CHAPTER I

VENTILATOR-ASSOCIATED PNEUMONIA (VAP) IN INTENSIVE CARE UNITS

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1. Introduction

Ventilator-associated pneumonia (VAP) continues to be important causes of morbidity and mortality in intensive care units despite advances in prevention, antimicrobial therapy and supportive care. It accounts for about half of hospital-acquired pneumonias (HAP) and estimated to occur in 9–27% of all mechanically ventilated patients (1). According to the 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines; VAP is a clinical diagnosis made in a patient who has been mechanically ventilated for ≥48 hours who develops a new or progressive lung infiltrate on imaging with clinical evidence of infection (eg, fever, purulent sputum, leukocytosis, and decline in oxygenation), together with a positive pathogen identified on microbiologic respiratory sample.VAP has been associated with long hospital stays, long duration of mechanical ventilation and significant costs (2).

2. Pathogenesis

The pathogenesis of VAP is related to the number and virulence of microorganisms entering the lower respiratory tract and the mechanical, humoral and cellular defense of the host. The primary route of infection is aspiration/microaspiration of organisms that have colonized the oropharyngeal or gastrointestinal tract. Aspiration can accure in healthy persons during sleep and in high proportion of severely ill patients. The presence of an endotracheal tube facilitates this event (3). Up to 75% of seriously ill patients will be colonized with microorganisms taken from the hospital environment within 48 hours of hospital admission mainly via the contaminated respiratory devices, water reservoirs and hands of hospital staff. Less frequently pneumonia may also develop as a result of bacteremia originating from a distant focus in intubated patients (4).

3. Clinical Presentation

There is no universally accepted, gold standard diagnostic criterion for VAP. Daily bedside assessment together with chest radiography gives clues about the presence of VAP. Fever, tachypnea, increased, purulent respiratory secretions, hemoptysis, rhonchi, decreased breath sounds, bronchospasm, decreased tidal volume and increased inspiratory pressure develop. In laboratory tests hypoxemia and lukocytosis can be detected with new or progressive infiltrates on chest radiograph or computed tomography (CT) (1). However none of these findings alone are indicative of VAP.

4. Diagnosis

The clinical diagnosis of VAP is difficult because the clinical findings are nonspecific. IDSA and ATS recommend a clinical diagnosis based upon a new lung infiltrate plus clinical findings that shows the infiltrat is of infectious origin which as mentioned above includes the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation (2). The chest radiograph can help to determine the severity of the disease (multilobar versus unilobar infiltrate) and identify complications such as pleural effusions or cavitation. The presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever >38ºC, leukocytosis or leukopenia, and purulent secretions) has a 69% sensitivity and 75% specificity for VAP (5). Chest CT, without contrast, is not routine in patients with suspected VAP but may be useful in symptomatic patients with a normal chest radiograph. It also helps in the follow-up of pulmonary infiltrates.

The diagnosis is confirmed when lower respiratory tract sampling identifies a pathogen. It has been shown that in bacterial diagnosis quantitative endotracheal aspirate cultures had a sensitivity of 48% and positive predictive value of 81%; quantitative bronchoalveolar lavage cultures had a sensitivity of 75% and positive predictive value of 77%. Respiratory samples should ideally be taken before starting antibiotic therapy or before making an antibiotic change because antibiotic therapy reduces the sensitivity of both microscopic analysis and culture. Peripheral blood cultures should be sent concomitantly (6). In 2017 guidelines published by the European Respiratory Society (ERS) / European Society of Intensive Care Medicine (ESCIM) / European Society of Clinical Microbiology / Infectious Diseases (ESCMID) / Asociación Latinoamericana del Tórax (ALAT), invasive sampling methods (eg. mini preferred bronchoalveolar lavage [BAL], bronchoscopic BAL or protected sample brush (PSB]) and quantitative cultures were recommended to be preferred for respiratory sampling (7). On the other hand the IDSA and

ATS recommendations are in line with noninvasive sampling with semiquantitative cultures for the diagnosis of VAP (2,6).

All respiratory tract samples should be sent for microscopic analysis (Gram stain) and cultures (preferably quantitative cultures). Microscopic analysis can be helpful in determining potential causative pathogen much earlier than the culture results (8). Quantitative cultures are not routinely performed in most laboratories. They are generally considered more labor-intensive and more costly than qualitative or semiquantitative cultures. In quantitative cultures typical thresholds for bacterial growth for endotracheal aspirates are; ≥1,000,000 colony forming units (cfu)/mL, bronchoscopic or mini-BAL ≥ 10,000 cfu/mL and for PSB ≥ 1000 cfu/mL. Noninvasive sampling (eg, endotracheal aspirates) with semiquantitative (or qualitative) cultures are the alternative approach preferred by IDSA and ATS because of the lack of clear evidence demonstrating superior outcomes (mortality or length of stay in hospital) with invasive sampling and quantitative cultures (described above) (2,6). However, it may be less accurate for sampling the alveolar component of the lower respiratory tract and lead to the over diagnosis of VAP. It may also be less suitable for patients with invasive pneumonia who are immunocompromised. Semiquantitative cultures are typically reported as heavy, moderate, low or no bacterial growth. Most experts consider moderate or heavy growth to be positive. Colonization is difficult to distinguish from infection with this method. So false-positive results are more likely, which can lead to over treatment of VAP. Qualitative cultures do not specify the amount of bacterial growth. VAP is considered to be present when a sample is positive and is less reliable than other methods.

Lung biopsy is not routinely performed in patients with suspected VAP. It may be reserved for patients in whom infiltrates are progressive under antibiotic treatment or if there is a suspicion of fastidious, difficult to growth microorganisms (eg, fungus, viruses) or non-infectious etiology (eg, cancer, cryptogenic organizing pneumonitis, vasculitis).

Molecular diagnostic tests can be used for more rapid identification of respiratory pathogens in VAP. Identification of resistance patterns (eg, methicillin resistance for *S. aureus*, carbapenemase presence for *Enterobacteriaceae*), by mulecular diagnostic tests offer the chance for rapid initiation of appropriate antibiotics (9). However these methods are not routinely performed and may be difficult to interpret. Polymerase chain reaction (PCR) is a fast and inexpensive technique that amplifies small segments of microbial DNA for identification. Multiplex PCR tests allow multiple pathogens to be investigated at the same time and assist in the diagnosis and appropiate antibiotic management of critically ill patients for whom the list of potential pathogens may be wide (10).

The entities of ventilator-associated conditions (VAC) and infection-related ventilator-associated complications (IVACs), which were introduced by the United States Centers for Disease Control and Prevention (CDC) for the purposes of surveillance and quality improvement, do not aid diagnosis and treatment decisions for individual patients.

5. Microbiology

A wide variety of microorganisms including aerobic gram-negative bacilli (eg, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp, *Pseudomonas aeruginosa*, *Acinetobacter* spp) and gram-positive cocci (eg, *Staphylococcus aureus*, including methicillin-resistant *S. aureus* [MRSA], *Streptococcus* spp) and viruses can cause VAP. Sometimes these infections are polymicrobial. In immunocompromised hosts a substantial fraction of these pneumonias may be due to fungal agents (11,12). According to the National Health Related Infections Surveillance Network (UHIESA) 2019, in Turkey the distribution of pathogens associated with VAP are as follows; gram-positive cocci 4,5% (S. aureus: 3,4%), enterobacteriacea 29,8% (Klebsiella spp 19.5%), non fermentative gram negative bacilli 63,5% (Acinetobacter spp: 40,6%, P. aeruginosa: 18,6%) and fungal agents 0,5% (Candida spp: 0,4%) (13). We evaluated mini-BAL and concomitant blood culture results in VAP cases in Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital during January 1, 2018 - December 31, 2019. The distribution of microorganisms isolated is shown in table 1. As seen in the table, *Acinetobacter baumanii* constitutes the majority of isolates (84.9%). Although there are differences according to the microorganisms that grow, simultaneous blood culture positivity has been detected in 17-100% of the cases.

Table 1: Microorganisms isolated from mini-BAL samples in VAP cases

(Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital)

Microorganisms	BAL/mini BAL N(%)	Concomitant bacteremia N(%)
Acinetobacter baumanii	45 (84.9)	6 (13.3)
Klebsiella pneumonia	4 (7.5)	1 (25)
Pseudomonas aeruginosa	3 (5.7)	1 (33.3)
Serratia marcencens	1 (1.9)	1 (100)
Total	53 (100)	9 (17)

The prevalence of certain pathogens (eg, anaerobes) may be underestimated because of special culturing techniques are required to identify them. Anaerobes may play a relatively minor role in the pathogenesis of VAP due to the successful treatment of VAP by regimens that do not include anaerobic coverage. Differences in host factors and hospital flora also influence the patterns of pathogens.

The role of multi drug resistant (MDR) pathogens has been increasing in VAP etiology in recent years. CDC and the European Centre for Disease Prevention and Control (ECDC) have developed standard terminology for antimicrobial-resistant gram-negative bacilli, which are important causes of HAP and VAP (14).

●MDR refers to acquired nonsusceptibility to at least one agent in three different antimicrobial classes.

●Extensively drug resistant (XDR) refers to nonsusceptibility to at least one agent in all but two antimicrobial classes.

●Pandrug resistant (PDR) refers to nonsusceptibility to all antimicrobial agents that can be used for treatment.

Prolonged hospitalization and recent exposure to antibiotics are two of the most important risk factors for MDR pathogens. Awareness of the

susceptibility patterns of nosocomial pathogens in hospitals is important in choosing the appropriate empirical antimicrobial therapy. Risk factors for MDR VAP are summarized in table 2.

Table 2: Risk factors for multidrug-resistant ventilator-associated pneumonia

Risk factors for MDR pathogens:
▪ IV antibiotic use within the previous 90 days ▪ Septic shock at the time of VAP ▪ ARDS preceding VAP ▪ ≥ 5 days of hospitalization prior to the occurrence of VAP ▪ Acute renal replacement therapy prior to VAP onset
▪ **Risk factors for MDR *Pseudomonas* and other gram-negative bacilli:** ▪ Treatment in an ICU in which >10 percent of gram-negative isolates are resistant to an agent being considered for monotherapy ▪ Treatment in an ICU in which local antimicrobial susceptibility rates are not known ▪ Colonization with OR prior isolation of MDR *Pseudomonas* or other gram-negative bacilli
▪ **Risk factors for MRSA:** ▪ Treatment in a unit in which >10 to 20 percent of *Staphylococcus aureus* isolates are methicillin resistant ▪ Treatment in a unit in which the prevalence of MRSA is not known ▪ Colonization with OR prior isolation of MRSA

MDR: multidrug resistant; IV: intravenous; VAP: ventilator-associated pneumonia; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; MRSA: methicillin-resistant *S. aureus*. *Adapted from: Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016; 63:e61.*

Antimicrobial susseptibility pattern of VAP cases in our hospital (Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital during January 1, 2018 - December 31, 2019) is shown in table 3. As seen in the table, *Acinetobacter baumanii*, the most frequently isolated

microorganism, were found as MDR and there is high antimicrobial resistance rate in *Klebsiella pneumonia* as the second most common isolate.

Table 3: Antimicrobial resistance pattern of microorganisms isolated from mini-BAL samples in VAP cases

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Microorganisms	3rd.G ceph[a]	4th.G ceph[b]	Carb[c]	AG	Colistin	Tig[e]	Cef-sulb[f]	Pip-taz	Lev[h]	TMP-SMX[i]
Acinetobacter baumanii N:45 (84.9%)	45 100%	45 100%	45 100%	40 88.8%	1 2.2%	13 28.8%	43 95.5%	45 100%	45 100%	45 100%
Klebsiella pneumonia N:4 (7.5%)	3 75%	3 75%	2 50%	1 25%	1 25%	1 25%	2 50%	3 75%	3 75%	2 50%
Pseudomonas aeruginosa N:3 (5.7%)	1 33.3%	1 33.3%	1 33.3%	0 0.0%	0 0.00%	1 33.3%	0 0.00%	1 33.3%	1 33.3%	1 33.3%
Serratia marcencens N:1 (1.9%)	1 100%	0 0.0%	0 0.0%	0 0.0%	1 100%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%
Total N: 53 (100%)	50 94.3%	49 92.4%	48 90.5%	41 77.3%	3 5.6%	15 28.3%	45 84.9%	49 92.4%	49 92.4%	48 90.5%

[a]:third generation cephalosporin, [b]: 4th generation cephalosporin, [c]:carbapenems, [d]: aminoglycosides, [e]: tygecycline, [f]: cefoperazone sulbactam, [g]: piperacillin tazobactam, [h]: levofloxacin, [i]:trimethoprim-sulfamethoxazole

6. Additional Diagnostic Tests

Biomarkers including procalcitonin, C-reactive protein (CRP), and soluble triggering receptor (sTREM-1) in BAL fluid and the clinical pulmonary infection score (CPIS), are additional diagnostic tests that have little role in the evaluation of suspected VAP (2). Procalcitonin may be useful in patients with confirmed VAP for making the decision to discontinue antibiotic therapy and it may be a useful prognostic marker (15,16). The CPIS combines clinical, radiographic, physiologic, and microbiologic data into a numerical result (table 4). At first a score of CPIS greater than 6 was thought to be related to VAP, but studies show that CPIS identified VAP with a sensitivity and specificity of only 60% and 59%, respectively (17).

Table 4: Clinical Pulmonary Infection Score

Body temperature ≥ 36.5 or ≤ 38.4 = 0 point ≥ 38.5 or ≤ 38.9 = 1 point ≥ 39 or < 36.5 = 2 point	**Pulmonary infiltration in chest X-ray** No infiltration = 0 point Diffuse infiltration = 1 point Localized infiltration = 1 points
Leukocyte count, microscopy ≥ 4000 or ≤ 11.000 = 0 point < 4000 or > 11.000 = 1 point Rod form ≥ % 50 = Add 1 point	**Progression in pulmonary infiltration** Radiographic progression (-) = 0 point Radyografic progression (+) (After the exclusion of HF and ARDS) = 2 points
Tracheal secretion Tracheal secretion (-) = 0 point Tracheal secretion with less purulence = 1 point Abundant purulent secretion = 2 points	**Pathogenic bacteria in tracheal aspirate culture** No or few pathogenic bacteria = 0 point Moderate or high levels of pathogenic bacteria = 1 point Pathogenic bacteria to be seen in Gram staining, add 1 point
Oxygenization PaO_2/FiO_2, mmHg > 240 or ARDS (ARDS: PaO_2/FiO_2 < 200, PaO_2/FiO_2 < 200, PAWP ≤ 18 mmHg and bilateral acute infiltration) = 0 point PaO_2/FiO_2, mmHg ≤ 240 or ARDS = 2 points	Total (>6 is accepted as pneumonia) ARDS: acute respiratory distress syndrome; HF: heart failure; PAWP: pulmonary artery wedge pressure

7. Prevention

Basic practices that were recommended by Society for Healthcare Epidemiology of America (SHEA) / IDSA for preventing VAP in all acute care hospitals include (18):

- Avoiding intubation when possible (eg, noninvasive ventilation)
- Minimizing transport while ventilated (when feasible)
- Implementation of weaning protocols
- Minimizing sedation
- Maintaining and improving physical conditioning
- Minimizing pooling of secretions above the endotracheal tube cuff
- Elevating the head of the bed and
- Maintaining ventilator circuits

In addition, proper hand hygiene, protective gloves and clothing of health staff, prevention of gastric distension, continuous active, prospective nosocomial infection surveillance are important in reducing nosocomial infections and VAP. Combining a set of key prevention measures into one bundle is a practical way to improve care and reducing the incidence of VAP among patients at risk. Typical bundle components include educational programs, technical measures, surveillance, and feedback. However, there is no consensus on what maintenance measures should be included in the bundles.

8. Treatment

Once VAP is suspected clinically, empiric antimicrobial therapy should be started as soon as possible specially in patients with signs of septic shock or rapidly progressive organ dysfunction (2)

Empiric therapy for VAP should include agents with activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli and should be based upon knowledge of the pathogens' susceptibility patterns within the health care setting as well as the patient's risk factors for multidrug resistance, including their prior microbiology data. Gram stain of respiratory secritions can help for guiding the choice of initial therapy. The appropriate approach would be early and aggressive antimicrobial initiation in patients with symptoms of sepsis or septic shock, and early de-escalation according to the causative pathogen and susceptibility pattern or when an alternative diagnosis is made. Empiric treatment choices should be based on the local distribution of pathogens causing VAP and their antimicrobial susceptibility patterns (19). Antimicrobial selection should also be based upon risk factors for MDR pathogens (table 2). For patients with risk factors for MDR pathogens, empiric broad-spectrum multidrug therapy is recommended. Potential drug toxicity and interactions, cost, availability, and clinician familiarity with the medications also should be considered. Antibiotic therapy should be narrowed/tailored based on microbiological results and susceptibility pattern of responsible microorganisms.

IDSA recommendations on initial treatment of VAP is summarized in table 5 (2).

Table 5: IDSA recommendations on initial treatment of VAP

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

Choose one gram-positive option from column A, one gram-negative option from column B, and one gram-negative option from column C. Note that the initial doses suggested in this table may need to be modified for patients with hepatic or renal dysfunction.

Abbreviations: CrCl, creatinine clearance; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Drug levels and adjustment of doses and/or intervals required.

[b] Extended infusions may be appropriate. Please see section XIII on pharmacokinetic/pharmacodynamic optimization of antibiotic therapy.

[c] On meta-analysis, aminoglycoside regimens were associated with lower clinical response rates with no differences in mortality.

[d] The dose may need to be lowered in patients weighing <70 kg to prevent seizures.

[e] Polymyxins should be reserved for settings where there is a high prevalence of multidrug resistance and local expertise in using this medication. Dosing is based on colistin-base activity (CBA); for example, One million IU of colistin is equivalent to about 30 mg of CBA, which corresponds to about 80 mg of the prodrug colistimethate. Polymyxin B (1 mg = 10 000 units) [136].

[f] In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam–based agent because it has different targets within the bacterial cell wall [137].

9. Conclusion

VAP occurs frequently in intensive care units and is one of the major causes of morbidity and mortality specially in critically ill patients. The first step in VAP management should be the preventive measures that can be directed by bundle applications created in line with the advice of international guidelines. The second important step is early diagnosis of VAP by continuous monitoring of patients' clinical condition, laboratory and imaging findings. Taking necessary culture samples and early initiation of appropriate empirical antimicrobial therapy based on hospital surveillance data are the next steps. Antimicrobial de-escalation according to the microbiological culture results and the clinical response of the patient is an important issue that plays an important role in preventing unnecessary and inappropriate use of antibiotics and the development of antibiotic resistance.

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