29 Ventilator-Associated Pneumonia and Other Complications

Jennifer P. Stevens and Michael D. Howell

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 five 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 x-ray at that time showed a lobar infiltrate. Cultures from endotracheal aspirates were negative. After three 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 PEEP was increased to 10 cm from 5 cm of water to maintain adequate oxygenation. A chest xray 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. Ventilator-associated pneumonia is defined as pneumonia in those patients who have been intubated for at least two to three days, with worsening radiographic features, increasing secretions, bronchospasm, or hemoptysis, or with worsening status 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 and noninvasive sampling is preferred [1]. Samples may be obtained either through tracheobronchial aspiration, bronchoalveolar lavage, 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* [2].

J.P. Stevens
Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

M.D. Howell (✉)
Center for Healthcare Delivery Science and Innovation, University of Chicago Medicine, Chicago, IL, USA
e-mail: mdh@uchicago.edu

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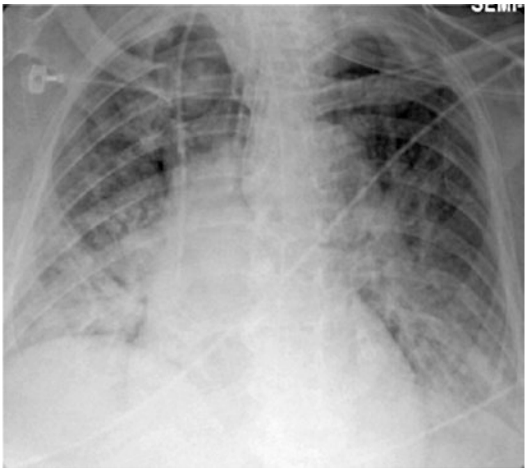

Fig. 29.1 Chest xray on ICU day 5

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 HCAP, inappropriate empiric antibiotic therapy was associated with a significant increase in mortality (30 % versus 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 [3]. 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 [4].

Treat Patients with VAP Broadly for Multidrug Resistant Organisms

Patients with VAP should universally initiated on therapy for (1) MRSA (for example, with vancomycin or linezolid) and for (2) resistant gram-negatives, such as *Pseudomonas aeruginosa, Klebsiella pneumoniase,* and *Acinetobacter* species. Treatment options could include: antipseudomonal cephalosporins (cefepime or ceftazidime), antipseudomonal carbapenems (imipenem or meropenem), β-Lactam/β-lactamase inhibitor (piperacillin-tazobactam). For patients for whom combination therapy is considered (see Evidence Contour below), addition of an antipseudomonal flouroquinolone 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 [5, 6].

In addition to MDR risk factors, appropriate antimicrobial therapy should consider the patient's risk factors for: (1) extended-spectrum beta-lactamase-producing *Enterobactereriaceae*; (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 fluroquinolone 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 or levofloxacin, moxifloxacin, or ciprofloxacin, ampicillin/sulbactam or ertapenem [2]. 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 [7, 8].

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 versus 15 days, although patients with *Pseudomonas* spp. had higher rates of recurrence [9]. A subsequent meta-analysis demonstrated patients with lactose non-fermenting gram-negative bacilli had nearly a 2-fold increased odds of recurrence with shorter therapy courses [10]. However, more recent systematic reviews and the ATS/IDSA 2016 guideline [2] has challenged this distinction. The current recommendation for all VAP, including non-fermenting gram-negative bacilli, is to treat for a short course (7 or 8 days) [11].

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 around 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 % versus 42 %) nor recurrent pneumonias (27 % versus 35 %) differed between patients with VAP who underwent de-escalation versus those who did not [12]. Among 398 patients with VAP in Kollef et al., 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 not change to their regimens (24 %) [13].

Another possible guide to safely de-escalate antibiotic therapy may be procalcitonin levels. 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 procalcitonin levels reached <0.5 μg) had 3.1 fewer days (95 % CI 0.7 days – 5.6 days) than those patients assigned to the control arm, without a difference in mortality found in the overall study [14]. 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 [15, 16]. Current recommendations, however, are to continue to use clinical evidence rather than biomarkers [2].

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, etc.) and for complications of pneumonia (such as empyema). This scenario should also prompt reconsideration of the potential presence of resistant pathogens, and it may warrant consultation with infectious disease specialists.

Evidence Contour

Invasive Versus 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, in 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 [17]. 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) [18]. Fabregas et al. found a score of greater than 6 had a sensitivity of 77 % but a specificity of 42 % [19]. Conversely, bronchoscopic sampling may be less sensitive but is more specific for pneumonia. Randomized

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 infiltrate	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 [19]

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 [20]. A more recent RCT of 740 patients found no benefit to bronchoalveolar lavage over endotracheal aspirate [21]. 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.

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 12 h with a target serum trough between 15 and 20 mg/kg OR (2) 600 mg of linezolid. One major prospective trial of 1184 patients, however suggested that linezolid may be superior to vancomycin. In this study, 46 % of patients treated with vancomycin had cultures 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 [22]. As research in this space continues to evolve, linezolid may be a particularly good option among patients with renal failure, although current guidelines suggest either therapy for treatment.

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 and was recommended by the 2005 recommendations for VAP treatment by the ATS/IDSA [2]. Current recommendations from the 2016 update are to prescribe 2 antipseudomonal antibiotics when patients have risk factors for antimicrobial resistance, when the prevalence of gram-negative isolates resistant to the proposed monotherapeutic agent exceds 10 %, and when antimicrobial susceptibaility rates are unavailable [2]. However, it is worth noting that synergy of medications has only been demonstrated *in vitro* and in neutropenic or bacteremic patients and one randomized controlled trial did not demonstrate differences in clinical outcomes between monotherapy and combination therapy groups [6, 23, 24]. 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 [25]. 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. Further research will be necessary to identify who, if anyone, should be receiving such broad antibiotic coverage from the outset.

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 [26–30]. As a result, several studies identified little agreement either across infection control experts at a single institution [31] or across multiple institutions [32]. Other definitions that sought to identify episodes of VAP either through greater invasive strategies or through other scoring mechanisms fared equally poorly [33].

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) [34]. 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 [35, 36]. 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 three days into the course of mechanical ventilation. Review of radiology has been removed from the definition. There are subsequent sub-categories of harm, including probably or possible pneumonia, which are based on antibiotic changes and evidence of positive qualitative or quantitative cultures. (Table 29.2) [34].

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 [37, 38]. Lilly and colleagues found that the new VAE definition captured neither pneumonias nor hospital-acquired complications 93 % of the time [39]. 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) [40]. Further, Adult Respiratory Distress Syndrome is likely to be captured alongside VAP under the larger label of VAE [39, 41]. The first major intervention study to date designed to attempt to reduce rates of VAE demonstrated found spontaneous awakening trials and spontaneous breathing trials

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 $FiO_2 \geq 0.20$ <u>OR</u> 2. An increase in daily minimum PEEP values of ≥3 cm H_2O Either must be sustained for 2 or more calendar days
Infection-related ventilator-associated condition (iVAC)	VAC <u>PLUS</u> 1. Temperature >38° or <36° <u>OR</u> WBC ≥12,000 cells/mm^3 or ≤4,000 cells/mm^3 <u>AND</u> 2. A new antimicrobial started and continued for 4 or more days
Possible ventilator associated pneumonia	iVAC <u>PLUS</u> 1. Purulent respiratory secretions <u>OR</u> 2. A positive qualitative, semi-qualitative, or quantitative culture of sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue or protected specimen brushing
Probable ventilator associated pneumonia	iVAC <u>PLUS</u> 1. Purulent respiratory secretions AND a positive semi-quantitative, or qualitative culture of sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue or protected specimen brushing <u>OR</u> 2. A positive pleural fluid culture, positive lung histopathology, a positive diagnostic test for Legionella spp., a positive test on respiratory secretions for influenza virus, respiratory syncytial 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

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 [36]

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 [43–46]	HIGH
Instituting early mobilization and physical therapy, which has been shown to decrease length of stay and improve earlier return to independent function [47]	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 [48–50]. A meta-analysis demonstrated reduction in VAP rates and length of mechanical ventilation [51]	MODERATE
Changing ventilator circuits only when needed rather than on a schedule, which does little to decrease VAPs but does reduce costs [52]	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) [53]. This recommendation, however, cautions use of NIPPV that may delay intubation, such as profound hypoxemia, acute respiratory distress syndrome or impaired consciousness [54]	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 [55–57]	LOW

to be effective [42]. However, this remains a significant area of evolving science.

New and Old Strategies to Prevent VAP

Other 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 [36].

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