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NOSOCOMIAL PNEUMONIA IN MECHANICALLY VENTILATED - A MULTIVARIATE ANALYSIS

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ABSTRACT

Background: The most frequent infection in ICUs, Ventilator-associated pneumonia (VAP); potentially life threatening, stands for another challenge in medicine. Earliness in diagnosis is pivotal. Constant surveillance is crucial to confront the issue by defining expedient strategies.

Purpose: The study intended to present our experience in the intensive care units (ICUs) of causative organisms of VAP and their antimicrobial susceptibility profile, with the effect of different variables; utilising this data to devise more pertinent empirical therapy.

Methodology: A prospective clinico-microbiological review of patients mechanically ventilated for ≥48 hrs and in agreement with a clinical criteria, at a tertiary care set up, from multidisciplinary ICUs was undertaken by standard microbiological techniques. Antimicrobial resistance was patterned.

Results: Occurrence of VAP was 49.07%. Late onset type (65.28%) was more frequent. Majority (85.95%) were caused by Gram Negative bacteria (GNB). Acinetobacter baumannii (30.58%) was most regular, followed by Pseudomonas aeruginosa (27.27%). 15 isolates (4 Escherichia coli, 9 Klebsiella spp., 2 Enterobacter spp.) produced ESBL (Extended Spectrum beta lactamase). 1 MRSA (Methicillin resistant Staphylococcus aureus) was isolated. Cases of OP (Organophosporous) poisoning- 31.48%; associated advancing age (>60 years) - 45.28%, Diabetes mellitus - 26.39% and COPD - 22.68% were pre-eminent.

Conclusions: Monitoring trends of drug profile of the causative agents is of cardinal benefit for restricting the use of empiric broad spectrum antimicrobials which predisposes to colonization. Constant evaluation of current practice on basis of antibiotic consumption patterns, timely availability of data and programs to reduce or alter antibiotic-prescribing practices is crucial to avert the terrible impact of antimicrobial resistance.

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

INTRODUCTION

Due to the high vulnerability of critically ill patients, and the use of procedures (invasive), the intensive care unit (ICU) is the focal point of nosocomial infections. These infections are associated with an important rise in morbidity, mortality and healthcare cost.

The widespread use of tracheal intubation and mechanical ventilation in the ICUs has defined a set of cases who are at risk of nosocomial pneumonia (NP). Patients who are intubated and require mechanical ventilation have a 6 to 20 fold increased risk of pneumonia.[1] Ventilator-associated pneumonia (VAP) is defined as

pneumonia that develops more than 48 hours after initiation of mechanical ventilation (MV). Conceptually, VAP is defined as an inflammation of the lung parenchyma caused by infectious agent/s not present or incubating at the time, mechanical ventilation was started.[1]

VAP may be caused by an array of bacterial pathogens. The etiology may be polymicrobial and rarely due to anaerobic bacteria, viruses or fungi. The etiological agents differ from that of the more common community-acquired pneumonia (CAP). In particular, viruses and fungi are uncommon causes in people who are immunocompetent. Prevalence of pathogens causing VAP may vary by hospital, patient population. Early diagnosis and initiation of appropriate antimicrobial(s) is of immense importance. The supplementary problem of multidrug-resistant pathogens boosts the impact of infections in ICUs. Several factors contribute to the rapid spread of multidrug-resistant pathogens in the ICU. These are new mutations, selection of resistant strains and suboptimal infection control.

NP is categorized by the American Thoracic Society (ATS)[2] as Early-onset NP (Nosocomial pneumonia occurring within 4 days after hospital admission) & Late-onset NP (Nosocomial pneumonia occurring 5 or more days after hospital admission). This categorization helps predict the implicated pathogens directing empiric therapy. 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 multidrug-resistant (MDR) pathogens following aspiration of oropharyngeal and gastric secretions.[3] Oropharyngeal or tracheal colonization with Pseudomonas aeruginosa or enteric Gram negative bacilli is common in ICU patients, increases with length of hospitalization.[4]

Rosenthal et al showed the incidence of VAP in eight developing countries to vary between 10%-52.7%.[5] The incidence was reported to be around 45% by some south Indian Prospective studies.[6,7]

GNB including Pseudomonas aeruginosa, Acinetobacter baumannii & Enteric Gram negative rods are implicated in majority of the VAP episodes (41-92%) with predominance of either Pseudomonas aeruginosa or Acinetobacter baumannii in majority of the studies and Gram positive cocci particularly Staphylococcus aureus accounting for 6-58% of the isolates.[8]

For diagnosis, bacteriologic strategy requires quantitative cultures of lower respiratory specimens (Endotracheal aspirate-ETA, Broncho-alveolar lavage-BAL or Protected specimen brush-PSB collected with or without a bronchoscope). Growth above a threshold concentration is used to diagnose VAP and to determine the causative microorganism(s). Growth below the threshold is assumed to be due to colonization or contamination. Quantitative cultures have been demonstrated to have good diagnostic utility for the presence of pneumonia, especially in patients with a low or equivocal clinical suspicion of infection.[1,9] The consensus threshold values of quantitative culture is 10^5 cfu/ml for ETA secretions, 10^4 cfu/ml for BAL specimens and 10^3 cfu/ml for PSB material.[1,10]

This study tends to highlight the trend of this clinical condition with a keen focus on the antibiogram of the causative agents.

MATERIALS AND METHODS

A prospective study was done undertaking 216 cases, intubated and mechanically ventilated for more than 48hrs with a clinical suspicion of pneumonia[10,11] (a new/progressive/persistent infiltrate on the chest radiograph and at least one of the following: leucocytosis $>12\times10^9$/ml, fever >38.3°C, or the presence of purulent tracheobronchial secretions) between January 2013 and October 2013 from the multidisciplinary ICUs of a tertiary care set up (M S Ramiah memorial hospital, Bangalore). Patients with pre-existing pneumonia were excluded. Personal details and data such as 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).

Immediate transport and processing of the Endotracheal aspirate (ETA) / Broncho-alveolar lavage obtained under aseptic precautions was undertaken. The sample was subjected to Gram's stain and KOH mount (Microscopy). The specimen was diluted using sterile saline (1 in 100) and inoculated onto MacConkey agar, Blood agar and Chocolate agar plates using a 4mm sterile Nichrome loop (0.01 ml) for quantitative culture using standard technique. Incubaton of the inoculated plates was done at 37^0c for upto 48 hrs. SDA medium in slope was also inoculated to detect fungal pathogens, when KOH mount was indicative. The cfu/ml was calculated, considering the reciprocal of dilution factor & volume (ml) of specimen used for inoculation. Bacterial growth with $\geq 10^5$ cfu/ml and $\geq 10^4$ cfu/ml was given significance as that of a pathogen for the inoculated ETA and BAL respectively, and was further identified using appropriate biochemical tests.[12] Growth below this threshold was considered to be due to contamination or colonization. If Fungal growth was suspicious, it was subjected to macroscopic identification by colony morphology and microscopic identification by standard mycological techniques.[13]

Antimicrobial susceptibility of the obtained bacterial 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.[14] Methicillin resistance in Staphylococcus aureus was recognized using Cefoxitin disc (30µg) by disc diffusion.[14] Extended Spectrum Beta Lactamase production in GNB was detected by screening and phenotypic confirmatory test using Ceftazidime disc (30µg) and Ceftazidime-clavulanic acid disc (30µg-10µg).[14] Data collected was analyzed statistically by computing different parameters.

RESULTS

This Prospective analysis of 216 patients with clinical suspicion of pneumonia assessed the occurrence of VAP and and its etiological pathogens with their antibiogram. The occurrence of VAP was shown to be 49.07%. Age group of >60 years (45.28%) was predominant. [Table-1] Male dominance (68.98%) was identified. [Figure-1] The frequently predisposing clinical condition was OP poisoning (31.48%). The associated conditions which are considered as important risk factors were advancing age (>60 years)- 45.28%, Diabetes mellitus- 26.39% and COPD- 22.68%. Majority of the VAP episodes were of late onset type (141/216-65.28%).

ETA and BAL cultured from 89 and 12 cases respectively showed significant growth and no organism was isolated from 85 cases. [Table-2] [Figure-2] The isolates were polymicrobial in 14.85% (15/101) of the samples showing significant growth. Out of the total isolates (121) obtained, 5 were fungi (4- Candida albicans, 1- Aspergillus fumigatus). [Figure-3] The presence of Aspergillus fumigatus as an invasive pathogen was further confirmed by a positive Serology (IgG/Galactomannan). Gram negative bacilli were significantly isolated in largest number (104/121) accounting for 85.95% of the total isolates. Acinetobacter baumannii (30.58%) was the preponderant organism isolated followed by Pseudomonas aeruginosa (27.27%), former being predominant in late onset variety & the latter in the early type.

The Streptococcus pneumoniae isolate was observed to be sensitive to all the drugs tested. All isolates of Streptococcus viridans (7/7) were sensitive to Vancomycin and Linezolid; while only 5 isolates (71.42%) showed susceptibility to Pencillin-G, Oxacillin, Ampiclox, Ceftriaxone and Levofloxacin and only 4 (57.14%) were sensitive

to Erythromycin and Doxycycline. None of the Staphylococcus aureus (0/2) isolate was resistant to Cotrimoxazole, Vancomycin, Linezolid and Teicoplanin; while 1 was resistant to rest of the drugs tested (Amoxyclav, Cloxacillin, Cephalexin, Cefoxitin, Pencillin-G, Ciprofloxacin, Erythromycin, Clindamycin and Doxycycline). The antibiogram of the isolated GNB (with Non-fermenters) is depicted in **Tables-3A, 3B,** with low susceptibility in bold numbers. There were altogether 15/104 isolates (4 Escherichia coli, 9 Klebsiella spp., 2 Enterobacter spp.), which exhibited ESBL production accounting for 14.42% of the GNB tested. Methicillin resistance was encountered in 1 isolate (50%) of Staphylococcus aureus.

DISCUSSION

This prospective study has addressed the occurrence, clinical peculiarities and microbiology of VAP at a tertiary care set up. There is a fluctuating incidence of VAP, as reported in different studies, and varies from 7% to 70%.[15,16,17] Our study showed occurrence of VAP to be around 50%, which is in accordance to various studies.[6,7,18,19]

The predominance of patients in the age group of 51-60 years could be attributed to the increasing number of hospital admissions occurring in this age group and to their high association with co-morbid conditions. This type of age dominance is documented in other studies too.[6,7] The male gender dominance identified here is also observed in some studies.[6,20]

The predisposing conditions identified may cause colonisation and pneumonia due to disease associated impairment in host defense function and are considered as important risk factors by various studies.[6,7,19] Majority of the VAP episodes were of late onset type. This data simulates the findings of other studies done.[20,21]

The report of high incidence of aerobic gram negative bacteria (87.60%) is consistent with some prior reports.[5,22] This can be attributed to oropharyngeal colonization of aerobic GNB, to which the critically ill patients in ICU are more susceptible.[23] The incidence of the polymicrobial isolates, though less, is well comparable to some studies performed.[22,24] Most of the Gram positive cocci isolated were susceptible to antibiotics tested, while majority of GNB were multi-resistant with considerable ESBL production. The results represent the experience from a single centre, and may not be generalizable to other areas with different epidemiologic or clinical settings.

Intuitiveness into trends of the causative agents responsible for this burdensome condition with their drug resistance is of cardinal benefit for restricting the use of empiric broad spectrum antibiotics which predisposes to colonization.

CONCLUSION

VAP creates a havoc in ICUs with its soaring incidence and due to detrimental effects of the upsurging antimicrobial resistance. Individuals with advancing age and associated co-morbid conditions in ICUs are more prone to develop VAP. Aerobic gram negative bacilli are the most common isolates found, Acinetobacter baumannii and Pseudomonas aeruginosa being the most regular.

Auxiliary efforts are much needed to curtail the perinicious outcome of antimicrobial resistance. Constant evaluation of current practice on the basis of trends in drug resistance and antibiotic consumption patterns, timely availability of data and programs to reduce or alter antibiotic-prescribing practices is pivotal to avert the terrible impact of antimicrobial resistance.

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TABLES AND FIGURES

Age in years	**Number of patients (%)**
11-20	5 (2.31)
21-30	17 (7.87)
31-40	22 (10.18)
41-50	22 (10.18)
51-60	54 (25)
>60	96 (45.28)

[Table-1]: Age and gender profile of the patients:

Specimen	**Significant growth (N=101)**	**Insignificant growth (N=30)**	**No growth (N=85)**
ETA(N=202)	89	30	83
BAL(N=14)	12	0	02

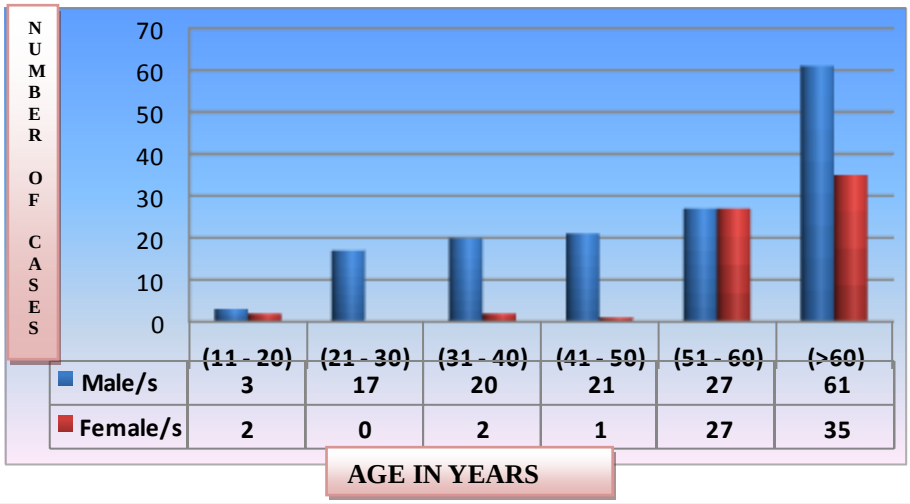
[Table-2]: Quantitative culture report:

Drugs	Klebsiella spp. (n-19)	Esherichia coli (n-9)	Enterobacter spp. (n-5)	Citrobacter spp. (n-1)
Ampicillin	0(0)	**1(11.11)**	**0(0)**	1(100)
Amoxyclav	0(0)	**1(11.11)**	**0(0)**	1(100)
Amikacin	8(42.10)	5(55.56)	**1(20)**	1(100)
Cephalexin	**3(15.79)**	**2(33.33)**	**0(0)**	1(100)
Cefuroxime	**5(26.31)**	**3(33.33)**	**0(0)**	1(100)
Ceftriaxone	**5(26.31)**	**3(33.33)**	**0(0)**	1(100)
Ceftazidime	**5(26.31)**	**3(33.33)**	**0(0)**	1(100)
Ceftazidime- Clavulanic acid	**5(26.31)**	**3(33.33)**	**0(0)**	1(100)
Ciprofloxacin	**4(21.05)**	**3(33.33)**	**1(20)**	1(100)
Cotrimoxazole	**3(15.79)**	**3(33.33)**	**0(0)**	1(100)
Gentamicin	**6(31.57)**	5(55.56)	**0(0)**	1(100)
Imipenem	19(100)	9(100)	5(100)	1(100)

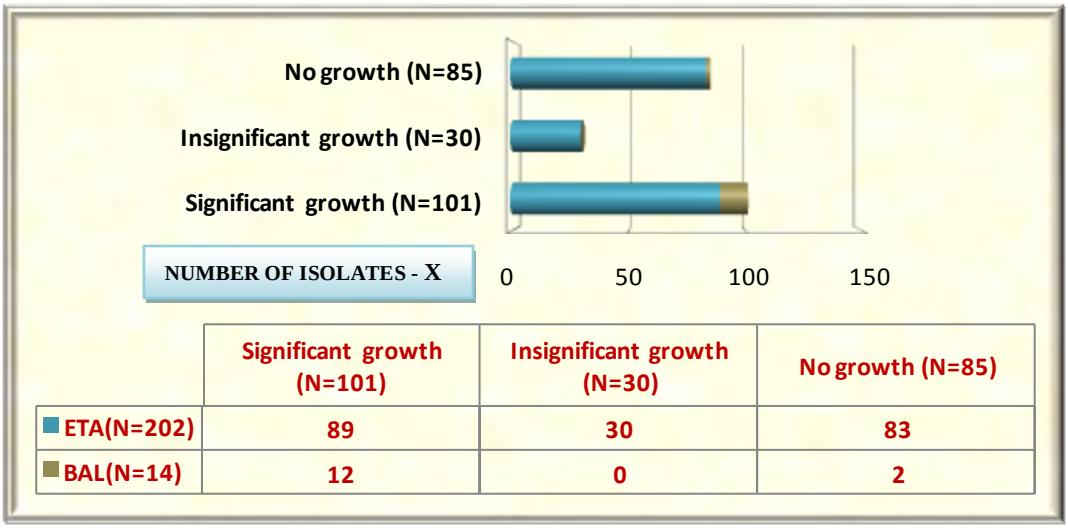
TABLE 3A- Antimicrobial profile of the etiological GNB:

Drug:	**Antimicrobial susceptibility of the isolates – n (%)**	
	Acinetobacter baumannii (n=37)	Pseudomonas aeruginosa (n=33)
Amikacin	**4 (10.81)**	21(63.63)
Aztreonam	**1 (2.70)**	21(63.63)
Ceftazidime	**1 (2.70)**	18(54.54)
Ciprofloxacin	**1 (2.70)**	**8(24.24)**
Piperacillin- Tazobactam	**3(8.10)**	16(48.48)
Gentamicin	**2(5.40)**	**13(39.39)**
Imipenem	**9(24.32)**	23(69.69)
Netilmicin	**4 (10.81)**	18(54.54)
Tobramycin	**3(8.10)**	15(45.45)
Colistin	37(100)	33(100)
Tigecycline	35(94.6)	-
Ampicillin / Sulbactam	-	**1(3.03)**

TABLE 3B- Antimicrobial profile of the etiological Non-fermenting GNB:

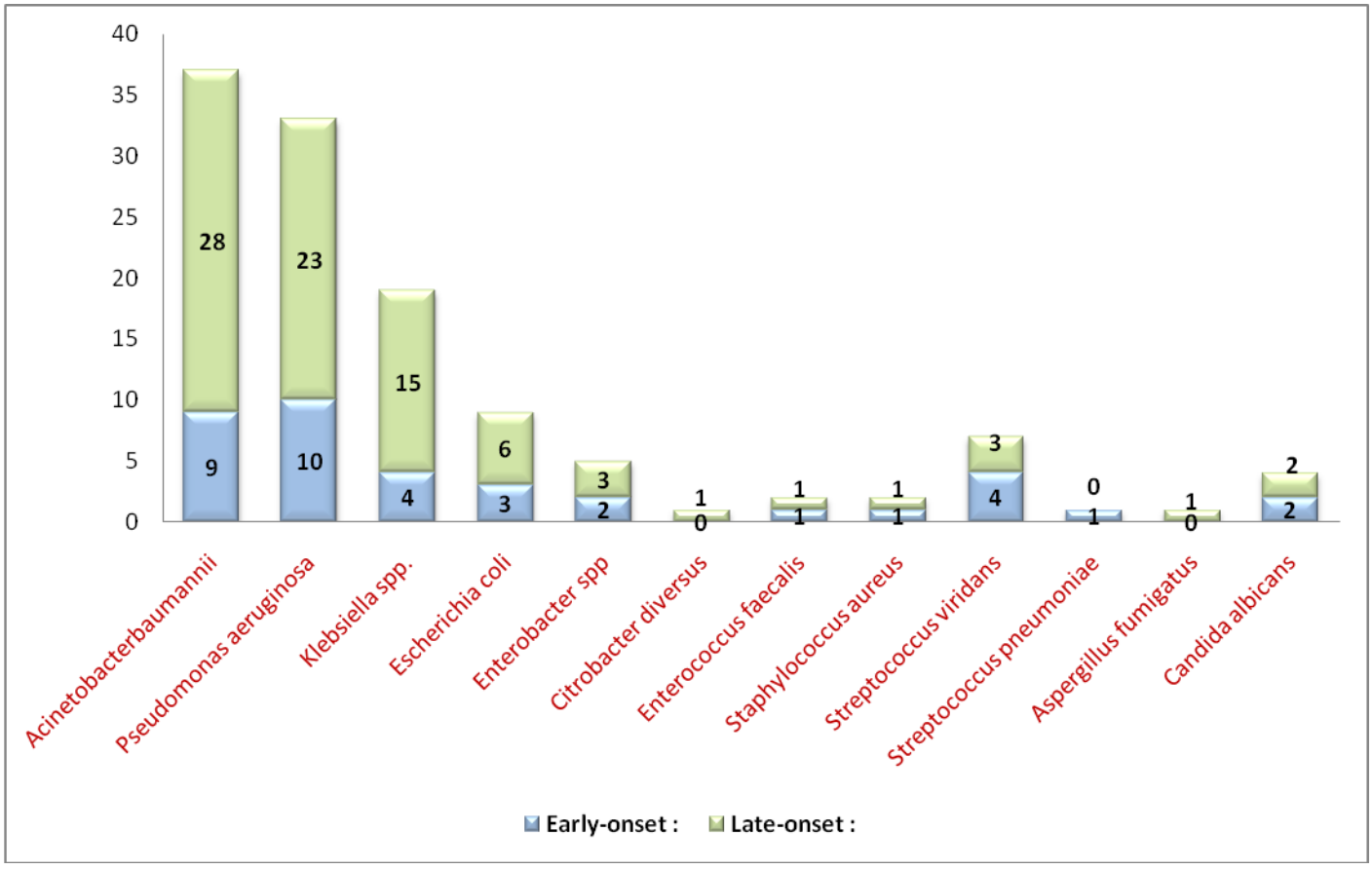


[FIGURE-1]: AGE AND GENDER PROFILE OF THE PATIENTS



	Significant growth (N=101)	Insignificant growth (N=30)	No growth (N=85)
ETA(N=202)	89	30	83
BAL(N=14)	12	0	2

[FIGURE-2]: QUANTITATIVE CULTURE REPORT OF CASES (N):



[FIGURE-3]: ETIOLOGICAL PROFILE OF INFECTIONS: