Ventilator-Associated Pneumonia

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Abstract

Ventilator-associated pneumonia (VAP) is an iatrogenic pulmonary infection that develops in tracheally intubated patients on mechanical ventilation for at least 48 hours. VAP is the nosocomial infection with the greatest impact on patient outcomes and health care costs. Endogenous colonization by aerobic gram-negative pathogens, that is, *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus* play a pivotal role in the pathogenesis of VAP. Several preventive strategies have shown efficacy in decreasing VAP incidence and are often implemented altogether as a prevention bundle. In patients with clinical suspicion of VAP, respiratory samples should be promptly collected. The empiric treatment should be based on the local prevalence of pathogens, duration of hospital stay, and prior antimicrobial therapy. The antibiotics can be stopped or adjusted to more narrow-spectrum once cultures and susceptibilities are available.

Keywords
- ventilator-associated pneumonia
- nosocomial pneumonia
- *pseudomonas aeruginosa*
- endotracheal tube
- mechanical ventilation

Ventilator-associated pneumonia (VAP) is a frequent iatrogenic infection that develops in patients admitted to the intensive care unit (ICU).[1] In comparison with other ICU-acquired infections, VAP is associated with worse morbidity and health care costs. Therefore, preventive strategies are of paramount importance to avoid VAP. The diagnosis of VAP is not accurate, which often leads to an overuse of antibiotics. Nevertheless, prompt and adequate antimicrobial treatment is mandatory following VAP development. Herein, we review the most recent evidence and developments on the epidemiology, etiology, preventive measures, diagnosis, and treatment of VAP.

Definition

VAP is defined as a pneumonia that develops in patients who have been tracheally intubated and on mechanical ventilation for at least 48 hours. Recently, the Center of Disease Control introduced the ventilator-associated events (VAE) surveillance definition algorithm[2] to monitor complications in mechanically ventilated patients. On the basis of this algorithm, in a patient with an infection-related ventilator-associated condition, possible and probable VAP are defined by signs of pulmonary infections (purulent secretions or a positive lower respiratory tract culture). In particular, probable VAP is defined by a positive lower respiratory tract culture, meeting specific quantitative or semiquantitative thresholds of pathogen growth (►**Fig. 1**).

Epidemiology

Incidence

VAP develops in approximately 10 to 40% of the patients on mechanical ventilation for more than 2 days, with large variations among countries and ICU types.[1,3–6] The exact incidence of VAP is difficult to establish due to the diagnostic limitations. In the latest report by the National Healthcare Safety Network,[7] mean VAP rates in American institutions were as low as 1 to 2.5 cases per 1,000 ventilator days. This

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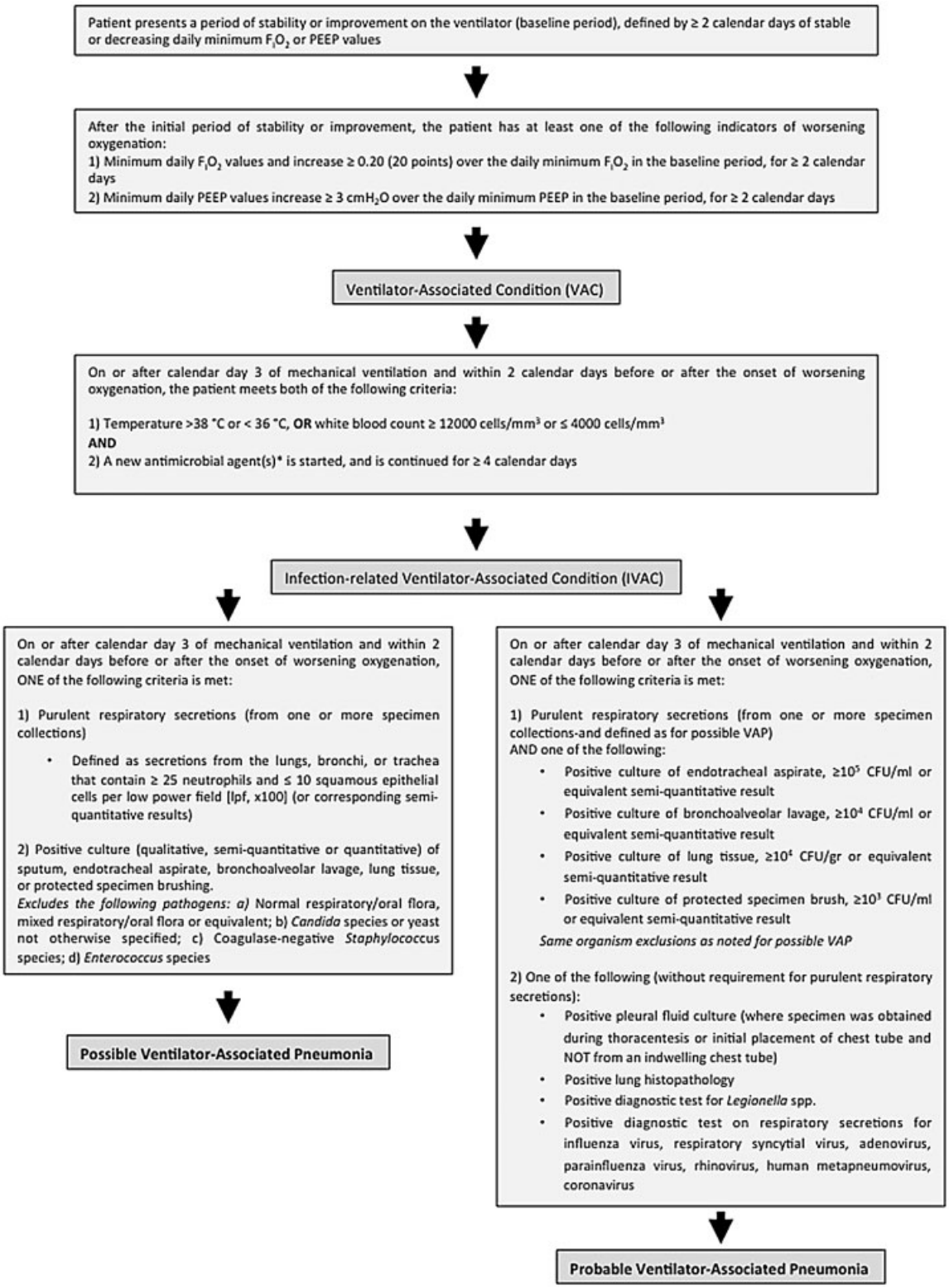

Fig. 1 Ventilator-associated events surveillance definition algorithm. *Full ventilator associated events surveillance protocol available at: http://www.cdc.gov/nhsn/acute-care-hospital/vae/index.html for eligible antimicrobials; CFU, colony-forming units; F_{IO_2}, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; VAP, ventilator-associated pneumonia.

strongly differs in comparison with the higher rates in Europe,[8,9] and suggests low diagnostic accuracy when VAP is detected through standard radiographic, pulmonary, and clinical signs of infection. Incidence rates greatly vary based on the studied population, for example, patients with acute respiratory distress syndrome (ARDS) have the highest risk for VAP, because of the severity of illness and the high requirement of sedatives.[10]

Morbidity and Mortality

Patients who develop VAP require longer periods of ventilatory assistance and have significantly longer ICU and hospital stays.[11–13] A recent report in patients with VAP indicates that the overall attributable mortality is 13%.[14] Nevertheless, the mortality rates are inconsistent among studies, and the prognostic impact of VAP is debated. In a study by Bekaert et al,[15] a relatively limited attributable VAP-associated mortality was reported. The time of VAP onset strongly affects outcomes. Late-onset VAP is often caused by multidrug resistant (MDR) pathogens and is associated with the worst outcome, in comparison with VAP that develops early during the course of mechanical ventilation.[16] The VAP PIRO score was introduced to assess VAP severity, and predict ICU mortality rate.[17] Finally, we recently demonstrated[18] in a retrospective analysis of 335 patients with VAP that the lack of improvement in $Pa_{O_2}/F_{I_{O_2}}$ and Sequential Organ Failure Assessment score within 5 days from the VAP diagnosis are strong predictors of mortality.

Economic Impact

On a per case basis, case VAP is associated with additional hospital costs of approximately US$ 40,000.[11,13,19] This is mainly related to the longer ICU and hospital stay, the increased level of care, and the need for additional procedures and treatments. Thus, preventive measures are pivotal in reducing the burden of the disease.

Pathogenesis

In critically ill, tracheally intubated patients several respiratory defense mechanisms, such as cough,[20] mucociliary clearance,[21] and the innate and adaptive immune responses are significantly depressed.[22,23] This leads to an increased risk of respiratory infections, because the host is incapable to control and clear inhaled pathogens.

Patients can be colonized through endogenous sources via contaminated respiratory equipment, the ICU environment, and the hands of the ICU staff. Several reports have described ICU outbreaks due to colonized bronchoscopes,[24] water supply,[25] respiratory equipment,[26] humidifiers,[27] ventilator temperature sensors,[28] respiratory nebulizers,[29] and contaminated environment.[30]

Endogenous colonization is believed to be pivotal for VAP development. In critically ill patients, the oral flora shifts early to a predominance of aerobic gram-negative and gram-positive pathogens.[31,32] As a result, pulmonary aspiration of oropharyngeal contents drastically increases the risk for airway colonization and infection. There is still controversy regarding the exact sequence of colonization and sources of infection in the pathogenesis of VAP. An early study by Feldman et al[33] found that in patients undergoing mechanical ventilation, the oropharynx is the first site to be colonized by pathogens (36 hours), followed by the stomach (36–60 hours), the lower respiratory tract (60–84 hours), and thereafter the endotracheal tube (ETT) (60–96 hours).

The Endotracheal Tube

Pulmonary aspiration of colonized oropharyngeal secretions across the ETT cuff plays a significant role in the pathogenesis of VAP. Long-term mechanically ventilated patients are intubated with an ETT comprising a high-volume low-pressure (HVLP) cuff, which was originally designed to control pressure exerted against the tracheal wall and prevent tracheal injury. The HVLP cuff diameter is larger than the tracheal diameter; hence, upon cuff inflation, folds invariably form along the cuff surface, causing micro and macro aspiration of oropharyngeal secretions.[34–37] Pathogens may also grow on the internal surface of the ETT and ultimately translocate into the lungs. The ETT is commonly made of polyvinyl chloride and bacteria hastily adhere to its surface to form a structure called biofilm.[38,39] Bacteria within the biofilm are difficult to eradicate and antibacterial efficacy of the host immune response and antibiotics are largely reduced.[40–42] During mechanical ventilation, biofilm particles may dislodge into the airways because of inspiratory airflow[43] and invasive medical interventions, such as tracheal aspiration[44] and bronchoscopy.

Oropharyngeal Colonization

There is an extensive presence of commensal microorganisms in the oropharynx.[45] Oropharyngeal colonization by pathogens is prevented by the physical–chemical properties of the oral mucosa surface and the continuous production of saliva, which efficiently clear pathogens. Saliva contains immune factors, that is, IgA, and several innate antimicrobials, such as lysozyme, lactoferrin, agglutinins, histatins, proline-rich peptides peroxidase, and other proteasis.[46–49] The oropharyngeal mucosal immunity appropriately coordinates the inflammatory reaction against potentially invading microorganisms or mediates tolerance for saprophytic microorganisms.

Hospitalization and critical illness is associated with a progressive impairment in oral health and increased dental plaque accumulation.[50,51] Several comorbidities and inherent patient's characteristics increase the risks of oropharyngeal colonization; in particular, alcohol abuse,[52] diabetes,[53] and chronic obstructive pulmonary disease (COPD)[54] are well-known risk factors for gram-negative oropharyngeal colonization. Elderly patients,[55] patients with disabilities,[56] and tracheally intubated patients are at increased risk for overgrowth of oropharyngeal pathogens, because of the inability to carry out an effective oral care. In addition, the vast use of antibiotics in critical settings promotes an overgrowth of oropharyngeal pathogens.[57] The antimicrobial effectiveness of saliva is highly impaired during critical illness. This is caused by a drastic reduction in the salivary flow,[58] which leads to a decrease in oral pH and enhanced adherence of pathogens to the buccal epithelial cells. Moreover, the saliva of subjects with poor oral health has an increased amount of proteases,[59] released by host immune cells and periodontal bacteria, which alters the oral mucosal epithelium and favors bacterial adhesion. Bacteria that colonize the oropharynx also produce a large variety of hydrolases that degrade cell-surface carbohydrates[60,61] and expose critical receptors for bacterial adhesion.[62]

Stomach

According to the gastropulmonary hypothesis of colonization, during the course of invasive mechanical ventilation the stomach is progressively colonized by pathogens. This is caused by the alkalinization of gastric contents through enteral nutrition and stress ulcer prophylaxis.[63,64] Supine horizontal position[65] and the presence of a nasogastric tube[66] favor gastroesophageal reflux and translocation of gastric microorganisms, into the oropharynx, which are ultimately aspirated across the ETT cuff.

Etiology

VAP is frequently caused by aerobic, gram-negative pathogens, that is, *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*, or *Acinetobacter* species; whereas *Staphylococcus aureus* is the predominant gram-positive pathogen.[12,67,68] VAP may be caused by multiple pathogens and this further complicates the therapeutic approach.[69,70]

Comorbid conditions and underlying diseases significantly increase the risk of colonization by specific pathogens. Patients with COPD are at increased risk for *Haemophilus influenzae, Moraxella catarrhalis*, *P. aeruginosa*, and *S. pneumoniae* infections[71,72]; patients with ARDS are at higher risk for developing VAP caused by *S. aureus*, *P. aeruginosa*, and *Acinetobacter baumannii*, and often in these patients VAP is caused by multiple pathogens.[10,73] Finally, trauma patients or patients with neurological diseases are at increased risk for *S. aureus, Haemophilus* spp., and *S.pneumoniae* infections.[4,74,75]

Importantly, VAP pathogens that are potentially MDR are *P. aeruginosa*, *S. aureus*, *Acinetobacter* spp., *Stenotrophomonas maltophilia, Burkholderia cepacia*, and extended-spectrum β-lactamase ESBL *K. pneumonia.* Patients at risk of being colonized by MDR pathogens are extremely heterogeneous, commonly present comorbid conditions and they receive antibiotics during the course of their hospitalization.[1] Interestingly, Nseir et al[76] found that patients colonized by MDR *P. aeruginosa* or *A. baumannii* influenced the acquisition of these bacteria by subsequent ICU occupants. A recent study demonstrated that severity of illness did not affect etiology and risk factors for MDR pathogens.[67] The incidence of MDR pathogens is also closely linked to local factors and widely varies from one institution to another.[77] Therefore, clinicians must be aware of the most common microorganisms, and pattern of resistance in their own institution, to properly administer empiric antimicrobial therapy.

Fungi rarely cause VAP. *Candida* spp. is the most common isolated yeast in critically ill patients.[78,79] Nonetheless, the clinical significance of *Candida* colonization is still argued. In a recent study,[80] an interesting association between pulmonary *Candida* colonization and MDR pathogens was found.

Finally, respiratory viruses may be responsible for VAP.[81] In particular, herpes simplex virus and cytomegalovirus, can be reactivated and cause VAP during the course of mechanical ventilation.

Prevention

VAP preventive strategies mostly aim at reducing oropharyngeal colonization and aspiration of colonized secretions across the ETT cuff. Strategies that have proven preventive efficacy are grouped and implemented together as a bundle, because together are expected to be more effective than applied individually. Yet, the application of VAP preventive bundles is challenging, and requires important efforts, such as the development of a multidisciplinary implementation team to custom design the bundle according with institutional policies, extensive educational programs, frequent reminders, and monitoring of compliance.[82]

General Prophylactic Measures

Maintaining high levels of education among ICU personnel on VAP pathophysiology and preventive strategies can be effective in reducing incidence of this complication.[82,83] Alcohol-based hand disinfection plays a pivotal role in the prevention of all nosocomial infections and should be strictly implemented.[84–86] Transport of intubated patients outside the ICU increases the risk of VAP.[87,88] Importantly, the ETT cuff internal pressure should be maintained within the recommended range throughout the transport, and ventilator circuits carefully manipulated to avoid aspiration of colonized secretions. Daily interruption or lightening of sedation, as well as the avoidance of paralytic agents and early mobilization, are highly recommended. These measures reduce the length of stay on mechanical ventilation, and ultimately risks for VAP.[89,90]

Noninvasive Ventilation

Tracheal intubation and mechanical ventilation are the main risk factors for VAP and consequently should be avoided whenever possible. Noninvasive ventilation (NIV) is an attractive alternative for patients with acute exacerbations of COPD or acute hypoxemic respiratory failure, and for some immunosuppressed patients with pulmonary infiltrates and respiratory failure.[91,92] In addition, NIV can be used to expedite extubation, especially in hypercapnic patients with COPD.[93]

The Endotracheal Tube

In the last decade, major improvement in the design of the ETT cuff design has been achieved. Cuffs made of new materials, that is, polyurethane,[94] silicone, and latex[95,96] have been developed and tested in laboratory and clinical trials.[34,37] Among the commercially available materials, polyurethane drastically enhances cuff-sealing performance.[34,94,97] Furthermore, cuffs designed with a smooth tapering shape allow elimination of folds for a full circumference of the trachea/cuff contact zone, irrespectively of the cuff material.[98] Nevertheless, till date, there is still a lack of evidence to support the general use of tapered cuffs for the prevention of aspiration and VAP.[34,99] The internal cuff pressure plays a pivotal role in the prevention of pulmonary aspiration. To prevent tracheal injury and leakage,[100] cuff pressure should be maintained between 25 and 30 cm H_2O,

particularly when no PEEP is applied. Further studies are needed to corroborate the impact of continuous control of cuff pressure on VAP.[101] Finally, ventilatory settings may contribute to the prevention of VAP. In particular, PEEP decreases the risk of VAP by preventing the aspiration of bacteria-laden subglottic secretions.[37,102]

Coating the ETT with antimicrobial agents, such as silver, prevent biofilm formation within its internal surface and VAP. In the NASCENT trial,[103] 2,003 patients were intubated with a silver-coated or a conventional ETT. The silver-coated ETT was associated with lower incidence of microbiologically confirmed VAP, with a relative risk (RR) reduction of 35.9%. On the basis of the available evidence and the associated costs, silver-coated ETT should be used in patients expected to be ventilated for longer periods of time and at greater risk for developing VAP.

Aspiration of Subglottic Secretions

Subglottic secretions aspiration reduces the hydrostatic pressure exerted by pooled secretions above the cuff, and consequently pulmonary aspiration. In an important study, Lacherade et al demonstrated a reduction of both early and late onset VAP applying intermittent aspiration of subglottic secretions.[104] A meta-analysis[105] that pooled data from 13 studies and 2,442 patients confirmed the efficacy of subglottic secretions drainage in the prevention of VAP (RR, 0.55; 95% confidence interval [CI], 0.46–0.66; $p < 0.001$).

Body Position

Intubated patients are at higher risk for pulmonary aspiration of gastric pathogens when placed in the fully supine position (0 degree), as compared with a semirecumbent position (45 degrees).[65,106,107] Thus, as strongly suggested by the American[1] and European[108] guidelines on nosocomial pneumonia, intubated patients should be kept in the semirecumbent position (30–45 degrees) rather than supine (0 degree), specifically when receiving enteral feeding.

Stress Ulcer Prophylaxis and Enteral Feeding

In the ICU, stress ulcer prophylaxis is usually achieved with sucralfate, histamine type 2 blockers (H2-blockers), or proton pump inhibitors (PPI). Colonization of the stomach is increased when gastric contents are alkalinized.[64] Sucralfate is the only treatment that potentially prevents gastrointestinal ulceration without raising gastric pH. Yet, there is a lack of firm evidence that this agent might reduce the risk of VAP in comparison with H2-blockers or PPI.[109] Enteral nutrition has been considered a risk factor for the development of VAP, mainly because of the resulting alkalinization of gastric content, gastroesophageal reflux, and gastropulmonary aspiration. A recent randomized clinical trial demonstrated that strict monitoring of residual gastric volume does not reduce incidence of VAP.[3] Finally, postpyloric feeding should be considered in critically ill patients who have impaired gastric emptying. Alhazzani et al[110] recently demonstrated that in critically ill patients small bowel feeding, in comparison to gastric feeding, reduces VAP.

Modulation of Oropharyngeal and Gastrointestinal Colonization

Several antiseptics have been employed to reduce oropharyngeal colonization with pathogens, such as, chlorhexidine gluconate, iseganan or povidone iodine.[111] Oral rinse with chlorhexidine reduces the odds of developing VAP of approximately 40% (odds ratio [OR], 0.60; 95% CIs 0.47–0.77, $p < 0.001$).[112] Most of the aforementioned studies used chlorhexidine concentrations of 0.12 and 0.2%. However, studies in general ICU patients have demonstrated significant reductions in VAP rates when chlorhexidine concentration was increased to 2%.[113,114] Iodine is a potential alternative to chlorhexidine. In comparison with chlorhexidine, povidone iodine is cheaper, does not irritate the oral mucosa, and does not exhibit discoloration of teeth. However, a recent study by Seguin et al[4] reappraised the use of povidone iodine to prevent VAP. Indeed, povidone iodine marginally reduced oropharyngeal colonization and did not have any impact on the reduction of VAP.

Selective digestive decontamination (SDD) comprises a combination of nonabsorbable antibiotics against gram-negative pathogens (i.e., tobramycin and polymyxin E) plus either amphotericin B or nystatin administered into the gastrointestinal tract, to prevent oropharyngeal and gastric colonization with aerobic gram-negative bacilli and *Candida* spp., while preserving the anaerobic flora. Some regimens also include a short course of systemic antibiotics (most commonly cefotaxime). Clinical trials[115,116] and meta-analysis[117] confirm that SDD drastically reduces VAP and improves survival. SDD is aimed at preventing overgrowth of aerobic gram-negative bacteria; as a result, colonization by gram-positive bacteria, that is, MRSA and *Enterococcus* spp. may be promoted.[115,118] Therefore, during the course of SDD it is highly recommended to conduct appropriate surveillance of antibiotic resistance patterns within the ICU and hospital. In addition, the efficacy of SDD in countries with high level of antimicrobial resistance needs further corroboration.

Finally, probiotics are viable microorganisms that colonize the gastrointestinal tract by adhering to the intestinal mucosa and compete with the adhesion of pathogens to epithelial binding sites, thus creating an unfavorable local milieu for pathogen colonization. A recent meta-analysis of seven trials failed to demonstrate benefits in the use of probiotics as a VAP preventive strategy (OR, 0.82; 95% CI, 0.55–1.24; $p = 0.35$).

Diagnosis

Strategies to diagnose VAP should reliably identify the greatest number of infected patients to promptly initiate appropriate antibiotic treatment and improve outcomes. Nevertheless, diagnostic strategies should also discriminate patients without an infection to avoid overtreatment and emerging antibiotic resistance. VAP is clinically suspected when a new or progressive infiltrate has developed at the chest radiograph, in patients with clinical signs of respiratory infection (fever or hypothermia, leukocytosis or leukopenia, and purulent secretions). Clinical suspicion is often confirmed based on the results of lower respiratory secretion cultures.[1]

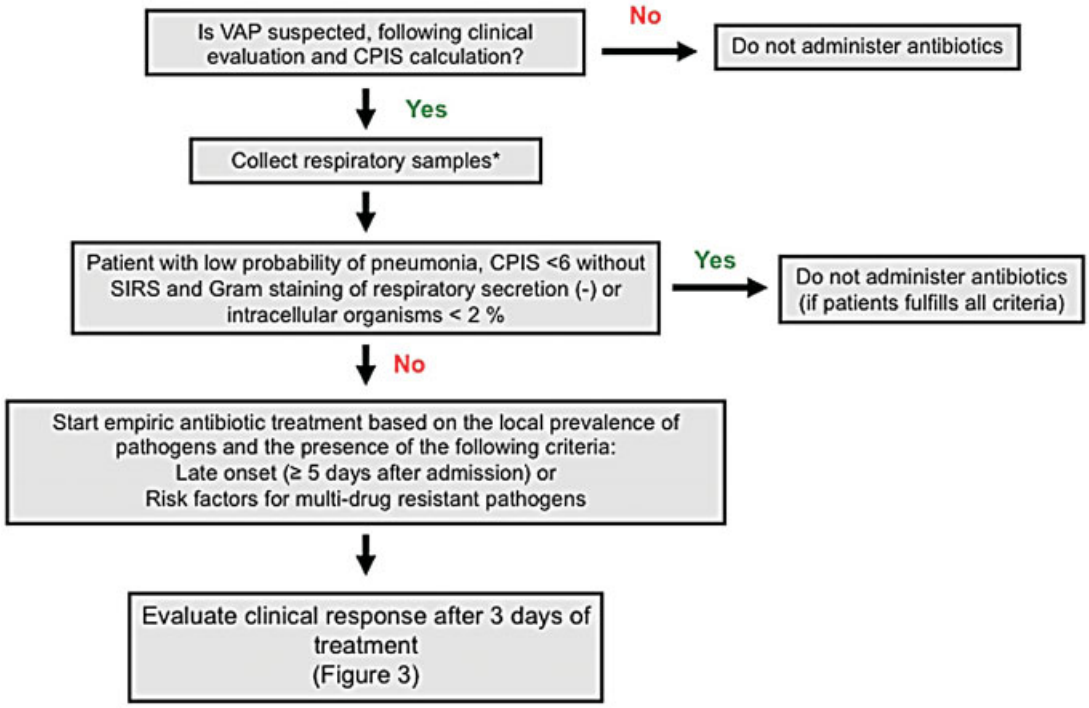

Fig. 2 Algorithm for the management of patients with ventilator-associated pneumonia and selection of appropriate antimicrobials. Algorithm for the treatment of patients with clinical suspicion of ventilator-associated pneumonia. Comprises at least two of the following: temperature > 38°C or < 36°C, heart rate > 90 beats per minute, respiratory rate > 20 beats per minute or $Paco_2$ < 32 mm Hg, and leukocytes > 12,000/mm^3, < 4,000/mm^3, or > 10% bands. *Before initiating new empiric antibiotic treatment, collect samples through tracheobronchial aspirate or bronchoalveolar lavage or protected specimen brush. Collect also two blood cultures. In case of pleural effusion obtain samples. Obtain *Legionella pneumophila* and *Streptococcus pneumoniae* antigens in urine. In patients with severe sepsis, the collection of lower respiratory secretion samples should not delay the initiation of empiric treatment. Other laboratory tests include complete blood cell count; serum electrolytes; liver and renal function tests; C-reactive protein; procalcitonin; arterial blood gases. CPIS, clinical pulmonary infection score; SIRS, systemic inflammatory response syndrome; VAP, ventilator-associated pneumonia

Regrettably, the diagnosis of VAP is highly challenging and lacks a reliable gold standard.[119] Clinical signs of pneumonia, such as fever, tachycardia, leukocytosis, and purulent secretions are highly common in mechanically ventilated patients and they are not specific for VAP.[120,121] An early study[122] confirmed the presence of lung infection in only 42% of the patients with clinically suspected VAP. Moreover, changes of the chest radiograph are often difficult to interpret in patients who present multilobar opacities upon admission. Radiographic signs of cardiogenic and noncardiogenic pulmonary edema, atelectasis, and ARDS often overlap with VAP.[123–125]

The clinical pulmonary infection score (CPIS) combines several clinical signs of pulmonary infection to improve accuracy in the diagnosis of VAP. It is based on six clinical assessments (temperature, blood leukocyte count, volume and purulence of tracheal secretions, oxygenation, pulmonary radiographic findings, and semiquantitative culture of tracheal aspirate), each worth between 0 and 2 points.[126,127] A value ≥ 6 is a threshold to identify patients with VAP. The sensitivity and specificity of CPIS approximate 65%.[128] Yet, the value of CPIS still needs to be validated in a large prospective study, especially in patients with bilateral pulmonary infiltrates.

Clinical suspicion of VAP is often confirmed through pulmonary cultures. Microbiological confirmation not only corroborates pneumonia, but also optimizes antimicrobial treatment. Many sampling procedures of respiratory secretions, such as endotracheal aspirates, bronchoalveolar lavage (BAL), and protected specimen brush (PSB) are available. In addition, there are several microbiological techniques including gram staining and intracellular organism count from specimens obtained via BAL. Microbiological confirmation of VAP is complicated by several factors: first, the extensive oropharyngeal and tracheobronchial colonization[31,32,129] in ventilated patients; second, VAP is a nonhomogeneous multifocal disease characterized by different phases of evolution, bacterial burdens, and histological severities within the affected lobes[120]; finally, antibiotics strongly reduce the odds of positive results. When patients develop pneumonia, pathogens are present in the lower respiratory tract secretions at concentrations of at least 10^5 to 10^6 CFU/mL,[130,131] and contaminants are generally present at less than 10^4 CFU/mL. The current diagnostic threshold proposed for endotracheal aspirates, BAL, and PSB is 10^5, 10^4, and 10^3 CFU/mL, respectively.[1] On the basis of aforementioned limitations, endotracheal aspirate cultures have a high percentage of false-positive results, due to the extensive colonization of the proximal airways. Conversely, distal sampling through BAL and PSB often yields false-negative results.

As mentioned earlier, based on the VAE surveillance definition algorithm, patients with sustained respiratory deterioration due to an infection (infection-related ventilator-associated condition, IVAC) could have probable or possible VAP. Possible VAP is defined by the presence of purulent secretions or a positive lower respiratory tract culture

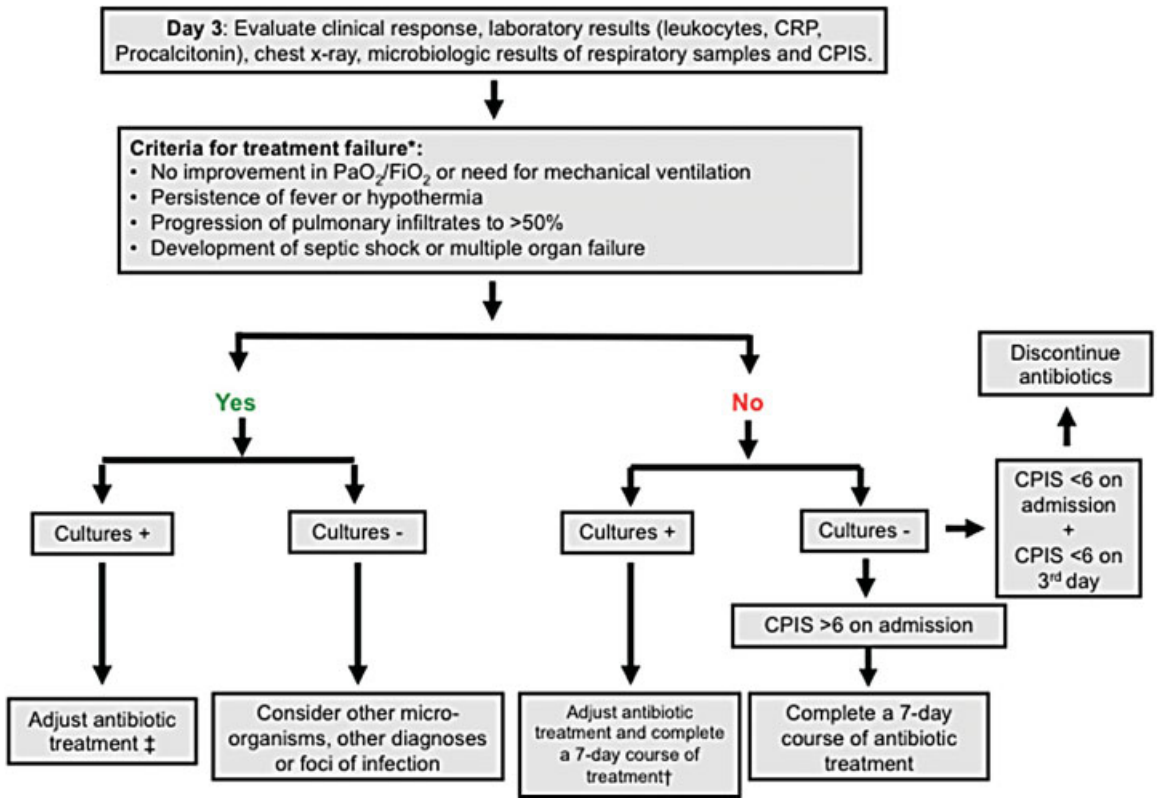

Fig. 3 Follow-up of patients with ventilator-associated pneumonia. †When VAP is caused by *Pseudomonas aeruginosa* or *Acinetobacter* spp. a 14-day course of treatment is advisable. ‡In case of treatment failure or presence of methicillin-resistant *Staphylococcus aureus*, linezolid should be administered. If gram-negative bacteria are isolated, consultation with a clinical microbiologist is advised CRP, C-reactive protein; CPIS, clinical pulmonary infection score.

(showing any growth); whereas, probable VAP is defined by a quantitative or semiquantitative culture of lower respiratory tract specimen (►**Fig. 1**). Importantly, the latest reports demonstrated poor concordance between IVAC, possible and probable VAP, as defined by the VAE algorithm, and VAP diagnosed with standard criteria.[132,133]

Finally, several alternative techniques to microbial cultures have been developed to achieve a more rapid and accurate diagnosis. Among the recent improvements, the direct antibiogram using E-test strips applied directly to respiratory tract samples have proved to be reliable and effective,[134] and can provide antimicrobial susceptibility earlier than standard methods.[135,136] Other advances include quantitative polymerase chain reaction for direct measurement of the principal VAP causative bacteria, as well as clinically relevant resistance genes.[137–139]

In our practice, we apply a diagnostic approach that combines clinical and microbiological confirmation of VAP, as detailed in ►**Fig. 2**. Thus, in a patient with clinical suspicion of pneumonia, CPIS is calculated. Then, samples of the lower respiratory tract are obtained to identify the causative microorganism, ideally before initiation or change of antibiotics. However, in septic patients, antibiotic therapy should not be delayed. Several additional samples should be collected, as noted in ►**Fig. 2**. After 3 days of treatment, the clinical response is reassessed as detailed in ►**Fig. 3**.

Treatment

In patients with clinical suspicion of VAP, an adequate and prompt empiric antibiotic treatment is pivotal to improve survival.[140–143] Nevertheless, an indiscriminate administration of antibiotics exposes the patient to unnecessary adverse effects, increases health care costs, and sustains a selective pressure for antimicrobial resistance.

The latest ATS/IDSA guidelines[1] recommend that the selection of empiric antibiotic therapy should be based on the timing of onset and presence of risk factors for MDR pathogens (►**Table 1**). Nevertheless, empiric antibiotic therapy should also be based on the local ecology and pattern of resistance,[77] and pharmacokinetics/pharmacodynamics of antibiotics. We previously demonstrated[144] that adherence to the 2005 ATS/IDSA guidelines improved adequacy of empiric antibiotic therapy in patients at high risks for MDR pathogens with late-onset VAP. However, the guidelines poorly predicted the occurrence of MDR pathogens in patients with early-onset pneumonia. Importantly, antibiotic treatment should be deescalated or adjusted based on culture results.[145]

The initial therapy against gram-negative pathogens is often a combination of two broad-spectrum antibiotics to increase the chance of adequate therapy against MDR pathogens (►**Table 1**). Unfortunately, till date, there is still

Table 1 Initial empiric antibiotic treatment based on risk factors for multidrug-resistant pathogens causing ventilator-associated pneumonia

Early-onset VAP in patients without risk factors for infection by multidrug resistant pathogens		Early-onset VAP in patients with risk factors[a] for infection by multidrug resistant pathogens	
Probable microorganism	**Recommended antibiotic**	**Probable microorganism**	**Recommended antibiotic**
• *Streptococcus pneumoniae* • *Haemophilus influenzae* • MSSA • Enteric gram-negative bacilli 1. *Escherichia coli* 2. *Klebsiella pneumoniae* 3. *Enterobacter* spp. 4. *Proteus* spp. 5. *Serratia marcescens*	Ceftriaxone or levofloxacin or moxifloxacin or ampicillin/sulbactam or ertapenem	• *Pseudomonas aeruginosa* • *K. pneumoniae* (ESBL +)[b] • *Acinetobacter* spp.[b] • Other nonfermenting GNB • MRSA • *Legionella pneumophila*[c]	Antipseudomonal cephalosporin (ceftazidime or cefepime) or carbapenem (imipenem, meropenem) or β-lactamic/β-lactamase inhibitor (piperacillin-tazobactam)[d] + antipseudomonal fluoroquinolone (ciprofloxacin, levofloxacin) or aminoglycoside[e] (amikacin) ± linezolid or vancomycin[f]

Abbreviations: ESBL, extended spectrum β-lactamase; GNB, gram-negative bacterial; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

[a]Antimicrobial therapy in preceding 90 days; Current hospitalization of 5 days or more; High frequency of antibiotic resistance in the community or in the specific hospital unit; Hospitalization for 2 days or more in the preceding 90 days; Residence in a nursing home or extended care facility; Home infusion therapy (including antibiotics); Chronic dialysis within 30 days; Home wound care; Family member with multidrug-resistant pathogen; Immunosuppressive disease and/or therapy.

[b]If an ESBL + strain, such as *Klebsiella pneumoniae* or *Acinetobacter* spp. is suspected, a carbapenem is the first choice.

[c]If *Legionella pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (e.g., azithromycin), or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

[d]Patients who have not received any antipseudomonal β-lactam within the last 30 days should receive piperacillin–tazobactam or an antipseudomonal cephalosporin. Patients who have received these drugs should receive carbapenems. Patients with infection by ESBL-producing microorganisms should be treated with carbapenems, regardless of the results of the antibiogram.

[e]Empiric combination therapy against multidrug resistant gram-negative bacteria is initiated with amikacin and maintained for a 5-day period. An antipseudomonal fluoroquinolone should be used in patients with renal failure or undergoing vancomycin therapy.

[f]Empiric therapy against MRSA is initiated in patients with proven colonization by MRSA or previous infection by this microorganism. The antibiotic of choice is either vancomycin (except in patients allergic to this medication, creatinine values ≥ 1.6 mg/dL or in patients presenting signs of empiric treatment failure after 48 hours of antibiotic therapy) or linezolid.

unconvincing evidence to fully support this practice.[146–149] Further randomized clinical trials, conducted in ICU with high prevalence of MDR pathogens, are needed to compare the effects of monotherapy versus combination therapy on major outcomes. As for gram-positive bacteria, the addition of antibiotics with activity against MRSA depends on the local prevalence of MRSA. In geographic areas with high prevalence of community-acquired MRSA, in cases of severe pneumonia with radiologic images of cavitation or presence of gram-positive cocci in respiratory secretions, empiric treatment against MRSA may be appropriate. The first-line antibiotics are linezolid and vancomycin (►**Table 1**). In previous meta-analyses, clinical cure and bacteriological eradication were similar with either therapy.[150,151] Nevertheless, in the latest randomized clinical trial[152] in 1,184 patients with nosocomial pneumonia, the clinical success rate was higher in patients treated with linezolid and nephrotoxicity occurred more frequently with vancomycin. Yet, all cause 60-day mortality and adverse events were similar. Thus, in patients at risk of acute kidney injury or infected by MRSA with elevated vancomycin minimum inhibitory concentration (higher than 1 μg/mL),[153,154] clinicians should consider the additional benefits of linezolid.

In most of the cases, VAP can be effectively treated for 7 days. A few clinical scenarios may justify prolonged treatment: (1) infection by microorganisms that multiply in the cellular cytoplasm, such as *Legionella* spp.; (2) the presence of biofilms or prosthetic devices; and (3) the development of tissue necrosis, abscesses, or infection with empyema. If the clinical course is favorable, as defined by defervescence, improvement in blood gas exchanges, and reduction in C-reactive protein levels within the first 3 to 5 days of antimicrobial therapy, a 7-day course of treatment is sufficient. If the causative microorganism is a nonfermenting gram-negative bacillus, the treatment can be extended. In patients with clinical suspicion of VAP who have a CPIS lower than 6 on the third day of treatment, the treatment may be withdrawn (►**Fig. 3**).

Lung penetration of intravenous antibiotics is often limited, and the risk of systemic toxicity increases as the dosage is escalated. Aerosolized antibiotics provide higher antibiotic concentrations at the site of infection; as a result, the antibacterial activity is enhanced, while systemic toxicity is marginal. Several clinical trials tested the feasibility and efficacy of nebulized antibiotics, that is, colistin,[155] ceftazidime, amikacin,[156] and imipenem.[157] In a recent clinical trial, patients with VAP by MDR *P. aeruginosa* or *A. baumannii* who were treated with nebulization of high-dose colistin[155] presented comparable curative rates to standard intravenous therapy. Thus, given the emerging antibiotic resistance and the lack of new antibiotics, in the upcoming years nebulized antibiotics will likely play a significant role in the treatment of VAP.

Finally, a recent study[158] failed to find any survival benefit in patients with VAP with the use of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (simvastatin, 60 mg daily). The study was stopped for futility, after enrollment of 300 patients. Day-28 mortality was 21.2% in the simvastatin group and 15.2% in the placebo group ($p = 0.10$)

Conclusions

VAP is the most common nosocomial infection in the ICU. VAP increases morbidity, mortality, length of stay, and hospital costs. Evidence-based preventive interventions should be implemented in all tracheally intubated patients on mechanical ventilation. VAP diagnosis is challenging and lacks a diagnostic gold-standard, leading to both false-positive and false-negative results. Importantly, a prompt administration of an appropriate broad-spectrum antibiotic(s) is mandatory in patients with microbiologic confirmation of VAP.

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