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ORIGINAL ARTICLE

Bacterial Nosocomial Pneumonia in Respiratory Intensive Care Unit of Assiut University Hospital

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ABSTRACT

Background: *Nosocomial pneumonia is the most frequent cause of hospital acquired infections in the Intensive Care Unit (ICU).* ***Objective:*** *This study aimed to study Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP) regarding clinical characteristics, risk factors, main bacterial causes and their antimicrobial susceptibility.* ***Methodology:*** *Sputum and endotracheal aspirates samples were collected from hospitalized adults who developed nosocomial pneumonia at the Respiratory Intensive Care Unit (RICU) of the Chest Department of Assiut University Hospital. Bacterial causes were isolated by culture and identified conventionally. Antibiotic susceptibility was done for isolated micro organisms by disc diffusion method.* ***Results:*** *This study included one hundred adult patients. Fifty four of the patients were males. HAP was accounted for 42% and VAP 58%. Klebsiella species and methicillin-resistant Staph aureus (MRSA) were the predominant isolated pathogens.* ***Conclusion:*** *Nosocomial Pneumonia, mainly VAP, is very important hospital-acquired infection which causes high mortality rate in the RICU. Identification of the causative pathogens and their antibiotic sensitivity patterns can help physicians choose appropriate antibiotics to improve the outcome.*

INTRODUCTION

Nosocomial pneumonia is classified into two categories: Hospital-Acquired Pneumonia (HAP), which occurs after 48 h of hospital admission, and does not need artificial ventilation, and Ventilator-Associated Pneumonia (VAP), that happens in patients who need mechanical ventilation for at least 48 h [1].

Nosocomial pneumonia is the second most common cause of all nosocomial infections, but it represents the most common cause in the Intensive Care Unit (ICU). HAP and VAP cause the highest mortality among nosocomial infections with mortality rates up to 62%. The time of onset of pneumonia is suggested to be a key risk factor for specific micro organisms and outcomes. The presence of multidrug-resistant (MDR) pathogens in ICU patients with pneumonia can affect the efficiency of empiric antibiotic treatment and can be related to an increase in morbidity and mortality[2].

The appropriate selection of antimicrobial therapy is an important indicator of mortality in nosocomial pneumonia. The early use of proper antimicrobial therapy decreases mortality in critically-ill patients with nosocomial pneumonia [3].

VAP is the most frequent form of nosocomial pneumonia, commonly occurring in ICUs. The mortality rates of VAP are ranging from 20% to 50%[4]. It occurs in 28% of patients requiring mechanical ventilation for more than 48 hours. VAP is a rising problem in hospitals which increases the patient morbidity and the cost of patient care. The Predisposing factors for VAP are an endotracheal intubation and mechanical ventilation which affect the normal defense mechanisms[5]. VAP is frequently caused by MDR pathogens such as *Acinetobacter baumannii* and Methicillin resistant *Staphylococcal aureus* (MRSA) [6,7].

The objective of this study was to detect the prevalence and antimicrobial sensitivity pattern of the main pathogens that cause HAP and VAP, in addition to clinical Characteristics and risk factors associated with such infections.

METHODOLOGY

The study was permitted by the Ethical Committee of the Faculty of Medicine, Assiut University, Assiut, Egypt, according to the code of ethics of the World

Medical Association (Declaration of Helsinki). Informed consent was taken from all participants.

Patient population:

Adult patients (>18 years old) diagnosed to have nosocomial pneumonia in the respiratory ICU (RICU) of the Chest Department of Assiut University Hospital during 6 months period were included. Nosocomial pneumonia was defined as infection of lung parenchyma that happens in patients hospitalized for more than 48 h after admission [8].

Pneumonia was diagnosed clinically and by laboratory findings and chest radiograph. The pneumonia was defined as the presence of a new pulmonary infiltration on chest radiograph in addition to 2 or more signs of respiratory tract infection as body temperature 38.3ºC or higher, purulent bronchial secretions, leukopenia or leukocytosis (＜4000 or 11000 /mm^3) [9].

Patient demographic and baseline data were collected at the time of diagnosis of pneumonia. Risk factors for nosocomial pneumonia as central venous catheter (CVC), obesity, diabetes mellitus (DM), immunosuppressive disease and/or therapy were assessed. Assessment of the vital status (alive or dead) was done at hospital discharge.

Laboratory diagnosis of bacterial causes:

Sputum and endotracheal aspirates samples were collected in sterile containers from each patient under complete aseptic conditions, and were transported to the Infection Control Research Lab. at the Medical Research Center of Assiut University.

Samples were cultured on blood agar, nutrient agar, mannitol salt agar, MacConkey's agar, Eosin Methylene Blue (EMB) agar and bile esculin agar to isolate the causative micro organism. Biochemical reactions as catalase, coagulase, DNase, citrate, urease, triple sugar iron, indole tests were done to identify the isolated bacteria.

Antibiotic susceptibility test was done for isolated micro organisms by the Kirby-Bauer disc diffusion method according to Clinical and Laboratory Standards Institute (CLSI) [10], using the following antimicrobial discs for *Staphylococci*: clindamycin (2µg), linezolid (30µg), oxacillin (5µg), amikacin (30µg), tobramycin (10µg), gentamycin (10µg), and the following antimicrobial discs for gram-negative bacilli: Imipenem (10µg), Meropenem (10µg), Gentamycin (10µg), Ceftriaxone (30µg) Levofloxacin (5µg) and Aztreonam (30µg).

MRSA was identified by culture of *Staphylococcus aureus* isolates on Oxacillin Resistant Screening Agar Base (ORSAB) plates supplemented with polymyxin B and oxacillin (Oxoid, UK), resistance to cefoxitin disk (HiMedia, India) and molecular detection of *mecA* gene[11].

Statistical analysis:

Statistical analysis was done using Statistical Package for Social Sciences, version 16 (SPSS Inc., Chicago, USA). Chi-square test, Student's t-test and ANOVA (Analysis of Variance) were used to compare categorical and continuous variables, when appropriate. *p*-value of <0.05 was considered statistically significant.

RESULTS

Characteristics of patients with HAP and VAP

This was a prospective, hospital-based, active surveillance study on HAP and VAP in hospitalized adults at the RICU of the Chest Department of Assiut University Hospital.

During the study period, one hundred patients admitted at the RICU developed nosocomial pneumonia. Of them, 42/100 (42%) developed HAP and 58/100 (58%) developed VAP. Chronic obstructive pulmonary disease (COPD) was the most frequent underlying medical condition in patients with nosocomial pneumonia. Obesity followed by DM were the most common risk factor among patients with HAP and VAP. No significant differences were detected between HAP and VAP patients regarding age, sex, underlying medical condition, serum albumin, serum creatinine or risk factors. Meanwhile, mortality rate was significantly higher among VAP patients (51.7%) than HAP patients (35.7%) (p=0.03). The clinical characteristics of HAP and VAP patients were described in table (1).

Table 1: Clinical Characteristics of patients with HAP and VAP

Characteristics	HAP (n=42)	VAP (n=58)	*p*- value
Age*	62.3± 10.6	64.6± 12.7	0.1
Male gender	22 (52.3%)	32 (55.1%)	0.09
Underlying medical condition			
COPD	23 (54.7%)	32(55.1%)	0.5
Overlap syndrome	3 (7.1%)	2 (3.4%)	0.3
Interstitial lung disease	6 (14.2%)	5 (8.6%)	0.9
Lung cancer	0	2 (3.4%)	0.09
pulmonary embolism	1(2.3%)	2 (3.4%)	0.7
Obesity hypoventilation syndrome	2(4.7%)	6 (10.3%)	0.4
Bronchiectasis	7(16.6%)	9 (15.5%)	0.5
Serum albumin* (g/dl)	3±0.8	2.6±0.6	0.5
Serum creatinine* (mg/dl)	2.9±1.3	2.4±1.1	0.7
Risk Factors			
CVC	5 (11.9%)	7 (12%)	0.8
Immunosuppression	6 (14.2%)	8 (13.7%)	0.9
Obesity	10 (23.8%)	20 (34.4%)	0.07
DM	7 (16.6%)	15 (25.8%)	0.06
Mortality	15 (35.7%)	30 (51.7%)	**0.03**

Results are expressed as n (%), * presented as mean± standard deviation, $p \leq 0.05$ is significant.
HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; CVC, central vascular catheter; DM, diabetes mellitus;; COPD, chronic obstructive pulmonary disease.

Frequency of different microoraganisms isolated from the collected nosocomial samples at the RICU:

In the present study**,** *Klebsiella pneumoniae* was the most frequent organism causing nosocomial pneumonia in the RICU followed by MRSA representing 31% (45/100) and 25% (25/100), respectively. *Acinetobacter* species were the least isolated organism (5%). There was non significant statistical difference between the HAP and VAP as regards the causative pathogens. The frequency of different organisms isolated from HAP and VAP patients was described in table 2.

Table 2: Frequency of bacterial pathogens associated with HAP and VAP

Organism	Total (n = 100)	HAP (n = 42)	VAP (n = 58)	*p*-value
MRSA	25 (25%)	(23.8%)10	(25.8%)15	0.09
Klebsiella pneumoniae	31 (31%)	11(26.1%)	20 (34.4%)	0.1
CoNS	20 (20%)	9 (21.4%)	11(18.9%)	0.06
E. coli	10 (10%)	5 (11.9%)	5 (8.6%)	0.9
Pseudomonas species	9 (9%)	4 (9.5%)	5 (8.6%)	0.6
Acinetobacter species	5 (5%)	3(7.1%)	2 (3.4%)	0.08

Results are expressed as n (%), $p \leq 0.05$ is significant.
MRSA, Methicillin-Resistant *Staphylococcus aureus*; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia, CoNS, coagulase negative Staphylococci

Frequency of different pathogens isolated from the early onset and late onset nosocomial pneumonia at the RICU

In the present study**,** 60/100 (60%) had early onset nosocomial pneumonia (3-5 days after admission) and 40/100 (40%) had late onset nosocomial pneumonia (after 5 days of admission). *Klebsiella* species were the most common pathogens causing early onset nosocomial pneumonia with isolation rate 33.3% while MRSA was the most common pathogen causing late onset nosocomial pneumonia (34.4%). Only *Acinetobacter* species were significantly associated with early onset nosocomial pneumonia (p=0.01), whereas no other organism showed significant association with the time of onset of pneumonia. The frequency of different organisms isolated from patients with early onset and late onset nosocomial pneumonia was described in table 3.

Table 3: Organisms isolated from nosocomial pneumonia according to the time of onset

Organism	Early onset nosocomial pneumonia (n = 60)	Late onset nosocomial pneumonia (n = 40)	*p*-value
MRSA	12 (20%)	(32.5%)13	0.06
Klebsiella pneumoniae	(33.3%) 20	11 (27.5%)	0.5
CoNS	10 (16.6%)	10 (25%)	0.7
E. coli	(11.6%)7	3 (7.5%)	0.09
Pseudomonas species	(11.6%) 7	2 (5%)	0.08
Acinetobacter species	(66.6%)4	1 (2.5%)	**0.01**

Results are expressed as n (%), $p \leq 0.05$ is significant.
MRSA = Methicillin-Resistant *Staphylococcus aureus*
CoNS =coagulase negative Staphylococci

Drug susceptibility of MRSA and *Klebsiella* causing HAP and VAP

MRSA isolates had the highest sensitivity to vancomycin (80%) followed by linezolid (44%), which were more among the HAP isolates (90% and 70%, respectively). The sensitivity rates of MRSA to Gentamycin, Clindamycin and Linezolid were significantly higher among HAP isolates (p=0.01, 0.03 and 0.01, respectively). *Klebsiella* isolates showed the highest sensitivity to Levofloxacin (29%) followed by Imipenem (22.5%), that were more among the HAP isolates (36.3% and 45.4%, respectively). Only Imipenem showed significantly higher sensitivity among the *Klebsiella* HAP isolates than the VAP isolates (p=0.01). Sensitivity rates of MRSA and *Klebsiella* isolates causing HAP and VAP to different antimicrobial agents were described in table 4.

Table 4: **Sensitivity rates of MRSA and *Klebsiella* isolates causing HAP and VAP to different antimicrobial agents**

Pathogen, antimicrobial agent	Total	HAP	VAP	p-value
MRSA	25	10	15	
Gentamycin	(8%) 2	(20%)2	(0%) 0	**0.01**
Oxacillin	(0%) 0	(0%)0	(0%)0	-
Vancomycin	(80%) 20	(90%)9	(73.3%)11	0.6
Clindamycin	(24%) 6	(40%)4	(13.3%) 2	**0.03**
Linezolid	(44%)11	(70%)7	(26.6%)4	**0.01**
Amikacin	(16%) 4	(20%) 2	(13.3%)2	0.8
Klebsiella pneumoniae	31	11	20	
Imipenem	(22.5%)7	(45.4%)5	(10%)2	**0.01**
Ceftriaxone	(0%)0	(0%)0	(0%)0	-
Aztreonam	(0%)0	(0%)0	(0%)0	-
Levofloxacin	(29%)9	(36.3%)4	(25%)5	0.6
Meropenem	(9.6%)3	(9%)1	(10%)2	0.5
Gentamycin	(9.6%)3	(0%)0	(15%)3	0.05

Results are expressed as n (%), $p \leq 0.05$ is significant.
MRSA = Methicillin-Resistant Staphylococcus aureus, HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia

DISCUSSION

Nosocomial pneumonia is the second most common hospital acquired infection and is associated with significant morbidity and mortality [8]. The prevalence of HAP and VAP among our patients were 42% and 58%, respectively. Variable prevalence has been reported in different studies where VAP ranged from 15.5-75.3%.[6,12-16]. Also, the prevalence of HAP was stated to be 6% -10% in Thailand [17]and 16.7% in India [18]. The great variability may be attributed to different geographical areas, patient population and hospital settings.

The mean age of patients with HAP and VAP was 62.3 and 64.6 years, respectively. Comparable results

were presented in previous studies[16,19,20]. Though, younger age (39.9 years) of VAP has been reported [21].

In the present study, DM was an associated risk factor for HAP and VAP in 16.6% and 25.8% of the patients, respectively. Quartin et al. [20] reported higher prevalence of DM in HAP and VAP (33.8% and 32.7% , respectively).

The mortality rate among patients having VAP was 51.7%. Lower mortality rate (40%) in VAP patients was reported by a previous study [21].

The principal causative micro organisms of HAP/VAP can differ greatly depending on geographic location[22,23] and even amongst different hospitals within the same country [24]. In this study**,** *Klebsiella pneumoniae* was the most frequent organism causing nosocomial pneumonia. This disagreed with previous studies which reported that MRSA and *Acinetobacter* species were the most common micro organisms, respectively [7,16]. Another study conducted in different countries revealed that the most common pathogen causing nosocomial pneumonia was *Acinetobacter* species in India, Pakistan, Malaysia and Thailand, while *Pseudomonas* species in China, Korea and Philippines[25].

The prevalence of *Klebsiella* species was 31% of all isolated nosocomial samples. This agreed with an earlier study that detected the same isolation rate [16]. On the other hand, very low prevalence of *Klebsiella* species (3.3%) was reported by a previous study [6].

Klebsiella species were the most frequent organism causing HAP and VAP in our study. Similar to these results, Werarak et al.[16] found that *Klebsiella* species was the most common micro organism causing HAP. On the other hand, *Acinetobacter*, *Pseudomonas* and MRSA were the most common pathogens causing VAP in previous reports [7,16,19].

In contrast to earlier studies [21,26], the prevalence of early onset pneumonia was higher than late onset pneumonia (60% and 40%, respectively). Though guideline recommendations propose the onset time of pneumonia as an significant epidemiologic variable and a key risk factor for specific causative microorganisms and outcomes [8], no significant association was found between the isolated organisms and the time of onset of pneumonia except for *Acinetobacter*.

In agreement with Chi et al. [21], *Klebsiella* species were the most predominant microorganism causing early onset pneumonia. However, *Acinetobacter* was the most common pathogen causing early onset pneumonia in another study[19].

On the other hand**,** MRSA was shown to be the most common causative pathogen of late onset pneumonia, agreeing with Gupta et al [19] and Chi et al [21].

Antimicrobial susceptibility testing of the isolated MRSA causing HAP and VAP revealed that the highest sensitivity was observed to vancomycin (905 and 73.3%, respectively). This agreed with Gupta et al. [19] who detected that the highest antibiotic susceptibility of MRSA causing VAP was observed to vancomycin. Previously, MRSA causing HAP and VAP had the highest susceptibility to Tigecycline [6]. MRSA isolates causing HAP in this study showed only 20% sensitivity rate for gentamycin and 0% for oxacillin. Higher rates of sensitivity were reported previously against oxacillin (41%) and gentamycin (87%) [6].

The highest susceptibility of the isolated *Klebsiella* causing nosocomial pneumonia were to Levofloxacin (29%) and Imipenem (22.5%). Considerably higher sensitivity rates for Levofloxacin, Gentamycin and Imipenem (95 %, 96.3% and 100 %, respectively) were reported previously [27]. Regular antibiotic susceptibility surveillance of locally isolated micro organisms is very crucial to guide empirical antibiotic treatment, especially for high risk ICU patients.

CONCLUSION

The results of the current study suggest that nosocomial pneumonia, mainly VAP, is very important hospital-acquired infection which causes high mortality rate in the RICU. Identification of the causative pathogens and their antibiotic sensitivity patterns can help physicians choose appropriate antibiotics to reduce the emergence of resistant strains and to improve the outcome.

Conflicts of interest: The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.

- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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