Ventilator-Associated Pneumonia

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Case Presentation

A 55-year-old woman with a history of type 2 diabetes mellitus, chronic obstructive pulmonary disease, obesity hypoventilation syndrome, and sleep apnea, along with coronary artery disease with a 3-vessel bypass 5 years prior, developed new onset shortness of breath and fever after babysitting her 3-year-old grandchild. She arrived at the emergency room with worsening respiratory status. Her ventilation rapidly deteriorated despite the use of noninvasive positive pressure ventilation and she became minimally responsive, prompting endotracheal intubation and admission to the medical intensive care unit. A chest radiograph at that time showed a lobar infiltrate. Cultures from endotracheal aspirates were negative. After 3 days of management of her COPD with intravenous steroids, antibiotic coverage with levofloxacin, and inhaled bronchodilator therapy, her oxygenation continued to improve. She continued to fail her spontaneous breathing trial, however, and remained intubated. On ICU day 5, however, she developed a new fever and her oxygenation worsened. Having previously been down to an FiO_2 of 0.3, this fraction was increased to 0.5, and her positive end-expiratory pressure was increased to 10 cm from 5 cm of water to maintain adequate oxygenation. A chest radiograph now shows diffuse, bilateral infiltrates (Fig. 29.1).

Question

What is this patient's diagnosis?

Answer Ventilator-Associated Pneumonia (VAP)—Despite aggressive and supportive management, pneumonias that arise from hospital settings remain a challenging and enduring clinical entity. Hospital-acquired pneumonia is defined as pneumonia in patients hospitalized for 2 or more days but who did not appear to have pneumonia on admission. The earlier designation of healthcare associated pneumonia was removed from the 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS); while patients with recent contact with healthcare settings are at increased risk of infection with multidrug resistant (MDR) organisms, this population of patients should have their antimicrobial therapy determined by clinical context [1]. Ventilator-associated pneumonia is defined as a new pneumonia in those patients who have been intubated for at least 2–3 days. Features of VAP include worsening radiographic opacities, increasing secretions, bronchospasm or hemoptysis, and worsening gas exchange

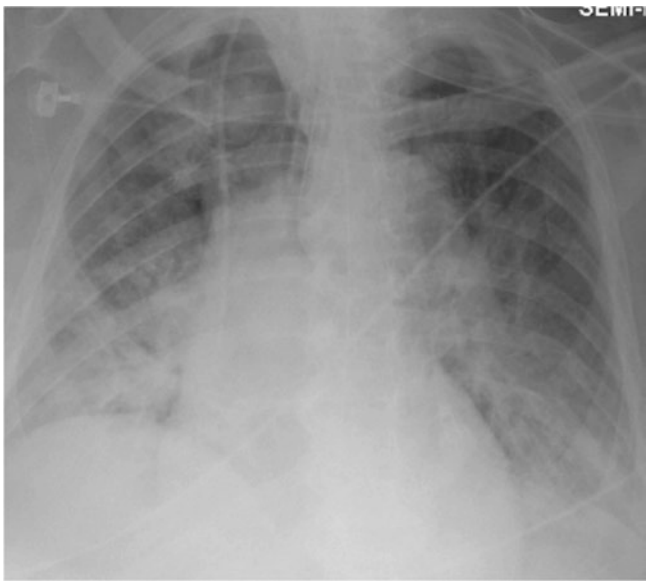

Fig. 29.1 Chest X-ray on ICU day 5

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on the ventilator. While early treatment is essential, rapid de-escalation of antibiotics in the face of negative culture results is also important. Sampling of the respiratory tract is necessary to further guide management; samples may be obtained either through tracheobronchial aspiration, bronchoalveolar lavage (BAL), mini-BAL, or protected specimen brush (PSB). Careful observation of individual hospitals' bacterial antibiogram is essential to provide treatment targeted to the resistance profile of each institution. The most common MDR pathogens include *P. aeruginosa, Escheriochia coli, Klebsiella pneumonia,* and *Acinetobacter* species as well as methicillin-resistant *S. aureus* [1].

Principles of Management

Rapid Identification and Empiric Treatment of VAP Is Essential

A high suspicion for VAP followed by rapid diagnosis and treatment is critically important. Zilberberg and colleagues found that among nearly 400 patients alive at 48 h with hospital-acquired pneumonia, inappropriate empiric antibiotic therapy was associated with a significant increase in mortality (30% vs. 18.3%, $p = 0.013$; OR 2.88 95% CI 1.46–5.67 in multivariable logistic regression). Treatment escalation did not change the risk of death in this single-center study [2]. Unfortunately, treatment is often delayed. In one study among 107 patients, 30.7% of patients had their therapy for VAP inappropriately delayed, defined as ≥24 h passing between VAP onset and providing the appropriate antimicrobial treatment. A delay in writing the antibiotic orders was the primary reason for delay in therapy in 75% of cases [3]. Endotracheal aspirate is the preferred means of sampling, prior to or at the time of antibiotic initiation, as multiple studies have demonstrated that this technique is equivalent to bronchoscopy with regards to patient outcomes and antibiotic exposure [4, 5].

Treat Patients with Vap Broadly for Multidrug Resistant Organisms

Patients with VAP should be universally initiated on therapy for (1) MRSA (for example, with vancomycin or linezolid) and (2) resistant gram-negative bacteria, such as *Pseudomonas aeruginosa, Klebsiella pneumoniase,* and *Acinetobacter* species. Treatment options for gram negative organisms include: antipseudomonal cephalosporins (cefepime or ceftazidime), antipseudomonal carbapenems (imipenem or meropenem), β-Lactam/β-lactamase inhibitor (piperacillin-tazobactam). When combination therapy for gram-negative bacteria is considered (see Evidence Contour below), addition of an antipseudomonal fluoroquinolone or an aminoglycoside should be considered. The dominant pathogens in one's local ICU should also contribute to decision making for appropriate choices of therapy but should be guided by the overall principles of the ATS/IDSA guidelines, as demonstrated by the IMPACT HAP collaboration [6, 7].

In addition to MDR risk factors, appropriate antimicrobial therapy should consider the patient's risk factors for: (1) extended-spectrum beta-lactamase-producing (ESBL) *Enterobacteriaceae*; (2) *Legionella*; and (3) anaerobes. If ESBL *Enterobactereiaceae* is suspected, a carbapenem should be used. Concerns about *Legionella* should prompt use of a macrolide or fluoroquinolone over an aminoglycoside. Some providers would treat patients with recent aspiration events for anaerobes, using clindamycin, β-Lactam/β-lactamase inhibitors, or a carbapenem.

For all other patients for whom the suspicion of VAP is low, appropriate therapy should be guided by the patient's risk factors for multidrug resistant organisms. In the absence of risk factors for MDR organisms, the ATS/IDSA guidelines recommend antibiotic therapy that targets *Streptococcus pneumonia, Haemophilus influenza,* Methicillin-sensitive *Staphylococcus aureus*, and antibiotic-sensitive enteric gram negatives: ceftriaxone, fluoroquinolone, or ampicillin/sulbactam [8]. While not all patients with HCAP have MDR organisms, distinguishing between the two may be difficult with recent residence in a nursing home or hospitalization for more than 48 h in the past 3 months appearing to increase the patient's risk the most [9, 10].

Duration of Therapy: 8 or 15 Days

Patients with ventilator-associated pneumonia should have the duration of antimicrobial therapy guided by type of organism. In a study of 401 patients using a randomized controlled design, there was no difference in mortality in the arm treated for 8 days vs. 15 days, although patients with *Pseudomonas* spp. had higher rates of recurrence [11]. A subsequent meta-analysis demonstrated patients with lactose non-fermenting gram-negative bacilli had nearly a two-fold increased odds of recurrence with shorter therapy courses [12]. In the absence of identification of lactose non-fermenting gram-negative bacilli (i.e. Pseudomonas, stenotrophomonas, and Acinetobacter), durations of 7–8 days should be used.

Rapidly De-escalate Antimicrobial Therapy

It is critical to de-escalate antimicrobial therapy when a specific pathogen has been identified, or when cultures are negative at 48–72 h. This helps prevent over-use of antibiotics and the development of resistance. Observational data provide a strong safety signal. In a study of surgical patients, neither mortality (34% vs. 42%) nor recurrent pneumonias (27% vs. 35%) dif-

fered between patients with VAP who underwent de-escalation vs. those who did not [13]. Among 398 patients with VAP, in a study by Kollef and colleagues, de-escalation of therapy occurred for 22% of patients. These patients had a lower mortality rate (17%) than those patients who underwent escalation (43%) or who had no change to their regimens (24%) [14].

Serum biomarkers, particularly C-reactive protein and procalcitonin (PCT), have been examined as guides for both the initiation and discontinuation of antibiotics. While the data are inconsistent regarding the clinical utility of these biomarkers [15], procalcitonin levels may help inform decisions to de-escalate antibiotic therapy. In subgroup analyses of the PRORATA trial, investigators found that patients with ventilator-associated pneumonia assigned to the study arm (where antibiotics were discontinued after PCT levels reached <0.5 μg) had 3.1 fewer days (95% CI 0.7 days—5.6 days) of antibiotics than those patients assigned to the control arm, without a difference in mortality [16]**.** In contrast, a multicenter randomized control trial of 1656 patients cared for initially in the emergency department for pneumonia had no difference in duration of antibiotic use when treatment decisions were guided by PCT, although under half of patients were hospitalized in this population [17]**.** Other studies that have looked at procalcitonin to guide therapy for undifferentiated septic shock or in broader settings have replicated that mortality does not appear to be affected when procalcitonin is used to guide therapy, although the findings on duration of antibiotics is more heterogeneous [18, 19]**.**

Clinicians Should Remain Vigilant for Other Causes of Fever in the ICU

Not all fevers are pneumonia, even in ICU patients with radiographic infiltrates. If patients are not improving at 48–72 h, and respiratory cultures taken before antibiotics are negative, be vigilant for other causes of fever (such as central line infections, intraabdominal process, etc.) and for complications of pneumonia (such as abscess and empyema). This scenario should also prompt reconsideration of the potential presence of resistant pathogens, and may warrant consultation with infectious diseases specialists.

Evidence Contour

Invasive vs. noninvasive sampling strategies

In all patients with suspected VAP, obtain an endotracheal aspirate for culture at minimum. Whether to pursue bronchoscopic sampling (or other invasive techniques) is more controversial. Endotracheal aspirates are very sensitive—a negative result is quite helpful because it has a high negative predictive value. Positive results can be harder to interpret. In one study of 52 episodes of pneumonia, endotracheal aspirate was found to have a sensitivity of 97.7% and specificity of 50% as compared with protected brush specimen [20]. Other studies have employed the Clinical Pulmonary Infection Score (CPIS) with a cut-off of 6 as a noninvasive method of identifying patients with VAP, using autopsy findings of pneumonia as the gold standard (Table 29.1) [21]. Fabregas et al. found a score of greater than 6 had a sensitivity of 77% but a specificity of 42% [22]. Conversely, bronchoscopic sampling may be less sensitive but is more specific for pneumonia. Randomized controlled trials are mixed. An RCT of 413 patients found no benefit to invasive sampling in unadjusted analyses, but did after adjustment for baseline factors [23]. A more recent RCT of 740 patients found no benefit to bronchoalveolar lavage over endotracheal aspirate [5]. Our practice is to perform immediate endotracheal aspirate in all patients with suspected VAP, but to reserve bronchoalveolar lavage or protected brush for selected cases, consistent with the IDSA/ATS guidelines but in contrast to the European Respiratory Society guidelines [1, 24].

Effective treatment strategies for MRSA VAP

The current recommendation from the ATS/IDSA is for coverage with either (1) 15 mg/kg of vancomycin every 8–12 h with a target serum trough between 15 and 20 mg/kg OR (2) 600 mg of linezolid every 12 h. One prospective trial of 1184 patients suggested that linezolid may be superior to vancomycin. In this study, 46% of patients treated with vancomycin had cul-

Table 29.1 Calculation of the Clinical Pulmonary Infection Score (CPIS)

Parameter		Points
Temperature	36.5–38.4	0
	38.5–38.9	1
	≥39.0 and ≤36.0	2
Blood leukocytes/mm^3	4000–11,000	0
	<4000 or >11,000	1
	Above + band forms ≥500	2
Tracheal secretions	<14+	0
	≥14+	1
	Above plus purulence	2
Oxygenation, PaO_2:FiO_2, mmHg	>240 or ARDS	0
	≤240 and no ARDS	2
Pulmonary radiograph finding	No infiltrate	0
	Diffuse or patchy infiltrate	1
	Localized infilitrate	2
Culture of tracheal aspirate specimen	Pathogenic bacteria cultured ≤1 or growth	0
	Pathogenic bacteria culture >1+	1
	Above plus same bacteria on gram stain >1+	2

The score may be calculated as a noninvasive method of determining whether a patient is a low-risk for pneumonia. A score of more than 6 has a 77% sensitivity and 42% specificity to identify VAP [22]

tures persistently positive for MRSA, while only 17% of patients treated with linezolid did. At 60 days, however, there was no difference in mortality rates, although nephrotoxicity did occur at greater rates with vancomycin [25]. As research in this space continues to evolve, linezolid may be a particularly good option among patients with renal failure.

Utility of ATS/IDSA recommendations for dual gram-negative coverage

Coverage with a second agent for gram-negative bacilli may be warranted based on local microbiologic patterns. For example, for patients with *P. aeruginosa* VAP who remain in shock or high-risk of death when antibiotic susceptibilities are known, the ATS/IDSA guidelines recommend combination therapy rather than monotherapy [1]. However, it is worth noting that synergy of medications has only been demonstrated *in vitro* and in neutropenic or bacteremic patients and randomized controlled trials have not demonstrate differences in clinical outcomes between monotherapy and combination therapy groups [7, 26, 27]. An observational cohort study in *Lancet* suggested combination therapy may be harmful, as the cohort of patients with ATS/IDSA-compliant antimicrobial therapy had a higher risk of death at 28 days than the noncompliant group [28]. This remains controversial, whether these individuals were at higher risk of death from the medications, the infections, or misidentification of them as at higher risk for MDR infection.

Evolving surveillance definitions

While clinical suspicion and identification of ventilator-associated pneumonia should remain high, significant controversy has revolved around establishing a reliable epidemiological surveillance definition. Prior to January 2013, the Centers for Disease Control's surveillance reporting definition the included several subjective components, including the change in the "character of sputum" and in radiographs [29–33]. As a result, several studies identified little agreement either across infection control experts at a single institution [34] or across multiple institutions [35]. Other definitions that sought to identify episodes of VAP either through greater invasive strategies or through other scoring mechanisms fared equally poorly [36].

In response, an effort of many professional societies and the CDC generated an alternative approach with the creation of the entity Ventilator Associated Event (VAE) [37]. Intended to cast a broader net, this newly-defined condition is intended to identify the majority of iatrogenic harm from mechanical ventilation, including but not limited to pneumonia [38, 39]. Further, it is designed to be reliable as it is solely based on any changes made to the ventilator that would indicate worsening oxygenation after a period of stability and at least 3 days into the course of mechanical ventilation. Review of radiology has been removed from the definition. There are subsequent subcategories of harm, including probably or possible pneumonia, which are based on antibiotic changes and evidence of positive qualitative or quantitative cultures (Table 29.2) [37].

While several studies have shown that this definition does lead to a reliable identification of individuals at higher risk of in-hospital mortality, it remains unclear the breadth of true disease states captured by definition [40, 41]. Lilly and colleagues found that the new VAE definition captured neither pneumonias nor hospital-acquired complications 93% of the time [42]. In contrast, Boudma and colleagues found ventilator-associated condition to be reasonably sensitive at identifying episodes of VAP (0.92) but not specific (0.28) [43]. Further, Adult

Table 29.2 National health safety network definition of ventilator-associated event

Type of ventilator-associated event	Definition
Ventilator-associated condition (VAC)	Either: 1. An increase in daily minimum $FiO_2 \geq 0.20$ *OR* 2. An increase in daily minimum PEEP values of ≥ 3 cmH_2O Either must be sustained for 2 or more calendar days
Infection-related ventilator-associated condition (iVAC)	VAC *PLUS* 1. Temperature > 38° or < 36° *OR* WBC ≥ 12,000 cells/mm^3 or ≤4000 cells/mm^3 *AND* 2. A new antimicrobial started and continued for 4 or more days
Possible ventilator associated pneumonia	iVAC *PLUS* 1. A positive qualitative, semi-qualitative, or quantitative culture of endotracheal aspirate (≥105 CFU/mL), bronchoalveolar lavage (≥104 CFU/mL), lung tissue (≥104 CFU/mL) or protected specimen brushing (≥103 CFU/mL) without purulent respiratory secretions *OR* 2. Purulent respiratory secretions PLUS a positive qualitative, semi-qualitative, or quantitative culture of sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue or protected specimen brushing that does not meet sufficient growth criteria from #1 *OR* 3. Organisms identified from pleural fluid, lung histopathology indicating abscess formation, positive *Legionella* species, or positive respiratory secretions for influenza, respiratory sysncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

A patient must be intubated with stable ventilator settings for 2 or more days before this may be applied

Respiratory Distress Syndrome is likely to be captured alongside VAP under the larger label of VAE [42, 44]. The first major intervention study to date designed to attempt to reduce rates of VAE demonstrated found spontaneous awakening trials and spontaneous breathing trials to be effective [45]. However, this remains a significant area of evolving science.

Strategies to prevent VAP

Data suggest that the rate of VAP remains stable, despite efforts at prevention, affecting around 10% of ventilated patients [46]. Modifiable risk factors for patients with VAP should be considered, in an effort to minimize the likelihood of developing VAP at the outset. These were described in a recent update on preventing ventilator associated pneumonia by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA) and are summarized in Table 29.3 [39].

Table 29.3 Recommendations from the Society of Healthcare Epidemiology of America and the Infectious Disease Society of America's 2014 updated recommendations for VAP prevention [39]

Recommendation	Level of recommendation
Minimizing sedation and assessing readiness to extubate daily through pairing spontaneous breathing trials and spontaneous awakening trials, which have been shown in two randomized control trials and one meta-analysis to reduce length of stay and duration of mechanical ventilation [47–50]	High
Instituting early mobilization and physical therapy, which has been shown to decrease length of stay and improve earlier return to independent function [51]	Moderate
Implementing strategies to reduce pooling of secretions above the endotracheal tube cuff, such as using endotracheal tubes with subglottic suctioning for patients requiring mechanical ventilation of 48 h or more [52–54]. A meta-analysis demonstrated reduction in VAP rates and length of mechanical ventilation [55]	Moderate
Changing ventilator circuits only when needed rather than on a schedule, which does little to decrease VAPs but does reduce costs [56]	High
Making use of noninvasive positive pressure ventilation (NIPPV) whenever possible, but only in the populations which have been shown to have some benefit (e.g. in chronic obstructive pulmonary disease or cardiogenic pulmonary edema) [57]. This recommendation, however, cautions use of NIPPV that may delay intubation, such as profound hypoxemia, acute respiratory distress syndrome or impaired consciousness [58]	High
Keeping the head of the bed elevated to at least 30°, which has only been shown to decrease VAP rates in one of three randomized control trials, but has little downside [59–61]	Low

References

1. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–e111.
2. Zilberberg MD, Shorr AF, Micek ST, Mody SH, Kollef MH. Antimicrobial therapy escalation and hospital mortality among patients with health-care-associated pneumonia: a single-center experience. Chest. 2008;134(5):963–8.
3. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest. 2002;122(1):262–8.
4. Berton DC, Kalil AC, Teixeira PJ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. Cochrane Database Syst Rev. 2014;10:CD006482.
5. Group CCCT. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med. 2006;355(25):2619–30.
6. Mangino JE, Peyrani P, Ford KD, Kett DH, Zervos MJ, Welch VL, et al. Development and implementation of a performance improvement project in adult intensive care units: overview of the Improving Medicine Through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP) study. Crit Care. 2011;15(1):R38.
7. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. Am J Respir Crit Care Med. 1996;153(5):1711–25.
8. American Thoracic Society, Infectious Diseases Society of America. 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.
9. Shorr AF, Zilberberg MD, Reichley R, Kan J, Hoban A, Hoffman J, et al. Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. Clin Infect Dis. 2012;54(2):193–8.
10. Aliberti S, Di Pasquale M, Zanaboni AM, Cosentini R, Brambilla AM, Seghezzi S, et al. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. Clin Infect Dis. 2012;54(4):470–8.
11. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA. 2003;290(19):2588–98.
12. Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. Cochrane Database Syst Rev. 2011;10:CD007577.
13. Eachempati SR, Hydo LJ, Shou J, Barie PS. Does de-escalation of antibiotic therapy for ventilator-associated pneumonia affect the likelihood of recurrent pneumonia or mortality in critically ill surgical patients? J Trauma. 2009;66(5):1343–8.
14. Kollef MH, Morrow LE, Niederman MS, Leeper KV, Anzueto A, Benz-Scott L, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. Chest. 2006;129(5):1210–8.
15. Nora D, Salluh J, Martin-Loeches I, Povoa P. Biomarker-guided antibiotic therapy-strengths and limitations. Ann Transl Med. 2017;5(10):208.
16. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to anti-

biotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375(9713):463–74.
17. Huang DT, Yealy DM, Filbin MR, Brown AM, Chang CH, Doi Y, et al. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. N Engl J Med. 2018;379(3):236–49.
18. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med. 2011;171(15):1322–31.
19. Shehabi Y, Sterba M, Garrett PM, Rachakonda KS, Stephens D, Harrigan P, et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med. 2014;190(10):1102–10.
20. Rumbak MJ, Bass RL. Tracheal aspirate correlates with protected specimen brush in long-term ventilated patients who have clinical pneumonia. Chest. 1994;106(2):531–4.
21. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis. 1991;143(5 Pt 1):1121–9.
22. Fabregas N, Ewig S, Torres A, El-Ebiary M, Ramirez J, de La Bellacasa JP, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. Thorax. 1999;54(10):867–73.
23. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med. 2000;132(8):621–30.
24. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). Eur Respir J. 2017;50(3):1–26.
25. Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, et al. Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis. 2012;54(5):621–9.
26. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for Pseudomonas aeruginosa bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med. 1989;87(5):540–6.
27. Heyland DK, Dodek P, Muscedere J, Day A, Cook D, Canadian Critical Care Trials Group. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med. 2008;36(3):737–44.
28. Kett DH, Cano E, Quartin AA, Mangino JE, Zervos MJ, Peyrani P, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. Lancet Infect Dis. 2011;11(3):181–9.
29. Klompas M. Does this patient have ventilator-associated pneumonia? JAMA. 2007;297(14):1583–93.
30. Klompas M. Ventilator-associated pneumonia: is zero possible? Clin Infect Dis. 2010;51(10):1123–6.
31. Klompas M. The paradox of ventilator-associated pneumonia prevention measures. Crit Care. 2009;13(5):315.
32. Klompas M. Eight initiatives that misleadingly lower ventilator-associated pneumonia rates. Am J Infect Control. 2012;40(5):408–10.
33. CDC. Ventilator-Associated Pneumonia (VAP) Event: CDC; 2009 [updated March, 2009. PNEU definitions from CDC]. http://www.cdc.gov/nhsn/PDFs/pscManual/6pscVAPcurrent.pdf
34. Klompas M. Interobserver variability in ventilator-associated pneumonia surveillance. Am J Infect Control. 2010;38(3):237–9.
35. Stevens JP, Kachniarz B, Wright SB, Gillis J, Talmor D, Clardy P, et al. When policy gets it right: variability in us Hospitals' diagnosis of ventilator-associated pneumonia. Crit Care Med. 2014;42(3):497–503.
36. Minei JP, Hawkins K, Moody B, Uchal LB, Joy K, Christensen LL, et al. Alternative case definitions of ventilator-associated pneumonia identify different patients in a surgical intensive care unit. Shock. 2000;14(3):331–6; discussion 6–7
37. Prevention CfDCa. Improving surveillance for ventilator-associated events in adults 2013. http://www.cdc.gov/nhsn/PDFs/vae/CDC_VAE_CommunicationsSummary-for-compliance_20120313.pdf
38. Klompas M. Ventilator-associated conditions versus ventilator-associated pneumonia: different by design. Curr Infect Dis Rep. 2014;16(10):430.
39. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, Lee G, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(8):915–36.
40. Stevens JP, Silva G, Gillis J, Novack V, Talmor D, Klompas M, et al. Automated surveillance for ventilator-associated events. Chest. 2014;146(6):1612–8.
41. Klompas M, Kleinman K, Murphy MV. Descriptive epidemiology and attributable morbidity of ventilator-associated events. Infect Control Hosp Epidemiol. 2014;35(5):502–10.
42. Lilly CM, Landry KE, Sood RN, Dunnington CH, Ellison RT 3rd, Bagley PH, et al. Prevalence and test characteristics of national health safety network ventilator-associated events. Crit Care Med. 2014;42(9):2019–28.
43. Bouadma L, Sonneville R, Garrouste-Orgeas M, Darmon M, Souweine B, Voiriot G, et al. Ventilator-Associated events: prevalence, outcome, and relationship with ventilator-associated pneumonia. Crit Care Med. 2015;43:1798–806.
44. Magill SS, Rhodes B, Klompas M. Improving ventilator-associated event surveillance in the National Healthcare Safety Network and addressing knowledge gaps: update and review. Curr Opin Infect Dis. 2014;27(4):394–400.
45. Klompas M, Anderson D, Trick W, Babcock H, Kerlin MP, Li L, et al. The preventability of ventilator-associated events. The CDC prevention epicenters wake up and breathe collaborative. Am J Respir Crit Care Med. 2015;191(3):292–301.
46. Metersky ML, Wang Y, Klompas M, Eckenrode S, Bakullari A, Eldridge N. Trend in ventilator-associated pneumonia rates between 2005 and 2013. JAMA. 2016;316(22):2427–9.
47. Mehta S, Burry L, Cook D, Fergusson D, Steinberg M, Granton J, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA. 2012;308(19):1985–92.
48. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008;371(9607):126–34.
49. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med. 1996;335(25):1864–9.
50. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med. 1995;332(6):345–50.

51. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82.
52. Lacherade JC, De Jonghe B, Guezennec P, Debbat K, Hayon J, Monsel A, et al. Intermittent subglottic secretion drainage and ventilator-associated pneumonia: a multicenter trial. Am J Respir Crit Care Med. 2010;182(7):910–7.
53. Shorr AF, O'Malley PG. Continuous subglottic suctioning for the prevention of ventilator-associated pneumonia : potential economic implications. Chest. 2001;119(1):228–35.
54. Hallais C, Merle V, Guitard PG, Moreau A, Josset V, Thillard D, et al. Is continuous subglottic suctioning cost-effective for the prevention of ventilator-associated pneumonia? Infect Control Hosp Epidemiol. 2011;32(2):131–5.
55. Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. Crit Care Med. 2011;39(8):1985–91.
56. Dreyfuss D, Djedaini K, Weber P, Brun P, Lanore JJ, Rahmani J, et al. Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 hours versus no change. Am Rev Respir Dis. 1991;143(4 Pt 1):738–43.
57. Hess DR. Noninvasive positive-pressure ventilation and ventilator-associated pneumonia. Respir Care. 2005;50(7):924–9. discussion 9–31
58. Carron M, Freo U, BaHammam AS, Dellweg D, Guarracino F, Cosentini R, et al. Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials. Br J Anaesth. 2013;110(6):896–914.
59. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet. 1999;354(9193):1851–8.
60. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, Joore HC, van Schijndel RJ, van der Tweel I, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. Crit Care Med. 2006;34(2):396–402.
61. Keeley L. Reducing the risk of ventilator-acquired pneumonia through head of bed elevation. Nurs Crit Care. 2007;12(6):287–94.