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ICU Associated Pneumonia and Management Approaches

[1]Dr. Fatimah AlGhawi, [2]Dr. Nada AlGhawi

[1]BSc, MD, [2]BCs, MD

Abstract: **The main goal of the following review is to detect the incidence, various risk factors and attributable mortality associated with VAP and secondary objective is to identify the various bacterial pathogens causing VAP in the ICU. A literature search was conducted using electronic databases such as MEDLINE, the Cochrane Library, and manuscript references for studies published in English up to December, 2017 for all studies concerning management of ICU associated pneumonia. VAP occurs frequently and is associated with significant morbidity in critically ill patients. The primary obstacle in diagnosing VAP is the absence of gold standard criteria and, therefore, VAP continues to be an inconspicuous clinical syndrome. There is enough evidence to indicate that VAP is preventable and that hospitals can decrease VAP rates, a factor that the new CDC VAP definitions are poised to demonstrate more objectively. The diagnostic challenge of VAP has multiple implications for therapy. Although a CPIS score > 6 may correlate with VAP, the sensitivity, specificity and inter-rater agreement of this criterion alone are not encouraging. Microbiological data should be used for tailoring antibiotic therapy and not be restricted only to diagnosis.**

Keywords: **ICU associated pneumonia, VAP, incidence, patients.**

1. INTRODUCTION

Ventilator-associated pneumonia (VAP) is specified as pneumonia that occurs 48-72 hours or thereafter following endotracheal intubation, characterized by the presence of a new or modern infiltrate, signs of systemic infection (high temperature, modified leukocyte count), modifications in sputum features, and discovery of a causative agent [1].VAP adds to roughly half of all cases of hospital-acquired pneumonia [1], [2].VAP is estimated to happen in 9-27 % of all mechanically ventilated patients, with the greatest danger being early during hospitalization [1], [3].It is the 2nd most typical nosocomial infection in the intensive care unit (ICU) and the most common in mechanically ventilated patients [4], [5].VAP rates vary from 1.2 to 8.5 each 1,000 ventilator days and are reliant on the definition utilized for diagnosis [6].Threat for VAP is best during the first 5 days of mechanical ventilation (3 %) with the mean duration between intubation and advancement of VAP being 3.3 days [1], [7].This risk decreases to 2 %/ day between days 5 to 10 of ventilation, and 1 %/ day after that [1], [8].Earlier researches placed the attributable mortality for VAP at between 33-50 %, yet this rate varies and counts heavily on the underlying clinical ailment [1]. Throughout the years, the attributable risk of fatality has lowered and is a lot more lately estimated at 9-13 % [9], [10], mostly as a result of implementation of precautionary approaches. Approximately 50 % of all prescription antibiotics administered in ICUs are for treatment of VAP [2], [4].Early onset VAP is specified as pneumonia that happens within 4 days and this is usually associateded with antibiotic sensitive microorganisms whereas late start VAP is more most likely caused by multidrug resistant (MDR) microorganisms and arises after 4 days of intubation [1], [4]. Therefore, VAP postures severe implications in endotracheally intubated grown-up patients in ICUs globally and results in boosted negative results and medical care expenses. Independent danger aspects for development of VAP are male sex, admission for trauma and intermediate underlying condition severity, with chances ratios (OR) of 1.58, 1.75 and 1.47-1.70, respectively [7].

The main goal of the following review is to detect the incidence, various risk factors and attributable mortality associated with VAP and secondary objective is to identify the various bacterial pathogens causing VAP in the ICU.

2. METHODOLOGY

A literature search was conducted using electronic databases such as MEDLINE, the Cochrane Library, and manuscript references for studies published in English up to December, 2017 for all studies concerning management of ICU associated pneumonia. Studies included in this review were limited to human subjects with English language.

3. DISCUSSION

- **Pathogenesis:**

The complex interaction between the endotracheal tube, presence of threat aspects, virulence of the getting into bacteria and host resistance largely determine the development of VAP. The presence of an endotracheal tube is by much one of the most crucial threat factor, resulting in a violation of natural defense reaction (the coughing response of glottis and throat) against mini aspiration around the cuff of the tube [4], [11].Contagious microorganisms acquire straight access to the lower respiratory system through: (1) micro aspiration, which can take place during intubation itself; (2) advancement of a biofilm stuffed with bacteria (normally Gram-negative germs and fungal varieties) within the endotracheal tube; (3) pooling and trickling of secretions around the cuff; and (4) disability of mucociliary clearance of secretions with gravity dependancy of mucous flow within the airways [11-13].Pathogenic product could additionally gather in bordering structural structures, such as the stomach, sinuses, nasopharynx and oropharynx, with substitute of regular flora by more virulent strains [11], [12], [14].This bacterium-enriched product is additionally frequently thrust ahead by the positive pressure put in by the ventilator. Whereas reintubation complying with extubation boosts VAP rates, using non-invasive favorable pressure ventilation has been connected with significantly lower VAP rates [4].Host aspects such as the extent of underlying condition, previous surgery and antibiotic exposure have all been implicated as danger elements for growth of VAP [1].

In addition, it has recently been kept in mind that seriously sick patients might have damaged phagocytosis and behave as functionally immunosuppressed even prior to development of nosocomial infection [4], [15], [16].This impact is associateded with the detrimental actions of the anaphylatoxin, C5a, which harms neutrophil phagocytic task and harms phagocytosis by neutrophils [15].More lately, a combined disorder of T-cells, monocytes, and neutrophils has been kept in mind to forecast acquisition of nosocomial infection [16].For example, elevation of regulatory T-cells (Tregs), monocyte deactivation (determined by monocyte HLA-DR expression) and neutrophil dysfunction (determined by CD88 expression), have cumulatively shown promise in predicting infection in the seriously unwell populace, as contrasted to healthy controls [16].

- **Microbiology:**

The kind of microorganism that creates VAP typically relies on the period of mechanical ventilation. As a whole, very early VAP is triggered by pathogens that are delicate to anti ¬ biotics, whereas late beginning VAP is triggered by multi-drug resistant and harder to deal with microorganisms. Nonetheless, this is by no implies a guideline and merely an overview to launch antibiotic treatment until more scientific information is available.

Usually, microorganisms triggering early-onset VAP consist of Streptococcus pneumoniae (along with various other streptococcus types), Hemophilus influenzae, methicillin-sensitive Staphylococcus aureus (MSSA), antibiotic-sensitive enteric Gram-negative bacilli, Escherichia coli, Klebsiella pneumonia, Enterobacter types, Proteus species and Serratia marcescens. Culprits of late VAP are typically MDR bacteria, such as methicillin-resistant S. aureus(MRSA), Acinetobacter, Pseudomonas aeruginosa, and extended-spectrum beta-lactamase producing bacteria (ESBL) [4].The exact prevalence of MDR microorganisms is variable in between organizations as well as within institutions [1].Patients with a history of medical facility admission for ≥ 2 days in the previous 90 days, nursing house residents, patients receiving chemotherapy or antibiotics in the last 30 days and patients going through hemodialysis at out ¬ patient facilities are vulnerable to drug resistant germs [1], [4].Typically located bacteria in the oropharynx could achieve clinically considerable numbers in the reduced air passages. These bacteria consist of Streptococcus viridans, Coryne-bacterium, coagulase-negative staphylococcus (CNS) and Neisseria varieties. Often, VAP results from polymicrobial infection. VAP from fungal and viral reasons has a really reduced incidence, especially in the immunocompetent host [1].

Table1: Pathogens causing VAP, their frequency (in paren¬thesis) and their possible mode of multi-drug resistance, if any, are listed below [1][2],[3]:

1. Pseudomonas (24.4 %): Upregulation of efflux pumps, decreased expression of outer membrane porin channel, acquisition of plasmid-mediated metallo-beta-lactamases.
2. S. aureus (20.4 %, of which > 50 % MRSA): Production of a penicillin-binding protein (PBP) with reduced affinity for beta-lactam antibiotics. Encoded by the mecA gene.
3. Enterobacteriaceae (14.1 % -includes Klebsiella spp., E. coli, Proteus spp., Enterobacter spp., Serratia spp., Citrobacter spp.): Plasmid mediated production of ESBLs, plasmid-mediated AmpC-type enzyme.
4. Streptococcus species (12.1 %).
5. Hemophilus species (9.8 %).
6. Acinetobacter species (7.9 %): Production of metallo-enzymes or carbapenemases.
7. Neisseria species (2.6 %).
8. Stenotrophomonas maltophilia (1.7 %).
9. Coagulase-negative staphylococcus (1.4 %).
10. Others (4.7 % -includes Corynebacterium, Moraxella, Enterococcus, fungi).

- **Diagnosis:**

At the present time, there is no widely accepted, gold standard diagnostic requirement for VAP. A number of clinical techniques have been advised however none have the required level of sensitivity or uniqueness to precisely determine this condition [17]. Daily bedside analysis combined with chest radiography can just be suggestive of the presence or lack of VAP, yet not define it [18].Clinical diagnosis of VAP can still miss out on concerning a third of VAPs in the ICU as compared to autopsy findings and can improperly diagnose more than half of patients, likely as a result of inadequate interobserver arrangement between clinical standards [8], [18], [19].Postmortem studies comparing VAP diag ¬ nosis with medical standards showed 69 % sensitivity and 75 % specificity, in comparison to autopsy findings [20].

The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) standards recommend obtaining reduced respiratory tract samples for society and microbiology [1].Analysis of these examples could be measurable or qualitative. This guideline also enables use tracheal aspirates for their unfavorable predictive value (94 % for VAP). Johanson et al. defined clinical criteria for diagnosis of VAP as complies with [21]: The clinical pulmonary infection score (CPIS) takes into account clinical, physiological, microbiological and radiographic proof to permit a numerical worth to forecast the existence or absence of VAP (Table 2) [18], [22].Scores could vary between zero and 12 with a score of ≥ 6 showing excellent correlation with the visibility of VAP [22].Despite the professional appeal of the CPIS, discussion continues concerning its diagnostic validity. One meta-analysis of 13 studies evaluating the accuracy of CPIS in diagnosing VAP reported pooled quotes for sensitivity and specificity for CPIS as 65 % (95 % CI 61-69 %) and 64 % (95 % CI 60-67 %), respectively [23].Regardless of its obvious simple calculation, the inter-observer variability in CPIS computation continues to be significant, jeopardizing its regular use in clinical trials [24].Of all the requirements utilized to calculate the CPIS, just time-dependent adjustments in the PaO2/FiO2ratio early in VAP might offer some predictive power for VAP results in clinical trials, particularly clinical failing and mortality [25].However, a test by Singh and associates [26] showed that the CPIS is an efficient scientific tool for establishing whether to stop or continue prescription antibiotics for longer than 3 days. In that study, prescription antibiotics were discontinued at day 3 for patients that had actually been randomized to get ciprofloxacin as opposed to standard of care, if their CPIS stayed ≤ 6. Mortality and length of ICU remain did not vary despite a much shorter duration (p = 0.0001) and reduced cost (p = 0.003) of antimicrobial treatment in the speculative as contrasted with the standard therapy arm, and the advancement of antimicrobial resistance was lower among patients whose anti-biotics were ceased contrasted to those that obtained requirement of care.

Table 2: The clinical pulmonary infection score (CPIS)

Assessed Parameter	Result	Score
Temperature (°Celsius)	36.5-38.4 °C	0
	38.5-38.9 °C	1
	≤ 36 or ≥ 39 °C	2

Assessed Parameter	Result	Score
Leukocytes in blood (cells/mm^3)	4,000-11,000/mm^3	0
	< 4,000 or > 11,000/mm^3	1
	≥ 500 Band cells	2
Tracheal secretions (subjective visual scale)	None	0
	Mild/non-purulent	1
	Purulent	2
Radiographic findings (on chest radiography, excluding CHF and ARDS)	No infiltrate	0
	Diff use/patchy infiltrate	1
	Localized infiltrate	2
Culture results (endotracheal aspirate)	No or mild growth	0
	Moderate or florid growth	1
	Moderate or florid growth AND pathogen consistent with Gram stain	2
Oxygenation status (defined by PaO_2:FiO_2)	> 240 or ARDS	0
	≤ 240 and absence of ARDS	2

- **Treatment:**

Choosing the proper antibiotic depends on the duration of mechanical ventilation. Late beginning VAP (> 4 days) requires wide spectrum anti-biotics whereas very early onset (≤ 4 days) could be treated with minimal spectrum antibiotics [1].An upgraded neighborhood antibiogram for each and every hospital and each ICU based upon regional bacteriological patterns and susceptibilities is necessary to assist ideally dosed preliminary empiric treatment [1].With any empiric antibiotic regimen, de-escalation is the vital to lower emergence of resistance [33].Delays in initiation of antibiotic treatment could contribute to the excess mortality danger with VAP [1].Table 3 highlight the advised treatment regimens for VAP.

Table 3: Comparison of recommended initial empiric therapy for ventilator-associated pneumonia (VAP) according to time of onset [1], [34]

Early-onset VAP	Late-onset VAP
Second or third generation cephalosporin: e. g., ceftriaxone: 2 g daily;	Cephalosporin
cefuroxime: 1.5 g every 8 hours;	e. g., cefepime: 1-2 g every 8 hours;
cefotaxime: 2 g every 8 hours	ceftazidime 2 g every 8 hours
OR	OR
Fluoroquinolones	Carbepenem
e. g., levofloxacin: 750 mg daily;	e. g., imipenem + cilastin: 500 mg every 6 hours or 1 g every 8 hours;
moxifloxacin: 400 mg daily	meropenem: 1 g every 8 hours
OR	OR
Aminopenicillin + beta-lactamase inhibitor e. g., ampicillin + sulbactam: 3 g	Beta-lactam/beta-lactamase inhibitor
every 8 hours	e. g., piperacillin + tazobactam: 4.5 g every 6 hours
OR	PLUS
Ertapenem	Aminoglycoside
1 g daily	e. g., amikacin: 20 mg/kg/day;

Early-onset VAP	Late-onset VAP
	gentamicin: 7 mg/kg/day;
	tobramycin: 7 mg/kg/day
	OR
	Antipseudomonal fluoroquinolone
	e. g., ciprofloxacin 400 mg every 8 hours;
	levofloxacin 750 mg daily
	PLUS
	Coverage for MRSA
	e. g., vancomycin: 15 mg/kg every 12 hours
	OR
	linezolid: 600 mg every 12 hours

Owing to the high rate of resistance to monotherapy observed with P.aeruginosa, mix therapy is constantly advised. Acinetobacter species react best to carbapenems (also active versus ESBL positive Enterobacteriaceae), colistin, polymyxin B and ampicillin/sulbactam [35], [36].Although MDR microorganisms are typically connected with late-onset VAP, current evidence recommends that they are significantly related to early-onset VAP too [36].The function of inhaled prescription antibiotics in the setup of failing of systemic anti-biotics is vague [1].The normal duration of treatment for early-onset VAP is 8 days and longer when it comes to late-onset VAP or if MDR microorganisms are suspected or recognized.

Despite therapy, if no reaction is observed, it could be prudent to reconsider the diagnosis, reassess the organism being dealt with or search for other reasons for indicators and signs. As a result of the obstacles associated with diagnosing VAP, specifically early in the course, the IDSA/ATS guidelines highlight the relevance of reassessing patients at 48-72 hrs when significant data are available to figure out whether the patient ought to continue antibiotic treatment for VAP or whether an alternate diagnosis must be pursued. In one research study, Swoboda et al. [37] found that half of the empiric antibiotic use for VAP in two surgical ICUs was suggested for patients without pneumonia.

- **Prevention:**

There are numerous recommended measures for avoidance of VAP. Institutions or ICUs could observe a reduction in VAP rates by using a 'VAP-bundle' approach [38] using elements.The 5-element Institute of Healthcare Improvement (IHI) VAP bundle [38] consists of: Head of bed elevation, oral care with chlorhexidine, stress ulcer treatment, deep venous thrombosis prophylaxis, and day-to-day sedation analysis and spontaneous breathing tests. Each of these components has been shown to decrease the incidence of VAP although the quality of evidence sustaining the efficiency and relevance of each treatment has been questioned. Also studies utilizing VAP bundles have been criticized as failing to show clinical and cost effectiveness [39].A before-after study which systematically implemented a VAP prevention bundle making use of IHI methodology showed a substantial reduction in VAP rates, antibiotic use and MRSA purchase. There was no reduction, nonetheless, in duration of mechanical ventilation or ICU admission. The IHI emphasizes the need for high (95 %) general compliance rates with VAP packages although this particular study reported overall bundle compliance rates of 70 %. Problems with completeness of documentation could underestimate compliance, which continues to be an essential feature of VAP bundle prevention techniques. One more important contribution towards VAP prevention and shortening periods of antibiotic direct exposure was a current potential research (n = 129), which wrapped up that a single-dose of anti-biotics within 4 h of intubation may be effective in stopping early beginning VAP in a cohort of comatose patients [40].A randomized professional test is should address this question.

4. CONCLUSION

VAP occurs frequently and is associated with significant morbidity in critically ill patients. The primary obstacle in diagnosing VAP is the absence of gold standard criteria and, therefore, VAP continues to be an inconspicuous clinical syndrome. There is enough evidence to indicate that VAP is preventable and that hospitals can decrease VAP rates, a factor that the new CDC VAP definitions are poised to demonstrate more objectively. The diagnostic challenge of VAP

has multiple implications for therapy. Although a CPIS score > 6 may correlate with VAP, the sensitivity, specificity and inter-rater agreement of this criterion alone are not encouraging. Microbiological data should be used for tailoring antibiotic therapy and not be restricted only to diagnosis. The pitfall in using empiric antibiotics for suspicion of VAP is the potential for antibiotic overuse, emergence of resistance, unnecessary adverse effects and potential toxicity. The major goals of VAP management are early, appropriate antibiotics in adequate doses followed by de-escalation based on microbiological culture results and the clinical response of the patient. Antimicrobial stewardship programs involving pharmacists, physicians and other healthcare providers optimize antibiotic selection, dose, and duration to increase efficacy in targeting causative pathogens and allow the best clinical outcome.

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