Ventilator-associated pneumonia: A review

Noyal Mariya Joseph a,⁎, Sujatha Sistla a, Tarun Kumar Dutta b, Ashok Shankar Badhe c, Subhash Chandra Parija a

a Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry-605006, India
b Department of Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry-605006, India
c Department of Anaesthesiology and Critical care, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry-605006, India

Abstract
Ventilator-associated pneumonia (VAP) is the most frequent intensive-care-unit (ICU)-acquired infection, with an incidence ranging from 6 to 52% [1,2,3,4]. Several studies have shown that critically ill patients are at high risk for getting such nosocomial infections [3,4]. VAP continues to be a major cause of morbidity, mortality and increased financial burden in ICUs [5,6,7,8]. Over the years there has been a significant advance in our understanding of ventilator associated pneumonia. This article reviews the various aspects of VAP such as definition, risk factors, etiological agents, diagnosis, treatment and prevention with emphasis on the recent advances.

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1. Definition
VAP is defined as pneumonia occurring more than 48 h after the initiation of endotracheal intubation and mechanical ventilation [1]. VAP can also be conceptually defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time MV was started [7]. Despite the clarity of this concept, numerous operational definitions have been proposed over the decades, none of which is universally accepted [8]. Even definitions based on histopathological examination of biopsy or autopsy tissue may lack precision in diagnosis of VAP. Involvement of focal areas of a lobe may be missed and culture may be negative despite the presence of inflammation in the lung [9–11]. The absence of a “gold standard” for diagnosis continues to fuel controversy about the adequacy and accuracy of these definitions.

Early-onset VAP, which occurs during the first 4 days of MV, usually is less severe, associated with a better prognosis, and is more likely to be caused by antibiotic sensitive bacteria. Late-onset VAP, which develops five or more days after initiation of MV, is caused by multidrug-resistant (MDR) pathogens, and is associated with increased morbidity and mortality [8].

2. Incidence
Ventilator-associated pneumonia (VAP) is the most frequent intensive-care-unit (ICU)-acquired infection, with an incidence ranging from 6 to 52% [1,2]. Several studies have shown that critically ill patients are at high risk for getting such nosocomial infections [3,4]. The incidence of VAP is varied among different studies, depending on the definition, the type of hospital or ICU, the population studied and the level of antibiotic exposure. The lack of consensus regarding the most appropriate method to diagnose VAP also partly explains why incidence rates vary widely from one study to another.

Hospital-acquired pneumonia (HAP) and VAP represented the second most common nosocomial infection affecting approximately 27% of all critically ill patients in the United States National Nosocomial Infection Surveillance involving over 14,000 ICU patients [12]. Nearly 90% of episodes of HAP among the ICU patients occur during mechanical ventilation [13].

In the recent reports the incidence rate of VAP ranges from 13.2 to 51 per 1000 ventilator days [14–16]. The rates of VAP vary from 5 cases per 1000 days in pediatric patients to 35 cases per 1000 days in burn patients [17]. Generally, the surgical ICUs have higher rates of VAP compared to the medical ICUs [17]. The incidence of nosocomial
pneumonia (NP) was reported as 21.6% in patients admitted to a cardiothoracic ICU, 14% in other surgical ICU, and 9.3% in a medical ICU [18].

3. Risk factors

The various risk factors for the development of VAP documented in different studies are listed in Table 1 [5,16,19–24].

In a study involving four multidisciplinary ICUs in Athens, univariate analysis indicated that tracheostomy, bronchoscopy, enteral feeding, duration of mechanical ventilation ≥ 5 days, mean duration of central vein catheterization, APACHE II score ≥ 18 on admission, and acute physiology score ≥ 10 on admission were significantly associated with VAP [19].

The following were demonstrated as independent risk factors for the development of VAP by multivariate analysis in different studies: tracheostomy, multiple central venous line insertions, re-intubation, the use of antacids, length of stay, coma, depressed consciousness, enteral feeding [5,20]. During the first 96 h of mechanical ventilation multiple central venous line insertions, emergency intubation and intravenous sedatives were found to be independent predictors of VAP, while after 96 h of ventilation the predictors of VAP were re-intubation, antacids and tracheostomy [16,20].

4. Etiological agents

The etiological agent varies according to patient population, unit, hospital or country. The organisms causing VAP and their susceptibility pattern may not only vary from unit to unit, but also in a given hospital or country. The organisms causing VAP and their susceptibility patterns are listed in Table 2 [7,8,25,26].

These agents may be part of the host’s endogenous flora, or may be acquired from other patients, health care workers, devices, or the hospital environment [17]. Early-onset VAP is often caused by *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*, while late-onset VAP is more frequently caused by multidrug-resistant *Pseudomonas aeruginosa, Acinetobacter* or *Enterobacter* spp., or methicillin-resistant *S. aureus* (MRSA) [6,17].

4.1. Multidrug-resistant (MDR) pathogens

Most of the VAP pathogens, such as *Pseudomonas* species, *Acinetobacter* species, MRSA, and enteric Gram-negative bacilli expressing ESBL and AmpC β-lactamas characteristically display high levels of antibiotic resistance. These bacteria are referred to as “multidrug-resistant” (MDR) pathogens [8,27]. Prior antibiotic therapy or prior hospitalization within the past 90 days predisposes to colonization and infection with MDR pathogens [8]. MDR pathogens are more frequently associated with late-onset VAP. The underlying mechanisms for resistance to β-lactams are production of β-lactamaes, lack of drug penetration due to mutation in porins, presence of efflux pumps and changes in penicillin-binding proteins (PBPs) that prevent their action [28]. Extended spectrum β-lactamaes (ESBL) and AmpC β-lactamaes primarily confer resistance to penicillins and cephalosporins, while metallo-β-lactamaes (MBL) contribute to carbapenem resistance [29–31]. Modified Hodge test and EDTA disk synergy (EDS) test are the commonly used phenotypic methods for detection of carbapenemases and MBL respectively [32,33]. AmpC disc test and Kirby-Bauer disc approximation (KBDA) method are used frequently to detect stably derepressed and inducible AmpC β-lactamaes respectively [34,35]. Oxacillin resistance screening agar containing 4% Sodium chloride and 6 μg/ml oxacillin in Mueller-Hinton agar (MHA) is a reliable method for screening of MRSA [36].

4.2. Polymicrobial infection

VAP caused by more than one microorganism was identified in around 30–70% of the cases [37]. In a study by Combes et al., polymicrobial infections were diagnosed in 48% cases of VAP [38]. In two Indian studies, 12.3% and 16.3% of VAP cases were polymicrobial [39,40]. It was also observed that the epidemiology and outcomes of patients with monomicrobial and polymicrobial VAP did not differ significantly [38].

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Table 1

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<thead>
<tr>
<th>Risk factors for VAP.</th>
<th>Intervention factors</th>
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<tr>
<td>Oro-pharyngeal colonization</td>
<td>Emergency intubation</td>
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<td>Gastric colonization</td>
<td>Re-intubation</td>
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<td>Thermal injury (Burns)</td>
<td>Tracheostomy</td>
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<td>Post-traumatic</td>
<td>Bronchoscopy</td>
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<td>Post-surgical</td>
<td>Nasogastric tube</td>
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<td>Impaired consciousness</td>
<td>Duration of hospital stay/ICU stay</td>
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<td>Immunosuppression</td>
<td>Multiple central venous line insertions</td>
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<td>Organ failure</td>
<td>Sedatives</td>
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<td>Sinusitis</td>
<td>Stress ulcer prophylaxis</td>
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<td>Severity of underlying illness</td>
<td>Prior antibiotics/no antibiotic prophylaxis</td>
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<td>Old age (≥ 60 years)</td>
<td>Immunosuppressives (Corticosteroids)</td>
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<tr>
<td>Presence of comorbidities</td>
<td>Supine head position</td>
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MV = mechanical ventilation; ICU = intensive care unit.
5. Pathogenesis

Pneumonia represents the overwhelmed host's inflammatory response to the microbial invasion of the normally sterile lung parenchyma [41]. The magnitude of this response is dependent on the type of the inoculum and its size, the virulence of the pathogen, and the competence of the host's immune system [41].

Normally, the host defence mechanisms, including filtration and humidification of air in the upper airways, non-immune antimicrobial agents in saliva, an intact cough reflex, mucociliary clearance, phagocytes and opsonins in lung, and systemic cell mediated and humoral immunity, prevent bacterial invasion [14,41]. In critically ill ICU patients, these host defences are usually altered because of the underlying diseases, comorbidities, malnutrition sedation, and devices like endotracheal tube [14,42]. Once the pathogens reach the distal lung, they multiply and cause invasive disease.

5.1. Role of oropharyngeal colonization

Numerous studies have shown that, upon admission to the ICU, in the critically ill patients, the oral flora shifts dramatically to a predominance of enteric Gram-negative bacilli, *Staphylococcus* and *P. aeruginosa* [42,43]. In the mechanically ventilated patient bacterial adherence is favoured by reduced immunoglobulin A, augmented protease production, denuded mucous membrane, elevated airway pH and increased numbers of airway receptors for bacteria, due to acute illness [42]. Ewig et al. proved that oropharyngeal colonization was a powerful independent predictor of subsequent tracheobronchial colonization [43].

5.2. Role of gastric colonization

The chief predisposing factors for gastric colonization include conditions that reduce the gastric pH, such as, achlorhydria, stress ulcer prophylaxis (H2 antagonists or proton-pump inhibitors), or enteral nutrition [42]. Recumbency and the presence of naso-gastric tube may favour reflux of the gastric microorganisms, which can later be aspirated into the trachea, despite the presence of an endotracheal cuff [42]. The stomach has been implicated as a potential reservoir for antibiotic-resistant bacteria particularly in late-onset VAP [13]. But the current view is that, though the stomach is often heavily colonized by enteric Gram-negative bacilli, the gastro-pulmonary route may not be a major route for the development of VAP [7,44].

6. Source of VAP pathogens

There are various sources from which the microorganisms can gain access to the lungs and eventually cause VAP. The source of infection can be endogenous or exogenous [42,45]. The endogenous and exogenous sources of VAP pathogens are depicted in Fig. 1. The oropharyngeal colonization and gastric colonization can act as the endogenous source of microorganisms [7,8,42,46]. Contaminated respiratory instruments (bronchoscopes, ventilator circuits, humidifiers and suction catheters), infective aerosols from the ICU environment and contaminated hands and apparels of the health care workers (e).

**Fig. 1.** Source of VAP pathogens. The endogenous sources are oropharyngeal colonization (a) and gastric colonization (b). The exogenous sources are aerosols from contaminated ambient air (c), contaminated respiratory instruments (d) and contaminated hands and apparels of health care workers (e).
workers (due to contact with other patients, contaminated taps, medicine trolley and other fomites) are the major exogenous sources of infection [8,42,45].

7. Diagnosis of VAP

There is no gold standard for diagnosis of VAP. However, a combination of clinical, radiological and microbiological criteria can be used effectively for early and accurate diagnosis of VAP. A simple algorithm for the diagnosis of VAP is depicted in Fig. 2, based on the recommendations by several authors [7,8,37,47–54].

8. Clinical diagnosis

VAP is clinically suspected usually based on the presence of fever (temperature >38.3 °C), blood leukocytosis (>10,000/mm³), or leukopenia (<4000/mm³), purulent tracheal secretions, and the presence of a new and/or persistent radiographic infiltrate. However, these clinical parameters individually have limited diagnostic value [55].

Hence, the clinical diagnosis of VAP is made when there is a new or progressive radiographic infiltrate plus at least 2 of the following 3 parameters: fever, leukocytosis, or purulent tracheal secretions [56,57]. Although this definition is highly sensitive, its specificity is low [56,57]. It has been shown that only as few as one third of clinically diagnosed VAP cases were confirmed microbiologically using quantitative cultures [7]. Fagon et al. have reported that the clinical diagnosis of VAP is associated with 20–25% false-positive and 30–35% false-negative results [14]. Postmortem studies in a series of patients with acute lung injury demonstrated that clinical criteria alone led to an incorrect diagnosis of VAP in 29% of clinically suspected cases [58].

The clinical diagnosis of VAP is overly sensitive because there are other potential causes of fever, leukocytosis, purulent tracheal secretions and pulmonary infiltrates [59].

The systemic signs of VAP, such as fever and leukocytosis, are non-specific and can be caused by any condition that releases cytokines like, interleukin-1, interleukin-6, tumor necrosis factor alpha, and gamma interferon [27]. The conditions that induce cytokine release as an inflammatory response are trauma, surgery, deep vein thrombosis, pancreatitis, pulmonary embolism, pulmonary edema, and pulmonary infarction [27]. In a prospective study by Meduri et al. 24% of fevers were found to be due to one of these non-infectious causes [60]. In the critically ill ICU patients, underlying diseases like immunosuppression, chronic renal failure may suppress the systemic signs of infection, accounting for the false negativity of these clinical parameters for diagnosis of VAP [14]. Purulent sputum can also be attributed to tracheobronchitis and does not always indicate pulmonary parenchymal involvement [61].

The only alternative approach to the clinical diagnosis of VAP is the Clinical Pulmonary Infection Score (CPIS), which was proposed by Pugin et al., based on 6 clinical assessments, each worth 0–2 points, including: fever, leukocyte count, quantity and purulence of tracheal secretions, oxygenation, type of radiographic abnormality, and results of sputum culture and Gram stain [37,47]. In their study, Pugin et al. showed that the correlation between the CPIS and the bronchoalveolar lavage (BAL) bacterial index was 0.8, proving that clinical diagnosis can be as accurate as microbiologic diagnosis based on quantitative culture of BAL [56]. In addition, a CPIS ≥6 as a clinical definition of VAP, was associated with a high likelihood of pneumonia with a sensitivity of 93% and a specificity of 100% comparing quantitative BAL culture [56]. In a prospective post mortem study Clinical Pulmonary Infection Score (CPIS) at a threshold of 6 achieved a sensitivity of 72% and a specificity of 85% [62].

Ambiguities in the scoring system or missing data that were required to calculate the CPIS could result in a large interobserver variability [56]. Another drawback of the CPIS is that it is associated with a delay of 24–48 h for the results of tracheal aspirate cultures. Therefore Singh et al. proposed that a modified CPIS with only the first five clinical variables can be used for the initial diagnosis of VAP, followed by calculation of CPIS based on all the 6 variables after 72 h, so that antibiotics can be stopped in patients with a persistent low score (CPIS ≤6) after 3 days of therapy, avoiding unnecessary use of antibiotics [63]. Farouk et al. reported that the modified CPIS had low diagnostic accuracy; however, incorporating Gram stain results into the score (by adding two more points when Gram stain was positive) may increase the sensitivity of the score and help clinical decision making in patients with clinically suspected pneumonia [55]. They also reported that CPIS ≤6 after incorporation of Gram stain results was still associated with a false-negative rate of 16 to 25% [55].

9. Radiological diagnosis

Numerous studies have shown that certain chest radiograph findings, like progressive rapid cavitation of the pulmonary infiltrate, an air space process abutting a fissure and a single air bronchogram are associated with 96% specificity for diagnosing VAP. But, such specific radiographic abnormalities being uncommon, chest radiographs are mainly helpful in excluding VAP when they are normal [2].

Asymmetric pulmonary infiltrates on chest radiograph consistent with VAP may be caused by various non-infectious conditions, such as atelectasis, embolism, chemical pneumonitis, asymmetric cardio-

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**Fig. 2. The algorithm for the diagnosis of VAP.** CPIS—Clinical Pulmonary Infection Score, PCT—procalcitonin, sTREM—soluble triggering receptor expressed on myeloid cells-1, CRP—C-reactive protein, EA—endotracheal aspirate, ICB—intracellular bacteria, CFU—colony forming units, VAP—ventilator associated pneumonia, BAL—bronchoalveolar lavage, PSB—protected specimen brush.
pulmonary edema, pulmonary embolism, cryptogenic organizing pneumonia, pulmonary contusion, pulmonary hemorrhage, and drug reaction [2,7,41]. The overall radiographic specificity of a pulmonary opacity consistent with pneumonia is only 27% to 35% [2].

10. Laboratory diagnosis

The microbiological diagnosis of VAP is based on direct microscopic examination, qualitative and quantitative culture of lower respiratory tract secretions obtained bronchoscopically or nonbronchoscopically.

The quality of lower respiratory secretions is of utmost importance for better interpretation of both microscopy and culture [64,65]. Although no absolute guideline exists, the recommendations for ensuring proper quality of the secretions are: 1) Lower respiratory tract secretions should be obtained before antibiotics are started or changed. 2) When collecting BAL, less than 10% return of instilled fluid probably represents inadequate sampling. 3) When protected specimen brush (PSB) is used for lower respiratory tract sampling, the brush must be placed into exactly 1 mL of fluid. 4) Specimens should be processed within 30 min or refrigerated if any further delay is expected [7,64,66].

10.1. Microscopy

10.1.1. Gram’s stain

The Gram’s staining is useful to detect bacteria and yeast cells in the respiratory secretions. The percentages of squamous epithelial or bronchial cells may be used to predict heavy upper respiratory contamination [7]. The presence of more than 1% epithelial cells or 10 epithelial cells per low-power field (magnification, ×100) has been proposed as a rejection criterion [2,7,64]. The number of polymorphonuclear (PMN) leukocytes is generally not predictive of an interpretable specimen in patients with VAP [67]. However, in a postmortem study, BAL fluid with <50% neutrophils had a 100% negative predictive value for histologic pneumonia [68]. The presence of leukocytes was not found to be specific for a positive culture, but in their absence, a positive culture was unlikely as it probably represents inadequate sampling [65,69].

Duflo F et al. showed that in patients with VAP, the correlation between the Gram’s stain and BAL quantitative cultures was complete in 39%, partial in 28%, and absent in 33% [70]. Hence, Gram’s stain is not reliable for the early adaptation of empirical chemotherapy.

10.1.2. Giemsa staining

Giemsa staining is recommended for evaluation of VAP, as it offers a number of advantages over Gram’s staining, including better visualization of host cell morphology, improved detection of bacteria, particularly intracellular bacteria, and detection of some protozoan and fungal pathogens, such as Histoplasma capsulatum, Pneumocystis jirovecii, Toxoplasma gondii, and Candida spp. [7,66].

In a study by Sirvent et al., the cut-off point of >2% of cells containing intracellular bacteria had the highest sensitivity (80%) and specificity (82%) in the microscopic examination of nonbronchoscopic protected bronchoalveolar mini-lavage (mini-PBAL) fluid for the diagnosis of VAP [71]. However, the sensitivity is too low to be clinically useful. The direct examination of mini-PBAL fluid is less accurate when previous antibiotic therapy has been administered [71].

Chastre et al. had shown that the presence of ≥5% intracellular organisms had a sensitivity, specificity, positive predictive value, and negative predictive value of 91%, 89%, 91%, and 89%, respectively [51].

10.2. Culture

The specimen for culture should ideally be collected before starting antibiotics or when there is no change in antibiotic therapy in the past 3 days. The negative predictive value is high (94%) for culture of such appropriately collected specimen [72]. A false-negative rate of 10 to 40% is observed in the presence of prior antibiotic therapy [2].

10.2.1. Qualitative culture

Qualitative tracheobronchial aspirates are highly sensitive (>75%) but poorly specific (<25%) for the diagnosis of VAP [37]. Qualitative cultures of tracheal aspirate (TA) is not a specific diagnostic tool as it is associated with a high percentage of false-positives due to colonization of the lower respiratory tract [14]. Nevertheless, due to the high negative predictive value, they may be useful to exclude VAP, particularly in the patients without prior antimicrobial treatment [37]. As qualitative culture is overly sensitive, continuation of antibiotic therapy based only on a positive qualitative culture report may lead to unnecessary antibiotic use, encouraging bacterial resistance and consequently higher costs [73]. In one study it was observed that 57% patients were overtreated with antibiotics based on qualitative endotracheal aspirate (EA) cultures [74].

In another study, quantitative cultures of tracheal aspirates in selected critically ill patients showed decreased sensitivity when compared with qualitative culture (65% and 81% respectively) [75]. Consequently, qualitative culture though not highly specific, should not be replaced by quantitative culture to confirm a clinical diagnosis of VAP as certain cases of VAP may be missed by the latter.

10.2.2. Semiquantitative culture

Semiquantitative culture is performed based on the four-quadrant streak technique using a calibrated loop. Endotracheal aspirate (EA) cultures are read semiquantitatively by observing the growth in the four quadrants, which suggests the approximate number of CFU/ml of the bacteria in the specimen [74].

In a study comparing the semiquantitative culture (calibrated loop technique) and the quantitative culture (serial dilution technique) of 121 BAL samples, a very good agreement between the techniques was observed with only one discordant result [52]. However, use of semiquantitative cultures for guiding antibiotic therapy may be associated with substantially more patients being overtreated as observed in a study by Brun-Buisson et al., wherein 18% patients were unnecessarily treated with antibiotics based on semiquantitative cultures of EA [74].

10.2.3. Quantitative culture

Quantitative culture is performed by serial dilution of the specimen. Cultures were reported as colony forming units per milliliter (CFU/ml), after correction for the initial dilution. If the number of CFU/ml is equal to or exceeds the threshold values for the particular technique, a diagnosis of pneumonia is made. Threshold values commonly employed for diagnosing VAP by quantitative cultures are ≥10³, ≥10⁴, and ≥10⁵ CFU/ml for EA, bronchoscopic BAL, and PSB, respectively [7,54,76].

Quantitative cultures are generally preferred over qualitative culture for making decisions regarding therapy for VAP [73]. The results of quantitative cultures is influenced by various factors, such as the stage of pneumonia, prior antibiotic therapy, the adequacy of the sample, the operator’s skill, method of processing, delay in transport [2]. False-positive quantitative cultures could be secondary to chronic obstructive pulmonary disease (have high bacterial counts without pneumonia) and bronchiolitis [2]. Considering these potential limitations, a quantitative culture that exceeds a threshold value is not always diagnostic of VAP.

10.2.4. Bronchoscopic specimens

The most commonly used bronchoscopic techniques are BAL or protected specimen brushing (PSB) [7]. The average sensitivity and specificity of BAL in several studies are 73% and 82% respectively, while PSB has 89% sensitivity and 94% specificity [41].
Chastre et al. showed that, BAL had a sensitivity of 91%, a specificity of 78%, a positive predictive value of 83%, and a negative predictive value of 87%, while PSB had a sensitivity of 82%, a specificity of 89%, a positive predictive value of 90%, and a negative predictive value of 89% compared to histopathological findings and quantitative culture of lung tissue [51]. Although bronchoscopy has only a low inherent risk even for critically ill patients, it may rarely lead to cardiac arrhythmias, hypoxemia, or bronchospasm [7].

10.2.5. Non-bronchoscopic specimens (endotracheal aspirate)

Quantitative endotracheal aspirate (EA) culture may be an acceptable tool for diagnosing VAP as this approach is non-invasive, inexpensive, and widely available [37]. Quantitative EA also had a high negative predictive (88.9%) value, warranting its early use in diagnosis of VAP [53]. When the diagnosis of VAP was based on postmortem lung examination, the quantitative EA at a threshold of 10^6 CFU/ml had 63% sensitivity and 75% specificity, while a cut-off of 10^6 CFU/ml was 55% sensitive and 85% specific [2].

10.2.6. Non-bronchoscopic vs. bronchoscopic specimens

Quantitatively cultured EA and bronchoscopically collected specimens have a very good correlation [77]. Sanchez-Nieto et al. observed a total agreement between quantitative culture results of the EA, BAL and PSB and there was no significant difference in mortality [54].

In a prospective observational clinical study the quantitative EA at threshold of 10^6 CFU/ml had a sensitivity of 92.8% and a specificity of 80% and it significantly correlated with PSB and BAL in patients with suspected VAP [53].

Several investigators have concluded that bronchoscopic techniques were not more accurate for diagnosis of VAP than clinical and radiological criteria combined with tracheal aspirates cultures [64]. Fagon et al. found that, in those suspected of VAP, the non-invasive strategy was associated with higher antibiotic use compared to the invasive strategy [78].

10.2.7. Role of blood and pleural effusion cultures

Though the recovery of organisms from blood and pleural fluid in VAP patients is considered significant, its role in diagnosis of VAP is limited, as the spread to the blood or pleural space occurs in < 10% of VAP [7].

The sensitivity of blood culture for disclosing the VAP pathogens was 26% with a positive predictive value of 73% [79]. Furthermore, the bacteremia may be due to extra-pulmonary infection in as many as 64% of cases even in the presence of VAP [2].

Besides, the presence of bacteremia does not indicate severe illness or predict future complications, and is also not related to the duration of illness [79]. Hence, most experts recommend blood and pleural effusion cultures only when no other source of infection is known [7].

10.3. Histopathological examination and lung tissue culture

Histopathological examination and culture of lung tissue obtained by biopsy or at autopsy are generally considered the “gold standard” for diagnosis of VAP [2]. But they are also associated with certain inherent problems. There is a significant variation of about 18% to 38% in interpretation of the histopathological findings by different pathologists [80]. Furthermore, patients included in the postmortem studies may not be truly representative of most patients with VAP and so the evaluation of other diagnostic tools in comparison to these “gold standards” may not be fully justified [2].

10.4. Role of biomarkers as diagnostic and prognostic markers of VAP

Over the past few years, biomarkers have emerged as an indispensible tool for the diagnosis and prognosis of VAP. C-reactive protein (CRP), procalcitonin (PCT), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and endotoxin are the various diagnostic biomarkers of VAP [81]. The other biomarkers like proadrenomedullin, natriuretic peptides, endothelin-1 precursor peptides, copeptin and cortisol levels are useful prognostic markers and may be of great help in the risk stratification of patients [81].

CRP at a cut-off of 9.6 mg/dl was noted to have a good accuracy, with a sensitivity of 87% and a specificity of 88% for diagnosing VAP [48]. CRP can also be used to predict the severity of the disease as high levels are associated with poor outcome [48]. Low PCT levels (<0.25 μg/l) in patients with no clinical signs of severe illness suggest safe withdrawal of antibiotics, thereby limiting the use of unnecessary antibiotics. Alternatively, PCT ≥ 0.5 ng/ml strongly recommends antibiotic treatment as it is indicative of active bacterial infection [49]. PCT was shown to be elevated on an average 2 days prior to the clinical diagnosis of VAP and therefore can be used as an early marker for diagnosis of VAP [82]. sTREM-1 has been noted to be elevated in BAL fluid of patients with pneumonia, in the plasma of septic patients, and in the exhaled breath condensate of VAP patients [50,83]. sTREM-1 levels in BAL were found to start rising 6 days prior to VAP diagnosis [83]. Detection of sTREM-1 in exhaled breath condensate may be a useful non-invasive means of diagnosing VAP.

Endotoxin allows rapid diagnosis of Gram-negative bacterial pneumonia [81]. MR-proANP (midregional pro-atrial natriuretic peptide), CT-proAVP (C-terminal provasopressin-copeptin) and procalcitonin have been found to increase with severity of sepsis and may be used as a predictor of mortality in VAP [81,84,85].

11. Mortality

The mortality rates for VAP range from 20% to 76% in various studies [7,14]. In two different studies Pseudomonas or Acinetobacter pneumonia was associated with high mortality rates of 65% and 87% which was significantly more compared with 31–55% for VAP due to other microbes [7]. Similarly, methicillin-resistant S. aureus (MRSA) was associated with 86% mortality directly attributable to pneumonia, compared to 12% mortality rate with methicillin-sensitive S. aureus (MSSA) [7].

Multivariate analyses conducted to evaluate the independent role played by VAP in inducing death failed to identify VAP as a variable independently associated with mortality in two studies [7].

12. Morbidity and cost

In a retrospective matched cohort study using data from a large US inpatient database patients with VAP had a significantly prolonged duration of MV (14.3 ± 15.5 days vs 4.7 ± 7.0 days), ICU stay (11.7 ± 11.0 days vs 5.6 ± 6.1 days), and hospital stay (25.5 ± 22.8 days vs 14.0 ± 14.6 days) [6].

The prolonged hospital and ICU stay underscore the significant financial burden imposed by the development of VAP. A precise and universal evaluation of such incremental costs associated with VAP is difficult. However, in a-three year retrospective case–control study the cost of VAP was approximately five-fold higher than non-infected patients [5].

13. Treatment

The successful treatment of patients with VAP remains a difficult and complex undertaking as it is influenced by various factors such as lack of definitive diagnosis of VAP, difficulty in differentiating colonization from active infection, lack of an adequate and feasible technique to directly sample the infection site in the lung, and frequent association with MDR pathogens [7]. The algorithm for the treatment of VAP based on different studies and recommendations by experts is shown in Fig. 3 [8,37,49,86–88].
The American Thoracic Society (ATS) guidelines for treatment of VAP recommends that the initial empiric therapy should be based on the presence or absence of risk factors for MDR pathogens such as prolonged hospitalization (5 days or more), admission from a healthcare-related facility, and recent antibiotic therapy [8]. The initial empiric therapy recommended by the American Thoracic Society for treatment of VAP patients with and without risk factors for MDR pathogens are summarized in Table 3 [8].

The selection of specific antibiotics should be dictated by local microbial flora, cost, feasibility and availability. Although the duration of empiric therapy is traditionally 14 to 21 days, in patients with good clinical response with resolution of infection, it can be shortened to 7 days, except when treating P. aeruginosa, Acinetobacter species or other non-fermenters [8].

In a study by Porzecanski it was observed that a guideline-based approach using the antibiotic susceptibility pattern of the local hospital or ICU pathogens, can increase the likelihood of adequate initial antibiotic therapy and reduce the overall use of antibiotics and the associated selection pressure for MDR bacteria [59].

Recently a new approach known as ‘de-escalation’ strategy has been suggested for effective delivery of appropriate empiric therapy for VAP, without the overuse of antibiotics [86]. De-escalation refers to use of microbiologic and clinical data to change from an initial broad-spectrum, multi-drug empiric therapy regimen to a therapy with fewer antibiotics and agents of narrower spectrum [86]. This is a promising approach for optimizing the use of antibiotics while permitting administration of prompt and appropriate empiric therapy of VAP.

In a study evaluating the role of nebulized colistin, it was shown to be reasonably efficacious and safe for treatment of MDR P. aeruginosa and Acinetobacter baumannii with an overall clinical and microbiological response rates of 57.1% and 85.7% respectively [89].

Despite the fact that the use of aerosolized antibiotics can effectively kill the bacteria limited to the airway epithelium in the early stage of infection, the clinical evidence to support this approach for treatment of VAP is lacking [90]. Several evidence-based consensus groups recommend against routine use of aerosolized antibiotics for VAP prevention due to concerns about the high cost and possible development of antibiotic resistance [90].

### 14. Prevention

The important measures for prevention of VAP include implementation of hand hygiene using alcohol rubs, reduction of duration of mechanical ventilation as far as possible, maintenance of semi-recumbent position and avoidance of the modifiable risk factors such as tracheostomy, re-intubation, corticosteroid therapy, stress ulcer prophylaxis and contaminated respiratory equipment, water or environment [2,91].

To conclude, VAP continues to be a major challenge to the critical care physicians. Most of the risk factors of VAP are preventable. VAP is increasingly associated with MDR pathogens. The multi-drug resistance of these pathogens was mainly due to production of ESBL, AmpC β-lactamases and metallo β-lactamases. VAP should be diagnosed based on a combination of different clinical and laboratory criteria such as CPIS >6, qualitative and quantitative culture of lower respiratory tract secretions collected bronchoscopically or non-bronchoscopically. VAP is associated with increased morbidity and imposes significant financial burden on the health care system. The initial empiric therapy of VAP should be based on the presence or absence of risk factors for MDR pathogens. Awareness of the important risk factors of VAP is essential for implementation of simple and effective preventive measures.

### 15. Learning points

- The incidence rate of VAP ranges from 13 to 51 per 1000 ventilator days
- VAP is increasingly associated with MDR pathogens
- The source of infection can be endogenous or exogenous

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**Fig. 3.** The algorithm for the treatment of VAP. VAP—ventilator associated pneumonia, MDR—multidrug resistant, CPIS—Clinical Pulmonary Infection Score, PCT—procalcitonin, CFU—colony forming units, BAL—bronchoalveolar lavage, PSB—protected specimen brush.

**Table 3**

<table>
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<th>Initial empirical therapy for VAP.</th>
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<td>VAP with no risk factors for MDR pathogens</td>
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<tr>
<td>Ceftriaxone</td>
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<tr>
<td>or Levofloxacin, moxifloxacin, or ciprofloxacin</td>
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<tr>
<td>or Ampicillin/sulbactam</td>
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<tr>
<td>or Ertapenem</td>
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MDR = multidrug-resistant. MRSA = methicillin-resistant Staphylococcus aureus.
• The quality of lower respiratory secretions is of utmost importance for better interpretation
• Both the clinical criteria (CPIS–5) and the microbiological criteria (quantitative culture) are essential for diagnosis
• Gram's stain is not reliable for the early adaptation of empirical chemotherapy

Biomarkers are an indispensable tool for the diagnosis and prognosis of VAP

Empirical treatment of VAP is based on the presence or absence of risk factors for MDR pathogens
• The choice of the antibiotics is based on the susceptibility pattern of local microbial flora, cost, feasibility and availability
• 'De-escalation' strategy is a promising approach for effective delivery of appropriate empiric therapy for VAP, without the overuse of antibiotics
• The mortality rates for VAP range from 20% to 76% in various studies
• Implementation of simple preventive measures is important.

References
