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Microbial Agents in Ventilation Associated Pneumonia (VAP) and their Resistance Pattern in Patients of ICU of Square Hospital, Bangladesh: An Observation for Two and a Half Year

Mirza Nazim Uddin[1], Raihan Rabbani[2], Nurun Nahar Mawla[3], Ahmed Mursel Anam[4], Arifa Hossain[5], Tahsin Monaem[6], Anowar Hossain[7]

[1]MBBS, MRCP (Medicine), Director, Medical services, Square hospitals Ltd

[2]MBBS, FCPS, MD (USA), Consultant, Internal Medicine & Critical Care

[3]MBBS, M Phil (Microbiology), Associate Consultant, Microbiology Laboratory, Square Hospitals Ltd

[4]MBBS, MRCP (UK), Specialist, Square Hospitals Ltd

[5]MBBS, MPH, Coordinator, Indoor Patient Department, Square Hospitals Ltd

[6]MBBS, Medical Officer, Infection control team, Square hospitals Ltd

[7]MBBS, MCPS, MCAP, FCAP (Clinical Pathology), Head, Laboratory Operation, Square Hospitals Ltd

Abstract: ***Background: Ventilator-associated pneumonia (VAP) is a major cause of higher morbidity and mortality among hospitalized patients especially in the intensive care unit (ICU) despite of recent advances in diagnosis and treatment. VAP is usually complicated by infection with multidrug-resistant (MDR) difficult-to-treat microorganisms. This study was conducted to evaluate the microbial agents, their antimicrobial characteristics, presence of MDR biomarkers such as ESBL, CRE and MRSA in VAP related infections. Methods: This study reviewed the records of admitted patients in the ICU of Square Hospital Ltd (SHL) who developed VAP between January 2015 and 30 June 2017. Evaluation included microbial isolates, their resistant pattern and the biomarkers detected in Microbiology laboratory following standard methods and analyzed information on VAP associated morbidity and mortality. Results: Of 2758 patients, 16% (442 of 2758) patients died. Among deaths, 50% (222 of 442) developed ventilator-associated pneumonia, more in males over 60 years. With regard to microbial isolates, Acinatobacter species (29%) was the most frequently isolated gram-negative pathogens followed by Klebsiella pneumoniae (26%), Pseudomonas (10%) and E. coli (5%). Acinatobacter had 86% resistance to meropenem, 17% resistance to collistin, but Klebsiella still 100% sensitive to both collistin and polymyxin B. Of gram-positive isolates, Staphylococcus aureus (9%) predominated over coagulase-negative Staphylococcus species (6%). Antimicrobials such as Amikacin, Meropenem, Collistin and Polymyxin B were more sensitive against gram-negative bacteria; while Linezolid and Vancomycin were the drugs of choice for other Staphylococcal species. Candia was associated 4.5% cases. Of MDR biomarkers, ESBL producer E. coli and Klebsiella were associated in VAP cases by 45% and 16% respectively; CRE producing Klebsiella and Acinatobacter in 61% and 86% cases; while MRSA producer S. aureus was in 55% cases. Thus for VAP patients, collistin, polymyxin B and minocycline are the treatment option for CRE, meropenem for ESBL and vancomycin for MRSA cases. Conclusion: Ventilator-associated pneumonia complicates the prognosis of patients receiving mechanical ventilation. Challenges remain with ESBL, CRE, MRSA and emerging collistin resistant Acinatobacter cases. Higher prevalence of VAP with MDR infections in ICU warrant early management plan using appropriate antibiotics followed by de-escalation based on culture-sensitivity and clinical response of the patient.***

Keywords: Intensive care unit/ICU, Ventilator-associated pneumonia/VAP, Multidrug-resistance/MDR

1. Introduction

The ICU patients are, in general critically ill, suffering from immunodeficiency syndrome which is a major risk of contracting the hospital acquired infection (HAI) when admitted either in Medical or Surgical Intensive Care Unit (MICU/SICU). Majority of the infections are caused by antimicrobial resistant strains of bacteria, fungi or viral agents. Most of such infections are associated with the use of indwelling catheter, intravenous fluid therapy, prosthetic devices, life support devices, immunosuppressive drug and long term antibiotics therapy etc. Long term use of broad spectrum antibiotic itself leads to several complications [1]. All these attributes drive a sequence of events to the patient condition such as severe morbidity and decreased mobility, and an increased vulnerability in developing other co-morbidities which ultimately lead the patient to septic syndrome with likelihood of growing multi-organ failure. The outcome of multi-organ failure results a critical orthostatic or hypostatic pneumonic condition rendering them to provide additional therapeutic interventional support for their survival through mechanical life support device. The end result of this morbid condition has not been well defined in a non-selected critically ill population.

The life support through the ventilator usage carries an added risk of acquiring superimposed infection (especially pneumonia of any cause) over the primary cause of multi-organ failure by micro-organisms associated with the

ventilator machine itself. The ventilator associated micro-organisms either gram+ve or gram-ve bacteria or fungal species are usually found to form a biofilm which contributes in developing multi-drug resistant (MDR) to commonly used antimicrobials, a major global health concern both in the developed and developing countries [2].

The MDR micro-organisms usually carry genes responsible for expressing pheno-typing characteristics and encode several biomarkers of multi-resistance, such as MRSA, VRA, ESBL and CRE etc [3]. Such micro-organisms are major challenges of critical patient management in the ICU settings with a positive outcome. The general aim of this study was thus to collect relevant information/data from the ICU records, analyze the data to look after the pattern of microbial isolates and their antimicrobial resistance in a group of patients admitted in the ICU of a private Tertiary Square Hospital. The specific objective was to attempt in identifying the occurrence and role of ventilator support and associated causative agents in patients with fatal outcome among the admitted patients in ICU. This report thus presents the results obtained.

2. Materials and Methods

Study place and period: This observational study was carried out in Microbiology Laboratory of Square Hospital Ltd (SHL) that processed clinical samples for microbial culture from patients admitted in the ICU, SHL between January 2015 and 30 June 2017. The study also analyzed some general information on number of morbidity and VAP-associated mortality of ICU patients during the period of two and a half year period.

Study tool: Only clinical samples processed for microbial isolation were studied along with their resistance pattern against selected antimicrobial drugs, presence or absence selected MDR biomarkers. Other information regarding the patient included the age, gender, number of death and microbial pathogens in ventilator associated death with pneumonia etc.

Study samples and microbial isolates: Clinical specimens obtained from patients who develop ICU associated infections that occur after 48 hrs of ICU admission or within 48 hrs after transfer from an ICU. Depending on clinical suspicion samples like blood, tracheal aspirates, sputum, urine, wound swab, pus and broncho-alveolar lavages were collected from these patients and were processed for microbial culture, isolation, identification and antimicrobial susceptibility testing following standard method described elsewhere [4, 5].

***Antimicrobial susceptibility testing (AST*)**: The AST was performed using Kirby-Bauer technique (20) against a selected panel of antibiotics discs listed in Table-- for gram positive and gram negative organisms following CLSI guidelines as detailed in recent publication [5].

***Detection of resistance biomarkers*:** The extended spectrum β-lactamase (ESBL) was detected in *Enterobactericeae*, such as, *E. coli*, *Klebsiella*, *Enterobacter* and *Citrobacter* after inoculating onto MHA media with amoxyclav disc in the centre while ceftazidime, ceftriaxone, cefixime and cefuroxime discs were placed peripherally at equi-distant away from amoxyclav disc. Band appearance between amoxyclav and any other discs were considered as ESBL positive [6, 7] These organisms were also regarded as Carbapenem Resistant *Enterobactericeae* (CRE) positive when zone diameter of meropenem was <19 mm [20]. The MRSA was detected by making a suspension of *S. aureus* and inoculated onto MHA plate onto which cefoxitin disc was placed and zone diameter of <21 mm referred to cefoxitin resistance which was regarded as MRSA [8].

3. Results

During the study period of two and a half year, a total of 2758 patients were admitted to ICU. Of 2758 patients, 16% (442 of 2758) were died (Table-1). Among the cause of death, 50% (222 of 442) was found ventilator associated pneumonia.

Table 1: Frequency of VAP among TOTAL Death by year

Year	Admission in ICU	Total Deaths N (%)	VAP/death N (%)
2015	1137	171 (15)	101 (59)
2016	1108	176 (16)	105 (60)
2017 (June)	513	95 (18.5)	16 (17)
TOTAL	**2758**	**442 (16)**	**222 (50)**

**VAP=Ventilator Associated Pneumonia, ICU=Intensive Care Unit*

Table 2 shows the distribution of VAP patients by the age and gender. By age group, the highest number of patients were above 60 years (.48%) followed by 40-60 years (>29%).Of the total VAP, males were infected more than twice the females (70.3% vs 29.7%).

Table 2: Demography of VAP Patients by age and gender

Age	*Male*	*Female*	*Total N (%)*
<5	03	00	03 (1.4)
5-15	02	01	03 (1.4)
16-40	21	23	44 (19.8)
40-60	44	21	65 (29.2)
>60	83	24	107 (48.2)
Total	**156 (70.3)**	**66 (29.7)**	**222 (100)**

The figure 1 indicates the number and type of specimens obtained from 222 patients from which agents of infections were isolated. Of the four types of specimens, the highest number of isolates were found from tracheal aspirates (73%) followed by sputum (19%) and Broncho-alveolar lavage (7%); while only 1% organisms were detected from urine.

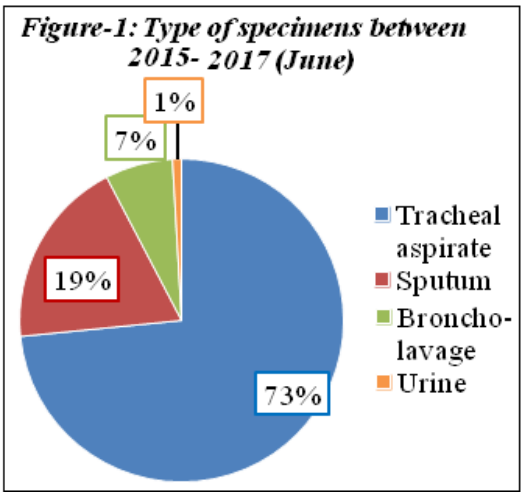

Figure 1: Categories of specimens submitted in 2015-2017 (June)

The VAP associated microbial agents isolated in this study are shown in Table-3.The patients infected by the gram negative bacterial agents were over 80% (178 of 222) and the rest 20% (44 of 222) were caused by the gram positive agents and the *Candida* species. Among the gram negative microbial agents, *Acinatobacter* species were the most frequently isolated (29.2%) followed by *Klebsiella* (25.7%), Pseudomonas (10.3%) and E.coli (5%). The Enterobacter, Proteus, *Stenotrophomonas* and *Burkholderia* are less frequently (1.4 to 4.5) recovered among VAP patients. Among the gram positive causative agents only *Staphylococcus aureus* (9%) and coagulase negative *Staphylococcus* (6.3%) are isolated. Of the fungal species, only *Candida sp* (4.5%) was found in table-3.

Table 3: Type and frequency of Isolates associated with VAP

ORGANISMS	*No of isolates*	*Percent (%)*
GRAM NEGATIVE BACILLI		
Kleb. pneumoniae	57	26
Esch. Coli	11	05
Enterobacter sp	03	01
Proteus sp	03	01
Acinatobactersp	65	29
Pseudomonas sp	23	10
Burkholderia	06	03
Steno. maltophilia	10	05
Total	**178**	**80**
GRAM POSITIVE COCCI		
Staph. Aureus	20	09
CONS	14	06
Total	***34***	***15***
FUNGUS		
Candida	10	05
TOTAL	***222***	***100***

Ventilator associated pneumonia usually has some kind of relation with the use of different types of devices which is shown in Table 4. A combination of uses of various devices in 222 VAP cases showed that the highest number of isolates (89.2%) involved in cases where combination of the ventilator, CV line, IV cannula and urinary catheter were in use, followed by 6.6% uses of urinary catheter, IV cannula and CV line; among the least number was the tracheotomy tube-in-situ (2.3%) plus urinary catheter and ventilator only.

Table 4: Microbial Isolates and Devices associated with VAP

Organisms	*UCath +IV*	*UCath+ Vent*	*UCath+ IV+CV*	*UCath+IV +CV+Vent*	*UCath+ IV+TT*	*Total*
Klebsiellasp		1	7	48	1	57
E.coli			1	09	1	11
Enterobacter				3		3
Proteus sp				3		3
Acinato		2	2	60	1	65
Pseudomonas	1		2	20		23
Burkholderia				6		6
Steno.malto				8	2	10
Staph.aureus			1	19		20
CONS			1	13		14
Candida			1	9		10
TOTAL	1 (0.5%)	3 (1.4%)	15 (6.6%)	198 (89.2%)	5 (2.3%)	222 (100%)

*UCath= Urinary catheter, IV=Intravenous line, CV=Center venous line, Vent=Ventilator, TT= tracheotomy tube

A panel of various antibiotics was tested for detecting the pattern of antimicrobial resistance of the four major gram-negative organisms isolated during two and half years (Table 5). Among the isolates, E. coli showed 91% resistant to amoxyclav, cefixime and ciprofloxacin followed by ceftriaxone (82%), cefuroxime (73%), gentamycin (64%) and piperacillin-tazobactam (54%).Resistance to cefepime and amikacin were less than 50% and no resistance found against meropenem, collistin and polymyxin B.

The majority isolates of *Klebsiella* exhibit 91%resistant to ciprofloxacin; while 86% were resistant against cefuroxime, cefixime and piperacillin-tazobactam followed by amoxyclav (84%) and ceftriaxone (82%) while 60-70% resistance was noted against amikacin, gentamycin and cefepime. VAP associated Klebsiella isolates showed 61% resistance to meropenem and 9% to collistin and no resistance recorded against polymyxin B.

The *Acinatobacter* isolates were found 92% resistance to gentamycin and levofloxacin, 91% to piperacillin-tazobactam, 89% to cefepime, 88% to amikacin, 86% to meropenem, 85% to ceftazidime, 77% to minocycline and 17% to collistin.

Pseudomonas showed low level resistance to all antibiotics, around 50%, with 9% to meropenem, 8% to piperacillin-tazobactam and no resistance to collistin and polymyxin B.

Table 5: Resistance pattern of selected Gram negative organisms

Antibiotics	*E.coli N=11 (%)*	*Klebsiella N=57(%)*	*Acinatobacter N=65(%)*	*Pseudomonas N=23(%)*
Amoxyclav	10 (91)	48 (84)	-	-
Cefuroxime	8 (73)	49 (86)	-	-
Cefixime	10 (91)	49 (86)	-	-
Ceftriaxone	9 (82)	47 (82)	-	-
Ceftazidime	-	-	55 (85)	12 (52)
Cefepime	5 (45)	39 (68)	58 (89)	14 (61)
Gentamycin	7 (64)	38 (67)	60 (92)	13 (56)
Amikacin	4 (36)	36 (63)	57 (88)	13 (56)
Ciprofloxacin	10 (91)	52 (91)	-	-

Levofloxacin	-	-	60 (92)	12 (52)
Pip-tazo	6 (54)	49 (86)	59 (91)	8 (35)
Meropenem	0 (0)	35 (61)	56 (86)	9 (39)
Collistin	0 (0)	55 (91)	11 (17)	0 (0)
Polymyxin b	0 (0)	0 (0)	0 (0)	0 (0)
Minocycline	-	-	15 (77)	-

Resistant organisms are distributed in relative frequency (%).

Of *Staphylococcus aureus* isolates, 100% were found resistant to penicillin followed by 95% to amoxicillin, 70% to ciprofloxacin, 65% to cefuroxime and 55% to cefoxitin; however it showed comparatively less resistance to gentamicin and rifampicin and interestingly 100% isolates were sensitive to both linezolid and vancomycin. The isolates of CONS contributed 93% resistance to penicillin but have 57% resistance to both amoxicillin and cefoxitin. It also showed 86% resistance to ciprofloxacin followed by 79% to cefuroxime and 73% to gentamycin, 43% resistant to rifampicin and 14% resistant to linezolid and no resistance was noted against vancomycin.

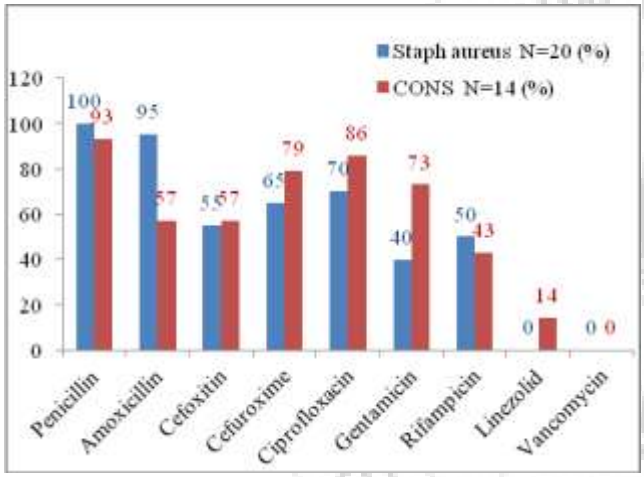

Figure 2: Showed the resistance pattern of gram positive isolates to various antibiotics during the study period. *Resistant organisms are distributed in relative frequency (%).*

Figure 3 showed the number of patients and the clinical isolates with positive MDR biomarkers. The microbial agents that caused VAP were Staphylococci, E. coli, *Klebsiella* or *Acinatobacter*. Of gram-negative bacteria, ESBL producing E. coli was associated in 45% patients and that of *Klebsiella* with 16% patients. Patients infected with CRE positive bacteria, the highest number were infected by the *Acinatobacter* (86%) followed by the *Klebsiella* (61%). No *CRE* positivity was found among the patients infected with *E. coli*. About 55% of patients infected with Staphylococcus aureus that produced MRSA.

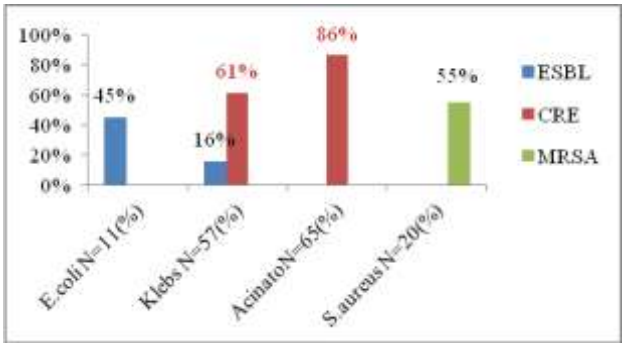

Figure 3: Special type of resistance

The carbapenem resistant bacteria that were sensitive to several important antimicrobials is shown in Figure 4. Of the carbapenem resistant Klebsiella isolates 100% were sensitive to collistin and polymyxin B while *Acinatobacter* isolates were 100% sensitive to polymyxinB and that to collistin was 93%. The sensitivity to other antibiotics such as amikacin, tetracycline and cotrimoxazole were found very low for both *CR-Klebsiella* and *Acinatobacter*. Of *Acinatobacter* isolates, only minocycline has 20% sensitivity.

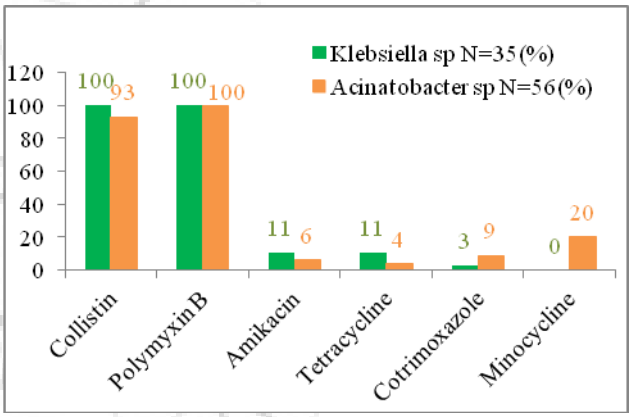

Figure 4: Sensitivity pattern of CR- Klebsiella &Acinatobacter. *Sensitivity isolates are distributed in relative frequency (%).*

Among ESBL producing E.coli, 100% isolates were found sensitive to meropenem followed by 80% each to piperacillin-tazobactam, amikacin and gentamycin while cotrimoxazole was only 20% sensitive (Figure 5). The isolates of Klebsiella that produced ESBL showed 100% sensitivity to meropenem, collistin and polymyxin B followed by 78% to gentamycin, 67% to amikacin and 44% to piperacillin-tazobactam.

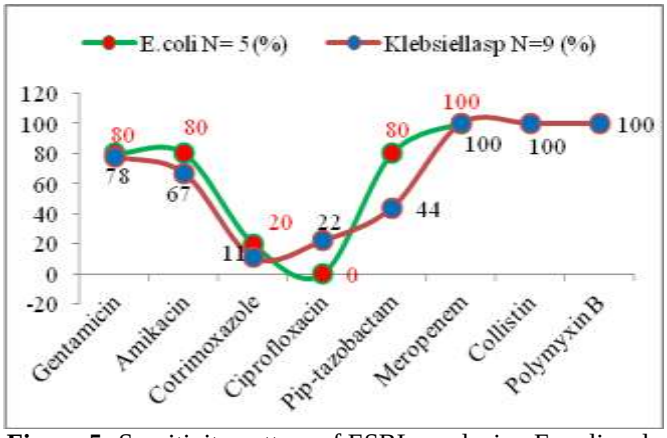

Figure 5: Sensitivity pattern of ESBL producing E. coli and Klebsiella. *Sensitivity isolates are distributed in relative frequency (%).*

4. Discussion

Hospital acquired infections (HAI) with multi-drug resistant (MDR) microorganisms are one of the leading causes of deaths and morbidity amongst hospitalized patients especially in the intensive care unit [9]. It is thus critical to evaluate the prevailing pattern of infecting microbial agents periodically in order to create appropriate strategies to reduce the risk of developing MDR infections; as it adds the clinical and economic burden to individual patient and to hospital authority as well. Various reports indicated that the ICU patients commonly develop infections from multiple sources especially from respiratory tract, majority of whom could have assisted ventilation and/or usages of other in-situ devices. Prolonged usages of the devices lead to other comorbidities and complications. The most common complication among the ICU patients having mechanical ventilation is ventilator-associated pneumonia (VAP), impact of its outcome is severe and renders to higher fatality [10].

Ventilation is required in bed-ridden critically ill patients with reduced lung expansion for extended periods of time. The lung alveoli in dependent zones suffer from blood stagnation and pulmonary congestion, a favorable condition for microbial colonization, multiplication and severe invasion. This leads the lung gradually to collapse which do not expand with each breath. The process if continues, more and more alveoli collapse and functional lung volume decreases, resulting in lower oxygen levels and higher CO_2 and with persisting condition the person is more fragile to prolonged morbidity and risk of increased mortality. This condition is then hastened the fatality with onset of hypostatic pneumonia followed by lung infection by various microorganisms, typically known as ventilator associated pneumonia (VAP); a major source and cause of increased illness and death. Common microbial agents contributing in VAP are gram negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter species* and gram positive bacteria such as *Staphylococcus aureus*, *Coagulase negative Staphylococcus*, *Streptococcus pneumoniae*, *Enterobacter* etc. The type of organism that causes VAP usually depends on the duration of mechanical ventilation. In general, early VAP is caused by pathogens that are likely sensitive to antibiotics, whereas late onset VAP is caused by multi-drug resistant and more difficult-to-treat bacteria.

Clinical isolates either gram negative or gram positive bacteria requires initiating the treatment by appropriate antibiotic therapy against VAP associated agents while differentiating between colonization and infection. Unfortunately, there is no single gold standard test for VAP and only few samples cannot rule out the VAP associated respiratory infections. Therefore regular updated knowledge of local antimicrobial susceptibility patterns of the most important isolates is the only tool to the hand of physicians for making therapeutic decisions. Of the specimens tested for microbial diagnosis of VAP, the tracheal aspirates and broncho-alveolar lavage (BAL) were the common and among the two, the tracheal aspirates yielded ten times higher isolates than that of the BAL. The isolation ratio may vary in different reports due to lack of standard diagnostic procedure adopted in the hospital laboratories and between the countries. This is however, valid evidence that respiratory infection is more commonly associated with the VAP than any other sources of infection.

The microbial analysis of this study noted that about 80% of isolates responsible for VAP were Gram-negative bacilli, which is consistent with the results of Fugon et al (79%) [11] and Simsek et al (75%) [12].The findings also reveal that 29% of Gram-negatives were *Acinatobacterspp* followed by 26% *Klebsiella pneumoniae* and 10% *Pseudomonas spp*. These rates are nearly closer to a recent study done in Korea where *Acinatobacter spp* (16%), *Klebsiella pneumoniae* (9%) and *Pseudomonas spp* (14%). [13]; while in other studies, *Pseudomonas* isolates ranges from 15 to 25% and *Klebsiellawas* 19% [14]. Among Gram-positive bacteria (15%) reported in this study, *Staphylococcus aureus* accounted for 9% cases associated VAP, and varied between 15-27% in a recent study in Korea [14, 15]. The Candida infection was 4.5% only noted in this study. Thus it is evident that the 4-5 microbial agents were more frequently found to be associated with the VAP which are the reported MDR pathogens. Thus once isolated and reported from respiratory specimens, a due importance should be given for early treatment with appropriate antimicrobials.

It is not unusual observation that VAP associated Gram-negative bacilli are resistant to many of the important antimicrobial drugs such as, fluoroquinolones by 91-92%, ceftriaxone by 82%, cefixime 86-91% and amoxyclav 84-91%. It is consistent with other reports [16, 17]. It probably reflects increasing inappropriate usage of quinolones for empiric and therapeutic treatment for respiratory infections as the quinolone penetrates very well into respiratory secretions, its advantage in dosage schedule and patient compliance. Resistance was comparatively less against gentamycin, amikacin, piperacillin-tazobactam and meropenem. Thus Amikacin, Piperacillin-tazobactam and carbapenem may remain as an option for treating VAP except *Acinatobacter spp*; which demonstrated as the difficult-to-treat organism because of its higher resistance to quinolone (92%), piperacillin-tazobactam (91%), amikacin (88%), meropenem (86%) and ceftazidime (85%). The observation is similar to an antibiotic surveillance study in

ICU of Thailand [18]. Interestingly, though low but collistin resistance was noted in this study among the *Acinatobacter* (17%) and *Klebsiella* (9%); while susceptibility to polymyxin B was still preserved by all Gram-negative organisms and the finding is similar to that of Haeili et al. [19].The study reported only the sole Gram-positive *Staphylococcus aureus* as the pathogen associated VAP, that was 100% sensitive to linezolid and vancomycin; while highly resistant to penicillin, amoxicillin, quinolones and cefuroxime, which is consistent to other national studies [20, 21]. Thus it is essential that efforts tobe made to preserve the efficacy of linezolid and vancomycin as the MRSA producing isolates requiring treatment by the two antibiotics.

MDR biomarkers such as ESBL, CRE and MRSA were studied for the VAP isolates as they are concern for developing difficult-to-treat pathogens. The ESBL producing *E. coli* was associated in 45% cases and *Klebsiella* in 16% cases; while CRE positive *Klebsiella* was in 61% cases and that in multi-resistant *Acinatobacter spp* in 86% cases. The MRSA positive Staphylococcus aureus was associated with 55% cases. Several studies documented the occurrence of MDR among the pathogens specially resistant to broad-spectrum antimicrobial agents like third-generation cephalosporins, imipenem or fluoroquinolones [5, 22].

The ESBL producers especially *E. coli* and *Klebsiella* pose threats to public health and major concern of healthcare giver as it encode and exhibit more resistance to different classes of antibiotics. Only Carbapenem was found 100% sensitive and regarded as the drug of choice for VAP caused by the two ESBL producers. The situation reported in this study is thus similar to other studies of ICU [23, 24]. The *Klebsiealla pneumoniae* carbapenemase (KPC) and New Delhi Metallo-beta-lactamase (NDM) induce resistance to *Enterobactericeae* specially *Klebsiealla* and *Acinatobacter* against all beta-lactam and in many non-beta-lactam antibiotics [21] and is a concern to caregivers to VAP associated cases. Fortunately, Collistin and Polymyxin B can be used for successful treatment of CRE and multi-resistant *Acinatobacter spp* in critically ill patients of ICU, though only 7% collistin resistance is reported in this study. A comparable finding has been seen between MRSA isolation of this study in Bangladesh (55%) and that of ICUs in Thailand [18]. However, in most ICUs, treatment of MRSA infected patient depends only on Vancomycin and the Linezolid remains as reserve in hand as the last line of choice.

VAP is a fatal condition and in most cases predicts a higher mortality; the scenario is almost similar in many of the hospitals in the same country or in the regions. However, a quick and timely diagnosis of contributing organisms is essential. In the early stage of VAP, it is usually caused less resistant microorganism; thus the rational use of appropriate antibiotics may reduce patient colonization and prevent subsequent severity and developing the MDR pathogens. However, the VAP prevention program should include rigorous nursing, practicing good hand hygiene in handling patient and ventilator and prescribing evidenced–based high impact interventions. Only small number of patients with VAP in a single center were evaluated which is a limitation of this study. Therefore, further multi-centered studies with larger patient numbers are suggested to confirm the findings.

5. Comments and Conclusions

Empiric antibiotic therapy in VAP cases in ICU should be based both on evidence-based guidelines and antibiotic susceptibility data of the local flora. VAP is predominantly associated with Gram-negative pathogens, more of them are MDR, and therefore, it is probably wise to start treatment with combination of carbapenem or piperacillin-tazobactam with an anti-pseudomonial fluoroquinolone or aminoglycoside. As substitution by Collistin and polymyxin B are to be in hand if CRE or *Acinatobacter spp* are suspected. Vancomycin and Linezolid are suggested for MRSA. Early antifungal therapy should be considered for invasive candidiasis. For prevention of VAP, antibiotic stewardship are incomparable measures.

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