetobacter* spp., or another MDR gram-negative organism identified by culture at the time of enrolment showed that combination therapy was associated with a significantly higher rate of adequacy of initial therapy.⁷ As expected, trends toward higher rate of eradication of infecting microorganisms, shorter duration of mechanical ventilation and ICU stay, and lower ICU and hospital mortality were also observed in the group receiving combination therapy. A retrospective, observational cohort study of 221 patients in Spain compared the use of a single antibiotic with combination antibiotic therapy for patients with VAP caused by *P. aeruginosa*.⁸ In that study, the rate of appropriate initial antibiotic therapy was significantly higher among patients who received combination therapy. A trend toward greater in-hospital mortality was observed for patients receiving empiric monotherapy.⁸

On the basis of these studies, appropriate combination therapy is recommended for patients with VAP and the above risk factors to increase the likelihood of that initial antimicrobial therapy will be appropriate.

References

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Appendix

Clinical Pulmonary Infection Score Calculation (3)

Temperature (°C)

- ≥ 36.5 and ≤ 38.4 = 0 points
- ≥ 38.5 and ≤ 38.9 = 1 point
- ≥ 39 and ≤ 36 = 2 points

Blood leukocytes (number per mm³)

- ≥ 4x10⁹/L and ≤ 11x10⁹/L = 0 points
- < 4x10⁹/L or > 11x10⁹/L = 1 point + band forms ≥ 50% = add 1 point

Tracheal secretions

- Absence of tracheal secretions = 0 points
- Presence of nonpurulent tracheal secretions = 1 point
- Presence of purulent tracheal secretions = 2 points

Oxygenation (PaO₂/FiO₂, mm Hg)

- > 240 or ARDS (ARDS defined as PaO₂/FiO₂ > 200, pulmonary arterial wedge pressure ≤ 18 mm Hg, and acute bilateral infiltrates) = 0 points
- ≤ 240 and no ARDS = 2 points

Pulmonary radiography

- No infiltrate = 0 points
- Diffuse (or patchy) infiltrate = 1 point
- Localized infiltrate = 2 points

Progression of pulmonary infiltrate

- No radiographic progression = 0 points
- Radiographic progression (after exclusion of CHF and ARDS) = 2 points

Culture of tracheal aspirate

- Pathogenic bacteria* cultured in rare or light quantity or no growth = 0 points
- Pathogenic bacteria cultured in moderate or heavy quantity = 1 point
- Same pathogenic bacteria seen on Gram staining, add 1 point

Definition of abbreviations:

ARDS = acute respiratory distress syndrome, CHF = congestive heart failure, PaO₂/FiO₂ = ratio of arterial oxygen pressure to fraction of inspired oxygen.

*Predominant organism in the culture.