DISEASE MANAGEMENT

Early intervention with empirical antibacterials is essential in the treatment of ventilator-associated pneumonia

Ventilator-associated pneumonia is common in patients in intensive care units. As treatment usually cannot wait until the causative organism has been identified, empirical antibacterial therapy should be initiated based on risk factors for virulent and/or resistant microorganisms.

Ventilated patients at high risk

Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring in patients with acute respiratory failure supported by invasive mechanical ventilation and which was absent at the time of endotracheal intubation.[1] VAP affects ≈10–20% of ventilated patients and is associated with high costs and increased morbidity and mortality in patients in the intensive care unit (ICU). This article summarizes the review by Vincent et al.[1] on the treatment and prevention of VAP.

Pneumonia in critically ill patients results from aspiration of nasal, oropharyngeal or gastric microorganisms and is complicated by impaired host defences, which facilitate colonization of the normally sterile lower respiratory tract and lung tissue.[1] The presence of an endotracheal tube in patients receiving mechanical ventilation helps bypass normal defence mechanisms, such as mucociliary clearance and cough, creates an unnatural passage between the trachea and upper airway, and may act as a source of contaminated secretions.[1]

Causative organism depends on time of onset and resistance patterns

The causative organism in VAP is influenced by a number of factors, including the duration of mechanical ventilation, length of ICU and hospital stay, presence of co-morbidities, prior antibacterial therapy and geographical location.[1] Despite these variables, generalizations can be made about common probable pathogenic organisms depending on the presence or absence of risk factors (table I). The most commonly isolated causative microorganisms causing VAP are Gram-negative enteric bacilli, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[1] Viral and fungal pathogens may also cause VAP, but are relatively uncommon in immunocompetent patients.[2,3]

The presence of antibacterial resistance complicates treatment and is associated with increased mortality.[1] As resistance patterns of pathogens differ with early- and late-onset VAP, the time of occurrence should be considered when selecting empirical drug therapy for VAP.[4] 'Community' organisms tend to be the cause of early-onset VAP, whereas late-onset VAP is more likely to be caused by more virulent pathogens (table I).

Initiate empirical therapy until causative organism identified

Treatment of VAP centres principally on antibacterial therapy and should be started as early as possible.[1] As

Table I. Common causative organisms of ventilator-associated pneumonia (VAP)[2]

Patient group	Commonly isolated organisms
Patients with no risk factors for multidrug-resistant organisms	*Streptococcus pneumoniae* *Haemophilus influenzae* Antibacterial-sensitive enteric Gram-negative bacilli *Escherichia coli* *Klebsiella pneumoniae* *Enterobacter* spp. *Proteus* spp. *Serratia marcescens*
Patients with late onset (>5 days) VAP *or* Patients with one of the following risk factors for multidrug-resistant organisms: antimicrobial therapy in the preceding 90 days; current hospitalization of ≥5 days; high frequency of resistance in the community or hospital; presence of risk factors for healthcare-associated pneumonia[a]; immunosuppressive disease and/or therapy	As above, *plus*: *Pseudomonas aeruginosa* *K. pneumoniae* (extended-spectrum β-lactamase) *Acinetobacter* spp. Meticillin-resistant *Staphylococcus aureus*

a Hospitalization for ≥2 days in the preceding 90 days, residence in a nursing home/extended care facility, home infusion therapy or wound care, chronic dialysis within 30 days, family member with multidrug-resistant pathogen.

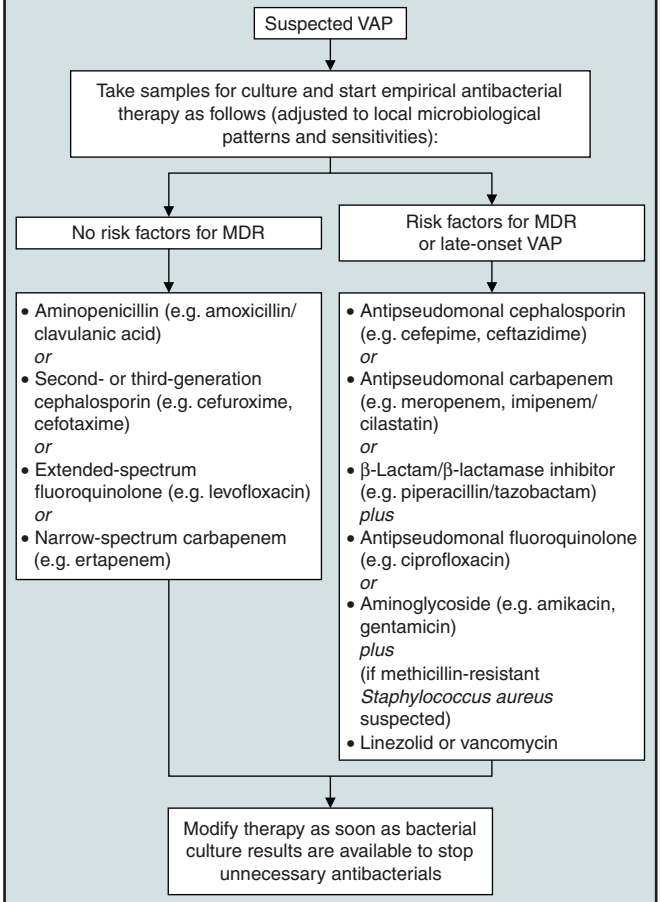
1172-0360/11/0006-0009/$19.95

inappropriate or delayed therapy is associated with poorer outcomes, local infection and susceptibility patterns should initially be used to guide the choice of empirical antibacterial therapy.[1] However, guidelines for treatment have been developed to aid selection of the most appropriate antibacterial therapy based on the time of onset and other risk factors for multi-drug resistant organisms (*Patient care guidelines*).[2,4] Once bacterial culture and sensitivity information is available, broad-spectrum therapy should be de-escalated to more specific, narrow-spectrum cover.[1]

Single-agent therapy generally preferred

Most data suggest that combination therapy has no benefits over single-agent therapy for VAP and is associated with increased costs and risk of adverse effects.[1] Indeed, a meta-analysis of 41 studies evaluating parenteral antibacterial regimens in adult patients with VAP concluded that the rates of mortality (relative risk [RR] 0.94; 95% CI 0.76, 1.16) and treatment failure (RR 0.88; 95% CI 0.72, 1.07) were similar for monotherapy and combination therapy, although the quality of the studies was generally poor.[5] US and European guidelines generally recommend single-agent therapy in patients with early-onset VAP, but combination therapy in patients at risk of multi-drug resistant pathogens[2,4] (*Patient care guidelines*).

Patient care guidelines



Empirical antibacterial therapy for patients with ventilator-associated pneumonia (VAP) according to risk factors for multi-drug resistant (MDR) organisms, as suggested by Vincent et al.[1]

Response determines therapy duration

US guidelines for the management of VAP recommend that the treatment duration be determined by the severity of disease, clinical response and causative organism.[2] For example, a course of 7–14 days is recommended for VAP caused by *S. aureus* or *Haemophilus influenzae*, whereas 14–21 days is more appropriate for infection caused by *P. aeruginosa*.[2] A multivariate analysis concluded that the duration of therapy was not an independent predictor of infection recurrence or death at 28 days.[6]

Dose affected by a number of factors

The efficacy of an antibacterial depends on its mode of action and ability to penetrate lung tissue. A number of factors need to be taken into account when considering drug dosing in ICU patients. These include renal or hepatic dysfunction, haemodilution, hypoalbuminaemia and drug interactions.[1] Patients in the ICU may need higher or more frequent doses than other patient populations; continuous infusions may even be required.[1]

Other possible treatments include aerosolized antibacterials ...

Administration of antibacterials via aerosolized formulations may achieve higher concentrations of the drug at the affected site than administration via other routes.[1] Inhaled tobramycin and colistin have been studied in the treatment of VAP, with promising results. A meta-analysis of randomized, controlled trials showed that administration of antibacterials via the respiratory tract (alone or in combination with systemic antibacterials) was associated with greater treatment success than treatment with controls, although there was no effect on mortality rates.[7]

... adjuvant treatment with clarithromycin ...

The addition of clarithromycin 1 g/day for 3 days to standard antibacterial therapy in patients with VAP and sepsis was associated with accelerated resolution of VAP and weaning from mechanical ventilation compared with placebo in a randomized, controlled trial.[8] Clarithromycin

has anti-inflammatory properties that may be beneficial in patients with VAP.[1]

… and statins

Results of studies assessing the potential effects of HMG-CoA reductase inhibitors (statins) in patients with community-acquired pneumonia have been conflicting; some studies have shown better outcomes in patients who were receiving statins prior to pneumonia onset, whereas other studies have shown no correlation between prior use of statins and pneumonia outcomes.[1] A review of the use of statins in the treatment of sepsis suggested that statins may have beneficial effects on the outcome of infection, but the poor quality of studies did not allow firm conclusions to be drawn.[9] An open-label, randomized trial of the effect of pravastatin 40 mg/day versus control on the incidence and natural course of VAP in patients in the ICU may help resolve this issue, but results have not been made available.[10]

Prevention is an important issue

A number of non-pharmacological strategies have been suggested for the prevention of VAP, including adequate hand hygiene, the use of protective gowns and gloves, semi-recumbent patient positioning, continuous lateral rotation (i.e. kinetic beds), heat and humidification, suctioning of secretions, positive end-expiratory pressure (PEEP) and early tracheotomy.[1] Recent clinical data indicate that reductions in the incidence of VAP were generally shown with semi-recumbent patient positioning,[11] PEEP,[12] suctioning of secretions (although the optimal technique is still a subject of debate)[13,14] and continuous lateral rotation,[15] but that early versus late tracheotomy did not affect VAP rates,[16] and that there are no apparent differences in the effects of heat and moisture exchangers and the more expensive heated humidifiers on the incidence of VAP.[17]

Pharmacological-related strategies to prevent VAP include the following:

- The use of probiotics (e.g. *Lactobacillus*). Although some studies have suggested that administration of probiotics can reduce the incidence of VAP,[18,19] results in other studies have been conflicting.[20]
- The use of aersolized antibacterials. According to a meta-analysis,[21] this strategy reduced the incidence of VAP (odds ratio 0.49; 95% CI 0.32, 0.76), but did not affect mortality rates. There are concerns that the increased use of antibacterials could result in the emergence of resistant bacteria.
- Treatment of ventilator-associated tracheobronchitis (VAT). The incidence of VAP may be reduced through antibacterial treatment of VAT,[22,23] but further studies are needed, and there are concerns about the possible emergence of resistant bacteria.[24]
- Reduced sedation. A nurse-implemented sedation protocol significantly reduced the risk of VAP (hazard ratio 0.81; 95% CI 0.62, 0.95) and duration of mechanical ventilation in patients relative to patients managed before the introduction of the protocol, but did not affect mortality rates.[25]
- Selective digestive or oral decontamination. The use of antibacterials to clear the stomach and oropharynx of potentially pathogenic organisms to reduce the pathogenicity of aspirated contents and, hence, the incidence of VAP, is controversial.[1] Oral decontamination alone has been promoted as being preferable to selective digestive decontamination, as fewer antibacterials are required. A number of randomized, controlled trials have investigated the effect of oral decontamination with various antiseptics (e.g. 0.12–2% chlorhexidine solution or gel used as a rinse or applied once to four times daily,[26-31] iseganan [an antibacterial peptide] solution applied six times daily[32] and 10% povidone-iodine solution used as a rinse every 4 hours followed by aspiration of oropharyngeal secretions[33]). In most trials, oral decontamination did not have a significant effect on the incidence of VAP,[26-30,32] with the exception of significant ($p \leq 0.03$) reduction in the risk of VAP with 2% chlorhexidine solution both with or without 2% colistin versus placebo,[31] as well as when the results of this trial were pooled with those of a trial of 2% chlorhexidine solution versus saline solution[30] (RR 0.53; 95% CI 0.31, 0.90),[30] and a significant ($p \leq 0.03$) decrease in incidence of VAP with 10% povidone-iodine solution rinse versus saline or control rinse (8% vs 39% vs 42%).[33] The heterogeneous nature of these trials make it difficult to draw conclusions on the effectiveness of this treatment.[1] In a meta-analysis of seven trials, oral decontamination with antiseptics was associated with a reduced incidence of VAP (RR 0.56; 95% CI 0.39, 0.81), although no effect on the duration of mechanical ventilation or mortality was seen.[34]

'Bundles' might be the key

Preventative care 'bundles' (i.e. careful implementation of multiple VAP preventive strategies) have been shown to be beneficial in a number of studies.[1] While not all studies have shown bundles to reduce the rate of VAP and none have shown an impact on outcomes, an approach to the prevention of VAP that contains a combination of factors is likely to be the future standard of care.[1]

Disclosure

This review was adapted from *Drugs* 2010; 70 (15): 1927-44[1] by Adis editors and medical writers. The preparation of these articles were not supported by any external funding.

References

1. Vincent JL, de Souza Barros D, Cianferoni S. Diagnosis, management and prevention of ventilator-associated pneumonia: an update. Drugs 2010; 70 (15): 1927-44
2. American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171 (4): 388-416
3. Park DR. The microbiology of ventilator-associated pneumonia. Respir Care 2005; 50 (6): 742-63
4. Torres A, Ewig S, Lode H, et al. Defining, treating and preventing hospital acquired pneumonia: European perspective. Intensive Care Med 2009; 35 (1): 9-29
5. Aarts MA, Hancock JN, Heyland D, et al. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. Crit Care Med 2008; 36 (1): 108-17
6. Combes A, Luyt CE, Fagon JY, et al. Early predictors for infection recurrence and death in patients with ventilator-associated pneumonia. Crit Care Med 2007; 35 (1): 146-54
7. Ioannidou E, Siempos II, Falagas ME. Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis. J Antimicrob Chemother 2007; 60 (6): 1216-26
8. Giamarellos-Bourboulis EJ, Pechere JC, Routsi C, et al. Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. Clin Infect Dis 2008; 46 (8): 1157-64
9. Kopterides P, Falagas ME. Statins for sepsis: a critical and updated review. Clin Microbiol Infect 2009; 15 (4): 325-34
10. Pravastatin and ventilatory associated pneumonia (EPRAVAP) [ClinicalTrials.gov identifier NCT00702130]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2011 Mar 21]
11. Alexiou VG, Ierodiakonou V, Dimopoulos G, et al. Impact of patient position on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. J Crit Care 2009; 24 (4): 515-22
12. Manzano F, Fernandez-Mondejar E, Colmenero M, et al. Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. Crit Care Med 2008; 36 (8): 2225-31
13. Niel-Weise BS, Snoeren RL, van den Broek PJ. Policies for endotracheal suctioning of patients receiving mechanical ventilation: a systematic review of randomized controlled trials. Infect Control Hosp Epidemiol 2007; 28 (5): 531-6
14. Chastre J. Preventing ventilator-associated pneumonia: could silver-coated endotracheal tubes be the answer? JAMA 2008; 300 (7): 842-4
15. Staudinger T, Bojic A, Holzinger U, et al. Continuous lateral rotation therapy to prevent ventilator-associated pneumonia. Crit Care Med 2010; 38 (2): 486-90
16. Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. JAMA 2010; 303 (15): 1483-9
17. Siempos II, Vardakas KZ, Kopterides P, et al. Impact of passive humidification on clinical outcomes of mechanically ventilated patients: a meta-analysis of randomized controlled trials. Crit Care Med 2007; 35 (12): 2843-51
18. Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. Am J Respir Crit Care Med 2010 Oct 15; 182 (8): 1058-64
19. Siempos II, Ntaidou TK, Falagas ME. Impact of the administration of probiotics on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. Crit Care Med 2010; 38 (3): 954-62
20. Barraud D, Blard C, Hein F, et al. Probiotics in the critically ill patient: a double blind, randomized, placebo-controlled trial. Intensive Care Med 2010 Sep; 36 (9): 1540-7
21. Falagas ME, Siempos II, Bliziotis IA, et al. Administration of antibiotics via the respiratory tract for the prevention of ICU-acquired pneumonia: a meta-analysis of comparative trials. Crit Care 2006; 10 (4): R123
22. Nseir S, Favory R, Jozefowicz E, et al. Antimicrobial treatment for ventilator-associated tracheobronchitis: a randomized, controlled, multicenter study. Crit Care 2008; 12 (3): R62
23. Palmer LB, Smaldone GC, Chen JJ, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. Crit Care Med 2008; 36 (7): 2008-13
24. Dallas J, Kollef M. VAT vs VAP: are we heading toward clarity or confusion? Chest 2009; 135 (2): 252-5
25. Quenot JP, Ladoire S, Devoucoux F, et al. Effect of a nurse-implemented sedation protocol on the incidence of ventilator-associated pneumonia. Crit Care Med 2007; 35 (9): 2031-6
26. Bellissimo-Rodrigues F, Bellissimo-Rodrigues WT, Viana JM, et al. Effectiveness of oral rinse with chlorhexidine in preventing nosocomial respiratory tract infections among intensive care unit patients. Infect Control Hosp Epidemiol 2009; 30 (10): 952-8
27. Scannapieco FA, Yu J, Raghavendran K, et al. A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients. Crit Care 2009; 13 (4): R117
28. Fourrier F, Dubois D, Pronnier P, et al. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: a double-blind placebo-controlled multicenter study. Crit Care Med 2005; 33 (8): 1728-35
29. Panchabhai TS, Dangayach NS, Krishnan A, et al. Oropharyngeal cleansing with 0.2% chlorhexidine for prevention of nosocomial pneumonia in critically ill patients: an open-label randomized trial with 0.01% potassium permanganate as control. Chest 2009; 135 (5): 1150-6
30. Tantipong H, Morkchareonpong C, Jaiyindee S, et al. Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 2008; 29 (2): 131-6
31. Koeman M, van der Ven AJ, Hak E, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 2006; 173 (12): 1348-55
32. Kollef M, Pittet D, Sánchez GM, et al. A randomized double-blind trial of iseganan in prevention of ventilator-associated pneumonia. Am J Respir Crit Care Med 2006; 173 (1): 91-7
33. Seguin P, Tanguy M, Laviolle B, et al. Effect of oropharyngeal decontamination by povidone-iodine on ventilator-associated pneumonia in patients with head trauma. Crit Care Med 2006; 34 (5): 1514-9
34. Chan EY, Ruest A, Meade MO, et al. Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis. BMJ 2007; 334 (7599): 889