Research Article

Clinical and microbiological facets of ventilator associated pneumonia in the main stream with a practical contact

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ABSTRACT

Background: Ventilator-associated pneumonia (VAP), the most apparent infection in ICUs; life threatening, symbolizes an additional healthcare burden. Clinical traits and etiological agents vary. Early diagnosis is capacious & apt tactic of quantitative culture is advocated. Regular surveillance is imperative to define strategies. The objective was to conceptualize VAP; put forth our experience of its occurrence, causative bacteria, clinical silhouette and associated variables; and to pattern antimicrobial resistance in ICUs; contributing this data to devise more pertinent approach.

Methods: A prospective survey, executed at a tertiary care set up (multidisciplinary ICUs) analysed clinical and microbiological aspects of 120 patients (>48 hours-mechanical ventilation) in congruence with a clinical criteria of pneumonia by standard microbiological means. Cases were keenly observed to assess mortality.

Results: Occurrence of VAP was 42.5% with dominance of males (65%) and age group of 41-60 years (Mean ± SD: 42.26 ± 19.53). Late onset type (60.8%) predominated. Principal symptom/sign was fever (82.5%)/crepitation (67.5%). Cases of OP poisoning (21.7%), associated diabetes mellitus (31.7%) were pre-eminent. Gram negative Bacteria (GNB) formed the major etiology (78.6%), cardinal being Acinetobacter baumannii (32.1%) and Pseudomonas aeruginosa (25%). Multi-drug resistant (MDR)-Acinetobacter baumannii, MDR-Pseudomonas aeruginosa, imipenem resistant Klebsiella pneumoniae and Methicillin resistant Staphylococcus aureus (MRSA) were noticed in 66.7%, 35%, 25% and 42.8% of respective isolates. Mortality record was 21.6%.

Conclusions: Reliable mode of isolation (quantitative culture), less invasive sampling (ETA) and antibiotic recycling will augment VAP management. Regular intuition into contemporary trends of antimicrobial profile of etiological agents is crucial to avert undesirable consequences.

Keywords: Acinetobacter baumannii, Gram negative bacteria, Intensive care units, Pseudomonas aeruginosa, Ventilator associated pneumonia

INTRODUCTION

It is indeed a paradox that the use of advanced medicine has brought in its wake the dangerous and too frequent botheration of nosocomial infections. The widespread use of tracheal intubation and mechanical ventilation to support critically ill has defined an expanding group of patients, at particularly high risk of nosocomial pneumonia (NP). Patients who are intubated and mechanically ventilated have 6 to 20 fold risk of pneumonia.1 The incidence of NP in all intubated mechanically ventilated patients ranges between 9–27%.1 Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops more than 48 hours after initiation of mechanical ventilation or conceptually, as an inflammation of the lung parenchyma caused by
For VAP to occur, the equilibrium between host defences and microbial propensity for colonization and invasion must shift in favour of the ability of the pathogens to persist and invade lower respiratory tract. VAP may be caused by spectrum of bacterial pathogens which may be polymicrobial and rarely due to anaerobic bacteria, viruses or fungi. The microbiology of VAP is different from that of the more common community-acquired pneumonia (CAP). In particular, viruses and fungi are uncommon causes in people who are immunocompetent. The clinical characteristics and organisms causing are unique to a set up. Frequency of specific bacterial pathogens causing VAP may also vary by patient population, and changes over time, emphasizing the need for timely local surveillance data. Rapid diagnosis and initiation of appropriate antimicrobial agent is critical, as this delay parallels rise in mortality.

The American Thoracic Society (ATS) consensus statement suggests the categorization of NP as Early onset NP-occurring within 4 days after hospital admission & Late onset NP-occurring 5 or more days after hospital admission. This categorization helps predict the implicated pathogens and guides us in the initial empiric therapy, which is known as the epidemiological approach. Early-onset pneumonia commonly results from aspiration of endogenous community acquired pathogens colonizing the oropharynx. Conversely, late-onset VAP may be caused by more unusual or MDR pathogens following aspiration of oropharyngeal and gastric secretions. Oropharyngeal or tracheal colonization with Pseudomonas aeruginosa or enteric Gram negative bacilli is common in ICU patients, increases with length of hospitalization.

The incidence of VAP in eight developing countries (Argentina, Brazil, Colombia, India, Mexico, Morocco, Peru and Turkey) was shown to vary between 10%-52.7% by Rosenthal et al. The incidence was reported to be around 45% by some south Indian Prospective studies. Bacterial pathogens associated with VAP are Streptococcus pneumoniae, Haemophilus influenzae, Serratia marcescens and more commonly Methicillin sensitive Staphylococcus aureus in early onset type, whereas members of Enterobacteriaceae (Escherichia coli, Klebsiella spp., Citrobacter spp., Enterobacter spp., Proteus spp.), Methicillin resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa and Acinetobacter baumannii are implicated in late-onset type. Gram negative bacteria including Pseudomonas aeruginosa, Acinetobacter baumannii & Enteric Gram negative rods are implicated in majority of VAP episodes (41-92%) with predominance of either Pseudomonas aeruginosa or Acinetobacter baumannii and Gram positive cocci particularly Staphylococcus aureus account for 6-58% of the isolates.

Risk factors can be those which can be patient related illnesses, cause colonisation and pneumonia because of disease associated impairment in host defence function. These include acute or chronic illnesses, coma, malnutrition, prolonged hospitalization, CNS dysfunction, COPD, diabetes mellitus, alcoholism, azotemia & respiratory failure. Advanced age is a predisposing factor due to increased frequency of serious comorbidity and associated immune changes. Poor infection control related practices can lead to the transmission of hospital acquired pathogens. A number of intervention related factors can impair host defence. Endotracheal intubation predisposes by impairing mucociliary clearance from lower respiratory tract as well as injuring epithelial surface and thereby increased bacterial binding. Prolonged & inappropriate usage of antibiotics may increase colonisation by antibiotic resistant bacteria.

The bacteriologic strategy for diagnosis uses quantitative cultures of lower respiratory specimens (Endotracheal aspirate-ETA, Broncho-alveolar lavage-BAL or Protected specimen brush-PSB collected with or without a bronchoscope) to define both the presence of pneumonia and the etiologic pathogen. Growth above a threshold concentration is required to diagnose VAP. Infra-threshold growth is assumed to be due to colonization or contamination. This has a good diagnostic utility especially if clinical suspicion is low or equivocal. The consensus threshold value of quantitative culture is $10^5$ or $10^6$ cfu/ml for ETA secretions, $10^6$ cfu/ml for BAL specimens and $10^7$cfu/ml for PSB material. Currently the exact role of VAP in worsening the prognosis of ICU patients is difficult to assess, as such patients are critically ill and thus their clinical status is severe enough to potentially cause death.

With a keen focus on its microbiology, this work highlights the trend of this clinical condition.

METHODS

A prospective clinico-microbiological analysis was undertaken enrolling 120 intubated patients who were mechanically ventilated for more than 48hrs, with a clinical suspicion of pneumonia (a new/progressive/persistent infiltrate on the chest radiograph and at least one of the following: leucocytosis $>12\times10^9$/ml, fever $>38.3^\circ C$, or the presence of purulent tracheobronchial secretions) extending from January 2011 to June 2012 from the multidisciplinary ICUs of a tertiary care set up (Kempegowda Institute of Medical Sciences and Research Centre, Bangalore). Patients with pre-existing pneumonia were excluded. A questionnaire was prepared and each patient was screened and monitored accordingly. Data such as name, age, gender, date of admission into intensive care unit, chief complaints, risk factors involved, duration of mechanical ventilation, clinical signs was obtained. Data related to
general physical examination, a battery of routine investigations-radiological and haematological investigations was collected. The VAP group was classified into two groups, early-onset type (<96 hrs) and late-onset type (≥96 hrs).

ETA was collected under aseptic precautions by non-bronchoscopic method. A sterile 22 inches suction catheter (Ramsons-12 F) was introduced into respiratory tract for a distance of 20-25cms and the specimen was aspirated into a sterile container, transported to the laboratory immediately. Samples were mechanically liquefied and homogenized by vortexing for 1 min. The specimen was subjected to Gram’s stain (Microscopy), further diluted using sterile saline (1 in 100) and was then inoculated for quantitative culture using standard techniques onto MacConkey agar, Blood agar and Chocolate agar plates using a 4mm sterile nichrome loop (0.01 ml), and then incubated at 37°C for up to 48 hrs. The cfu/ml was calculated, considering the reciprocals of the dilution factor & volume (ml) of specimen used for inoculation. Bacterial isolate obtained with 10⁵ or more cfu/ml was regarded as a pathogen (otherwise as a contaminant or colonizer), further identified using appropriate biochemical tests.

Antimicrobial susceptibility of the obtained isolate was done by Kirby-Bauer’s disc diffusion method using commercially available disks (Himedia Laboratories, Mumbai) and interpreted as per Clinical laboratory Standards Institute (CLSI)-guidelines. Methicillin resistance in Staphylococcus aureus was recognized using cefoxitin disc (30μg) by disc diffusion.

The patients were observed till their stay in the hospital to record their mortality.

Data collected was analyzed statistically by computing percentage, mean and standard deviation. Appropriate tests were employed. Wherever necessary, the results were depicted in the form of charts.

**RESULTS**

This review analysing 120 patients clinically assessed the occurrence of VAP and has delineated the profile of pathogens. The occurrence of VAP in this study was 42.5% (51/120). Age group of 41-60 years (34.2%) predominated with Mean ± SD: 42.26 ± 19.53. Male dominance (65%) was identified. (Figure 1) The pre-eminent conditions were OP poisoning (21.7%), and road traffic accident (17.5%). (Figure 2) The associated factors were Diabetes mellitus-31.7%, advancing age (>60 years)-20%, COPD-17.5% and head trauma-17.5%. (Figure 3) Majority (82.5%) had fever, while the major signs elicited were crepitations, tachycardia and tubular breathing in 67.5%, 55% and 30% of the cases respectively. Consolidation was predominantly seen in lower lobe of right lung (60%). Majority of the confirmed VAP episodes were of late onset type (60.8%).

51 patients (42.5%) showed significant growth (above threshold) while there was insignificant result in 8 cases and no bacteria could be recovered in 61 cases. The isolates were polymicrobial in 9.8% (5/51) of the samples showing significant growth. (Table 1) Gram negative bacteria were the major etiological agents (78.6%). Acinetobacter baumannii (32.1%) was the preponderant organism isolated followed by Pseudomonas aeruginosa (25%), former being predominant in late onset (5/21 isolates) variety & the latter in the early type (14/35 isolates) (Figure 4).
**Table 1: Aetiological profile of the polymicrobial infections.**

<table>
<thead>
<tr>
<th>Profile (above threshold)</th>
<th>Early-onset cases</th>
<th>Late-onset cases</th>
<th>Total isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Pseudomonas aeruginosa + Klebsiella pneumoniae)</td>
<td>1</td>
<td>2</td>
<td>(2\times3)=6</td>
</tr>
<tr>
<td>(Acinetobacter baumannii + Pseudomonas aeruginosa)</td>
<td>-</td>
<td>1</td>
<td>(2\times1)=2</td>
</tr>
<tr>
<td>(Acinetobacter baumannii + Escherichia coli)</td>
<td>-</td>
<td>1</td>
<td>(2\times1)=2</td>
</tr>
</tbody>
</table>

**Figure 4: Frequency of the etiological agents isolated.**

High mean antibiotic resistance was exhibited to pencillins - ampicillin (100%), amoxyclav (93.9%); cephalosporins - cefuroxime (75.6%), cefepime (63.9%); fluoroquinolone - ciprofloxacin (62.8%). MDR Acinetobacter baumannii & Pseudomonas aeruginosa were noticed in 66.7% and 35% of the respective isolates. Imipenem resistance in Klebsiella pneumoniae isolates was seen in 25%. Methicillin resistance in Staphylococcus aureus was exhibited in 42.8%.

The drugs which were highly efficient as per our study were ceftriaxone - tazobactam (100%), tobramycin (100%), piperacillin - tazobactam (94.9%), gentamicin (83.8%), levofloxacin (83.8%) and amikacin (83.5%) for gram negative bacteria. For gram positive bacteria, efficacious drugs were Linezolid (100%), vancomycin (90%), clindamycin (90%) and tetracycline (86.9%). Mean resistance exhibited by Gram-Positive and Gram-negative bacteria is depicted (Table 2).

Mortality rate in cases showing significant growth was found to be 21.6% (11/51).

**Table 2: Mean antiibiogram of the isolates.**

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Antibiotics</th>
<th>Mean antibiotic resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive bacteria</td>
<td>Amoxyclav</td>
<td>78.5</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime</td>
<td>61.4</td>
</tr>
<tr>
<td>Gram negative bacteria</td>
<td>Ampicillin</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Amoxyclav</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime</td>
<td>75.6</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>67.9</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>63.4</td>
</tr>
<tr>
<td></td>
<td>Cotrimoxazole</td>
<td>63</td>
</tr>
<tr>
<td>Both</td>
<td>Amoxyclav</td>
<td>93.9</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime</td>
<td>75.6</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
<td>63.9</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>62.8</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This local survey has addressed the occurrence, clinical peculiarities and microbiology of VAP. It has used the more appropriate channel i.e. quantitative culture (to differentiate pathogens from colonizers/contaminants) of ETA (obtained by minimally invasive technique) as advocated by various studies. In different studies, the incidence of VAP was reported different; depending on the type of hospital or ICU, the population studied and the organisms prevalent; and varied from 7% to 70%. Our study showed occurrence of VAP to be 42.5%, which was in close agreement with many other studies.

The higher incidence seen in age group of 41-60 years can be attributed to more number of patients getting admitted in that age and to their associated comorbid conditions. This type of age dominance was documented in other studies too. The male gender predominance identified here was also observed by other studies.

The predisposing conditions identified cause colonisation and pneumonia because of disease associated impairment in host defence function and were considered as important risk factors, as shown by various studies.

The higher percentage of infiltrates in the right lung-lower lobe is due to more common occurrence of aspiration there, attributed to anatomical fact of more deviant left bronchus. Late onset type of VAP was found in majority, as seen in other studies.
The report of high incidence of aerobic gram negative bacteria is consistent with some prior reports,\textsuperscript{5,23} which can be attributed to oropharyngeal colonization of aerobic Gram negative bacteria, to which the critically ill patients in ICU are more susceptible.\textsuperscript{24} The incidence of the polymicrobial isolates was well comparable with other studies (Table 3).\textsuperscript{2,20,22,25-29}

In early onset VAP, the organism found in large number was Pseudomonas aeruginosa accounting for 23.8\% of isolates which was in accordance with a study.\textsuperscript{30} Acinetobacter baumannii-40\% and Pseudomonas aeruginosa-25.7\% were the commonly isolated pathogens in late onset VAP in our study. The results are concordant with a study.\textsuperscript{6}

**Table 3: Comparison of pathogens isolated from various Indian studies.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Total isolates</th>
<th>No. of isolates (%)</th>
<th>Acinetobacter spp.</th>
<th>Pseudomonas spp.</th>
<th>Klebsiella spp.</th>
<th>Staph. aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singhal et al\textsuperscript{26} (2005)</td>
<td>192</td>
<td>86 (44.8)</td>
<td>77 (40.1)</td>
<td>11 (5.7)</td>
<td>2 (1.05)</td>
<td></td>
</tr>
<tr>
<td>Rakshit et al\textsuperscript{29} (2005)</td>
<td>34</td>
<td>4 (11.7)</td>
<td>11 (32)</td>
<td>7 (20)</td>
<td>6 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Rajashekar et al\textsuperscript{27} (2006)</td>
<td>16</td>
<td>5 (31)</td>
<td>4 (25)</td>
<td>2 (1.2)</td>
<td>1 (6.25)</td>
<td></td>
</tr>
<tr>
<td>Ahmed et al\textsuperscript{28} (2007)</td>
<td>103</td>
<td>5 (4.8)</td>
<td>37 (35.9)</td>
<td>4 (3.8)</td>
<td>25 (24.2)</td>
<td></td>
</tr>
<tr>
<td>Arindam Dey et al\textsuperscript{2} (2007)</td>
<td>47</td>
<td>23 (48.9)</td>
<td>12 (25.5)</td>
<td>6 (12.7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Kumari et al\textsuperscript{29} (2007)</td>
<td>489</td>
<td>*156 (31.9)</td>
<td>106 (21.5)</td>
<td>93 (19)</td>
<td>38 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Goel et al\textsuperscript{25} (2009)</td>
<td>161</td>
<td>38 (23.6)</td>
<td>57 (35)</td>
<td>22 (13.6)</td>
<td>3 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Joseph et al\textsuperscript{22} (2010)</td>
<td>47</td>
<td>14 (29.8)</td>
<td>10 (21.3)</td>
<td>03 (6.4)</td>
<td>07 (14.9)</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>56</td>
<td>18 (32.1)</td>
<td>14 (25)</td>
<td>09 (16.1)</td>
<td>07 (12.5)</td>
<td></td>
</tr>
</tbody>
</table>

(* indicates non-fermenters)

The frequency of drug resistant pathogens in our series was comparable in part with other studies;\textsuperscript{22,25,29} but en masse, this frequency was quite low compared to recent verdicts.

A Medline review concluded that VAP is associated with a crude mortality ranging between 16 to 94 \%.\textsuperscript{9} The conflicting results could be explained by differences in patient characteristics, adequacy of initial antimicrobial treatment, antimicrobial resistance of the organisms responsible, severity of illness, co-morbid factors, and host response factors.

**CONCLUSION**

Nosocomial infections can negate the interest of even the best of medical care, underscoring the need for regular surveillance. Among hospital-acquired infections, VAP has been contemplated to be the most detrimental, if not promptly managed.

VAP has evolved as a frequent culprit in ICUs. Due to concordant risk factors and comorbid conditions, intubated individuals with advancing age in ICUs show a soaring tendency to develop VAP. The risk tends to upsurge with the duration of mechanical ventilation, and accordingly late onset VAP is usually predominant. Aerobic gram negative bacteria are the isolates frequently found, especially Acinetobacter baumannii and Pseudomonas aeruginosa. Antimicrobial resistance varies in different settings. As per recent reviews and according to this series, some drugs tend to possess high efficacy, and hence could be given due consideration.

More apt tactic of isolating the pathogen (quantitative culture), less invasive sampling (ETA) & rotational antibiotic usage will augment enhanced and prompt management of VAP. Regular intuition into contemporary trends of the etiological agents responsible with their drug resistance is of paramount importance for restricting the use of empiric broad spectrum antibiotics.
which predisposes to colonization. Practice of microbiological surveillance with timely availability of data and programs to reduce or alter antibiotic prescribing practices is vital to avert the terrible impact of antimicrobial resistance.

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Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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