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Ventilator-Associated Pneumonia (VAP): Clinical Strategies, Treatment Challenges and Economic Concerns

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Abstract

The clinical and economic features of Ventilator-Associated Pneumonia (VAP) are quite unclear, with an extensive array of values and contradictory results. The real challenge in this connection is to present the real estimate of the clinical and associated economic consequences of VAP. In developing countries like Pakistan, it is important to formulate an optimal institutional antimicrobial policy that can be used as a guide for empirical/prophylactic and specific therapies of antibiotics in VAP with more rational approach to lessen the rates of mortality and morbidity, decline the length of treatment and hospitalization and the significant impact in prevention of development of multidrug resistant strains and cost reduction.

Keywords: Ventilator-Associated Pneumonia (VAP); Multidrug resistant; Clinical; Economic consequences

Introduction

Ventilator Associated Pneumonia (VAP) and Hospital-Acquired Pneumonia (HAP) are imperative basis of mortality and morbidity around the world. Rate of mortality has been reported up to 62%. VAP and HAP are the succeeding cause of nosocomial contagion, however rate of such infections in the intensive care settings are documented with comparatively higher frequencies. VAP is defined as a subset of hospital acquired pneumonia which incorporates all patients receiving mechanical ventilation for more than 48 h. VAP happen exclusively in the ICU settings [1]. It is the significant cause of mortality and morbidity around the globe in hospital settings. Considerable economic impact of VAP is endorsed to significant increased extent of hospital stay with high expenditures [2,3]. Diagnostic criteria of VAP are summarized in Table 1.

Incidence

According to the National Nosocomial Infections Surveillance (NNIS) report, the rate of VAP is documented 7.6 for each 1000 ventilator-days. The recurrence of the VAP was reported to be 22.8 for each 1000 patient days, 29.6 for each 1000 patient days at risk, 35.7 for every 1000 ventilator-days, and 44.0 for every 1000 ventilator-days at peril. It was also observed from NNIS statistics that the rate of VAP was most imperative for ICUs cases (15.2 for each 1000 ventilator-days). The general pervasiveness of VAP was 9.3%. In a surveillance study carried out in Canada on a cohort of 1014 patients, who received ventilation up to 48 h or more, depicted 17.4% (n=177) with VAP. The onset of VAP was also tabulated with respect to ICU admission in this study and reported to be 7 days [4-10].

Parameters	Diagnostic Criteria
Temperature (°C)	Between 38.5-38.9 OR ≥ 39 or ≤ 36
Count of White blood cells (WBC)/mm^3	<4.000 or >11.000 and 50% bands
Secretions	purulent (>25 neutrophils/high-power field)
X-ray (Chest) permeates	Disseminate (diffused)/irregular (patchy) or confined (localized)
Partial pressure of O_2 in arterial blood (PaO_2).	Decreased; ≤240 and no ARDS
Sputum	Culture >1+ and same Gram staining organisms

Table 1: The diagnostic criteria for VAP [4].

Ventilator-Associated Pneumonia (VAP) in Children and Neonates

A high incidence rate in children and neonates has been reported for VAP over the couple of years. Interestingly a contradictory value may also have been viewed as 1/1000 ventilator-days to 63/1000 ventilator-days in different literature across the variable geographical area. A reconnaissance study also evaluated the rate of VAP in teaching and non-teaching hospitals and reported higher rates in former [11]. The same study reported higher rates in lower-middle-income compared to upper-middle-income countries. A similar review revealed higher rates in lower-center salary contrasted with upper-center wage nations. Significantly high incidences were observed from India i.e., 36.2% and Egypt as 31.8/1000 ventilator-days [12,13]. While a lower frequency was reported from USA and Germany [14-16]. A value of 23.6% of VAP incidence was reported from European origin 41 followed by 6.6% and 6.7% from Italy and Australia [17-19]. A challenging situation in relevance to the surveillance definitions in pediatric situation is due to the amalgamation of radiological and clinical scenarios which creates an excessively huge space for elucidation.

Risk factors for VAP

The existence of definite host, pharmacological or environmental factors can lead to increase propensity of VAP in critical care patients.

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Risk factors identified from literature for the development of VAP have been detailed in Table 2. These factors can be distinguished into non-modifiable and modifiable risk factors [11,20] (Table 2).

Pathophysiology of VAP

Pathophysiology of VAP is classified as the respiratory and digestive regions colonization and secreted micro aspiration of superior and inferior segments of airway [12]. Initiation of VAP is categorized into 2 forms:

a) Rapid onset: VAP associated with antibiotic-susceptible species and occurs within 48-96 h after intubation.

b) Late-onset: It is connected with resistant organisms and occurs more than 96 h after intubation [12].

The growing incidence of multi-resistant organisms in VAP and the mortality benefit related with initial appropriate treatment have emerged to an amplified use of wide spectrum antibiotics [13-16]. The requirement to balance such factors with augmented selection pressure for the resistance emergence has led to the development of the appropriate guidelines to optimize the diagnosis, treatment and management of VAP based on local patterns of susceptibility [17-20].

Microbial Etiology

Transcendence of certain destructive (virulent) microorganism strains in VAP has generated the concept of core pathogens. Such pathogens ought to be considered as potential reasons for VAP amongst the patients. This group of pathogens incorporate *Streptococcus* species, *Streptococcus pneumoniae*, *Haemophilus influenzae*, Enterobacteriaceae, like (*Klebsiella*, *Proteus*, *Escherichia coli*, *Enterobacter*, *Serratia marcescens*), and in addition methicillin-vulnerable *Staphylococcus aureus* [21-23] (Table 3).

Treatment Strategies

Overarching philosophy of VAP treatment is depicted by the following:

- Prompt commencement of empirical therapy.
- Association of the level of infectivity and clinical staging.
- Appropriate treatment to reduce mortality rates.
- Association of delayed onset of VAP with resistant isolates.
- Careful utilization of combination treatment for specific resistant pathogens (*P. aeruginosa* and MRSA) [24-26].

Existing Guideline to Antimicrobial Selection in VAP

According to the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) guidelines (IDSA/ATS) recommended Antibiotic management of VAP is based on multiple interconnecting principles. The core of such idea proposes that treatment of VAP should be commenced as early as the diagnosis is entertained. In an attempt to reduce patient impairment and experience to unnecessary antibiotics resistance, utilization of antibiogram data is recommended to diminish the redundant use of twofold antibiotic treatment including gram-negative empiric methicillin-resistant *Staphylococcus aureus* (MRSA). Further stress on crash course of antimicrobial treatment for subjects with VAP sovereign of microbial etiology, in addition to de-escalation of antibiotic has been accounted for. In specific situations, the appropriate regimen may diverge from the standard protocol in the IDSA/ATS guidelines44-46. Various treatment options have been summarized in the Table 4.

Host associated	Non-modifiable risk factors	• Age • Sex • Medical conditions (Underlying) • ARDS, COPD • Head trauma
	Modifiable risk factor	• Intubations (number and frequency) • Time comparisons for circuit change (24 h vs. 48 h) • Body position of patient • Consciousness scale • Use of medications/antibiotic
Device associated		• Endotracheal tubing • Ventilator circuit • Orogastric or Nasogastric tubes
Personnel related		• Inappropriate hand washing practice • Poor gloves changing protocol during patients contact • Lack of use of personal protective utensils when antibiotic resistant pathogens have been recognized

Table 2: Risk factors for VAP [15-18,24,34].

Disease Condition	Categorization	Diagnostic Indications	Responsible Pathogens
VAP	A-Group	Absence of resistance, possible risk factors† and mild to moderate stage‡	Core-organisms (pathogens)*
	B-Group	Resistance risk factors† and severe stage§	Core pathogens*, MRSA and multi drug resistant organism¤
	C-Group	Control; ICU patients/ventilated but not developed VAP	-

*__Core pathogens__: *Streptococcus pneumoniae, Haemophilus influenzae, Enterobacter* species, *Escherichia coli, Klebsiella*, Proteus strains, and methicillin-susceptible *Staphylococcus aureus* MSSA.
¤__Multi drug resistant organism:__ *Pseudomonas aeruginosa, netobacter, Legionella* and *Stenotrophomonas maltophilia* strains.
†Resistance risk factors embrace antibiotic treatment in last ninety (90) days and delayed inception >5 days during hospital stay.
‡__Mild to moderate stage:__ no intubation, hypotension, sepsis, fast development of infiltrates or end organ damage.
§__Severe stage:__ presence of intubation, hypotension, sepsis, quick evolution of permeates and end-organ dysfunction.

Table 3: Group classification with respect to diagnostic features and pathogens [22-23,26,34].

Organism Responsible	Treatment Strategies
Antibiotics (Gram-Positive): MRSA sensitive	Glycopeptide Vancomycin 15 mg/kg q8 to12h IV (consider a loading dose of 25-30 mg/kg × 1 for severe illness) OR Oxazolidinones Linezolid 600 mg q12h IV
Antibiotics (Gram-Negative): Anti-pseudomonal products: Non-β-Lactam moities	Fluoroquinolones Ciprofloxacin 400 mg q8h IV Levofloxacin 750 mg q24h IV OR Polymyxins Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) Polymyxin B 2.5-3.0 mg/kg/day divided in 2 daily IV doses OR Aminoglycosides Amikacin 15-20 mg/kg q24h IV Gentamicin 5-7 mg/kg q24h IV Tobramycin 5-7 mg/kg q24h IV
Antibiotics (Gram-Negative) Anti-pseudomonal range: β-Lactam-moities	Antipseudomonal penicillins Piperacillin-tazobactam 4.5 g q6h IV OR Carbapenems Imipenem 500 mg q6hd IV Meropenem 1 g q8h IV OR Cephalosporins Cefepime 2 g q8h IV Ceftazidime 2 g q8h IV OR Monobactams Aztreonam 2 g q8h IV

Table 4: Recommended empiric treatment options for clinically suspected ventilator-associated pneumonia [47-50].

Clinical Outcome Measures

Clinical outcome of disease comprised of percent mortality rate with respect to age, duration of disease, pathogens (isolates) and comorbidities for VAP. Physiologic measures such as laboratory examination outcomes, health status and functionality characteristics of patient may be utilized as conclusive (clinical) measures [26-30].

Economic Features of VAP

The rate of mortality of VAP may increase from 27 to 43% if antibiotic resistant organisms are causative agent with 2-3 folds increment in hospital ICU stay [25,26]. Additional cost of VAP is calculated to be $40000 per patient/hospital admission with specific ailment, with an approximated $1.2 billion per annul cost [3,27]. In a recent study [23-29] the advancement of VAP was connected with an expansion of $41,294 as average treatment charges per admission ($104,983 ± $91,080 vs. $63,689 ± $75,030 with P values <0.001). To rationalize the optimal economic outcome of specific disease, various pharmacoeconomic evaluation methods are utilized including cost utilization, cost effectiveness, cost benefit and cost utility analyses. Pharmacoeconomic is the field which assesses the experimental and economic features of health care products, services and plans to health care providers, patients and policy makers [28,29]. These methods provide the means to compare the treatment options. The decision of perspective from which the analysis should be conducted, is an important consideration in pharmacoeconomic analysis. At present the pharmacoeconomic evaluation is valuable in individual patient treatment, total cost of care, resource allocation, and effective formulary management [29-31].

Assessment of VAP

Clinical Pulmonary Infection Score (CPIS) as a marker of diagnosis can be used to measure the progress of VAP. The value of CPIS is estimated by assigning points (0, 1, and 2) for various conditions of pneumonia including fever and level of oxygenation defacement [32]. Acute Physiological Assessment A and Chronic Health Evaluation (APACHE II SCORE) can be used as a vital factor to stratify the degree of risk for progression of VAP and to predict the possible rate of mortality [26,33-39].

Measures Commonly Taken to Prevent VAP

Effective projects consolidated different mediations, for example, practice of hand sanitation, use of gloves and sterilized gown for endotracheal tube control, elevation of backrest position, use of chlorhexidine as oral care product, prophylaxis for ulcers stress, and evasion of gastric over distension, a suitable maintenance of cuff pressure, insertion of oro-gastric tubes, and disposal of unnecessary tracheal suction [40-45]. Numerous stratagems have been illustrated to accomplish the various objectives including the incidence and risk of VAP and reduction in days of ventilation including Non-invasive Positive Pressure Ventilation (NPPV), weaning trials, sedation episodes, re-intubation avoidance, and an early tracheostomy. At the point when connected as a multimodal procedure by an interdisciplinary group, these intercessions are destined to be fruitful among children's and adults and have demonstrated viability in various regions of the world [46-52].

Conclusion

It is need of time to identify trends and set therapeutic priorities in the interests of patients with effective management of drug therapy at relatively affordable cost. Moreover, a strategic plan based on the existing statistics, specialist view and contemporary practice for the stipulation of patient care should be established to evaluate risk stratification factors and to facilitate correct diagnosis, treatment rationale and improve cure for challenging pathogens with decrease morbidity and better survival. It is also recommended to conduct related studies to assess the frequency and location of associated risks in local population. Results of these investigations may benefit the seriously ill ICU patients receiving mechanical ventilation by improving the clinical outcomes. Furthermore, pharmacoeconomic studies can also be effectively used to save the economic resources, and thus satisfy patient's needs at optimal rate.

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