Int.J.Curr.Microbiol.App.Sci (2018) *7*(4): 1448-1463

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 7 Number 04 (2018)**
Journal homepage: http://www.ijcmas.com

Original Research Article https://doi.org/10.20546/ijcmas.2018.704.164

Multi Drug Resistant *Acinetobacter* Ventilator Associated Pneumonia in a Tertiary Care Hospital

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Keywords

Ventilator associated pneumonia, *Acinetobacter baumannii*, Multi drug resistance, Biofilm production

Article Info

Accepted:
12 March 2018
Available Online:
10 April 2018

A B S T R A C T

Ventilator associated pneumonia (VAP) is a common hospital acquired infection. Its prevalence ranges from 9-24%. It leads to increased mortality and increased health care costs. VAP due to *Acinetobacter baumannii* is notorious for its multidrug resistance potential. The study reveals the characteristics of *Acinetobacter baumanii* in a tertiary care hospital. This is a prospective study of 100 patients. The endotracheal aspirates were collected, processed and isolate identified. Antimicrbial susceptibility testing was done, biofilm testing and MIC testing for Meropenem was also done. The incidence of *Acinetobacter* VAP was 31%. Multisystem disorders and neurological disorders were associated with *Acinetobacter* VAP. 83.87% isolates were multidrug resistant. 54.84% of isolates were strong biofilm producers. 61.29% of isolates were resistant to Meropenem by MIC testing by microbroth dilution method. Proper infection control measures, judicious use of antibiotics with implementation of ventilator care bundle will retard the development of VAP in ICU.

Introduction

Ventilator associated pneumonia is defined as pneumonia that occurs after 48 hours of mechanical ventilation. The prevalence varies from 9 to 24% (Morehead and Pinto, 2000). Pneumonia is the most common infection in the Intensive care unit and affects about 27 % of critically ill patients. About 86% of them occur in intubated patients and are termed ventilator associated pneumonia. The mortality due to VAP is 50% and can reach upto 76% when VAP is caused by multidrug resistant pathogens (Richards *et al.*, 1999; Chastre and Fagon, 2002). It leads to increased duration of mechanical ventilation, increased duration of stay in the intensive care unit and the hospital and also increased health care costs (Amin, 2009).

Early onset VAP (VAP onset < 4 days) is usually caused by Methicillin sensitive *Staphylococcus aureus*, *Hemophilus influenza* and *Streptococcus pneumonia*e while Late onset VAP is caused by Methicillin resistant *Staphylococcus aureus*, Multidrug resistant

Acinetobacter, Pseudomonas and beta lactamases producing Gram negative bacteria (Gastmeier *et al.,* 2009). Nowadays *Acinetobacter* is an emerging pathogen in VAP. It is aerobic, non- motile, Gram negative coccobacilli, catalase-positive, oxidase-negative bacteria. It is ubiquitous and is present in the soil, water and environmental surfaces (Hanlon, 2005). It colonises the human skin and respiratory tract. It has been implicated as an opportunistic pathogen and causes a spectrum infections ranging from wound infections, respiratory infections, urinary tract infections (Howard *et al.,* 2012). *Acinetobacter* can survive on abiotic surfaces in hospitals and colonise medical devices in the ICU. It has the ability to form biofilms which are aggregates of bacteria within a matrix called extracellular polymeric substances, by attaching to devices in situ (Tomaras *et al.,* 2003). The most troublesome part is that these organisms can gain multi drug resistance by adapting to changes in environmental pressure. It has the capacity to upregulate resistance determinants and acquire resistance to a variety of antibiotics including Carbapenems (Peleg *et al.,* 2008).

Materials and Methods

This was a prospective study conducted in the Respiratory intensive care unit complex of a tertiary care hospital for a period of one year. A total of 100 patients on ventilator were selected.

Inclusion criteria

The cases included both males and females, age greater than 18 years who were on mechanical ventilation.

Exclusion criteria

Patients who developed pneumonia within 48 hours of admission or those who were admitted with other respiratory tract infections.

Methodology

A proforma was prepared and all the details like age, gender, diagnosis at the time of admission, date and indication for ventilation, antibiotics given, investigations done, x -ray findings, duration of mechanical ventilation, duration of ICU and hospital stay were noted. The patient was monitored from the time admission till the discharge and the outcome was recorded.

VAP was diagnosed on clinico microbiological basis using the modified CPIS (Clinical Pulmonary infection score).VAP was classified as early onset VAP (within 48–96 hours) and late onset VAP (>96 hours) (Gastmeier *et al.,* 2009).

The endotracheal aspirates were collected processed immediately. A Gram's stain was done and sample cultured on 5% sheep blood agar, Mac Conkey agar, Chocolate agar and incubated at 37º C for colony identification. The routine biochemical tests were performed. All non-fermentative, oxidase-negative, catalase-positive non motile, Gram-negative coccobacilli were identified as *Acinetobacter* spp. (Constantiniu *et al.,* 2004).

Antimicrobial susceptibility testing

The purpose of the Kirby-Bauer disk diffusion susceptibility test was done to determine the sensitivity or resistance of pathogenic bacteria to various antimicrobial drugs.

Antibiotics tested

Acinetobacter

Ceftazidime (30µg), Ceftriaxone (30µg), Cefepime (30µg), Cefoperazone Sulbactam

(75/30µg), Piperacillin Tazobactam (100/10 µg), Amikacin (30µg), Ciprofloxacin (5µg), Cotrimoxazole (1.25/23.75 µg), Imipenem (10 µg), Meropenem (10 µg), Tigecycline (15µg), Colistin (10µg) (Clinical and Laboratory Standards Institute, 2013).

Biofilm production (Rewatkar and Wadher, 2013; Mathur *et al.*, 2006)

Biofilms are multicellular communities of microorganisms attached to a surface. Both Gram positive and Gram negative bacteria have the capacity to produce biofilm.

The microtitre plate was employed to estimate the biofilm production quantitatively (Morehead and Pinto, 2000).

Microtitre plate method

Colonies of the isolated bacteria causing VAP were inoculated in Trypticase soy broth (TSB) and incubated at 37°C for 24 hours. The culture was diluted 1:100 with trypticase soy broth. A 96 well microtitre plate with flat bottom was taken and filled with 230 µl of TSB. First three wells were filled with broth only to check for sterility and non- specific binding. Known positive and negative controls were inoculated in each plate.

Then 20µl of the diluted cultures were added to the wells in triplicate and incubated at 37° C for 24 hours. After incubation the plates were washed with phosphate buffer saline PBS (pH-7.2). 300 µl of methanol was then added to each well and after 15 minutes, it was discarded and stained using 0.1% safranin dye.

After 20 minutes, the stain was discarded and washed with PBS. The adherent cells were resolubilised with 33% glacial acetic acid.

Optical densities (OD) of the stained adherent bacteria were measured with an ELISA reader at a wavelength of 490 nm. The averages of the three OD values were taken. The cut off value of OD (ODc) was calculated.

Minimum inhibitory concentration (Andrews, 2001)

MICs are used in laboratories to confirm antimicrobial resistance. Microbroth dilution was performed with Meropenem powder for all *Acinetobacter* isolated from VAP cases. *Escherichia coli* ATCC 25922 was used as the Quality control.

Preparation of stock solution

Stock solutions were prepared using the formula:

$1000/P \times V \times C = W$

Where P = potency given by the manufacturer (µg/mg), V = volume required (mL), C = final concentration of solution (mg/L) and W = weight of antibiotic in mg to be dissolved in volume V (mL).

Procedure

The organisms suspensions were prepared by inoculation into brain heart infusion broth. Prepare inoculum equivalent to a 0.5 Mcfarland standard. A final inoculum of 5 x 10^5 CFU/mL is required and therefore suspensions should be diluted 1:100 in broth medium.

A 96 well microtitre plate was labeled with the appropriate antibiotic dilutions.75 µl of each antibiotic dilution was added to all the rows of wells.75 µl of ATCC *E. coli* 25922 was added to the first row followed by the isolates to be tested in the subsequent rows.

Inoculated and uninoculated wells of antibiotic-free broth were included. The first

control was to check the adequacy of the broth to support the growth of the organism; the second was for check of sterility. The plates were covered with lid and incubated at 35-37°C for 18- 20 hours. MIC endpoint is the lowest concentration of antibiotic, at which there is no visible growth of the bacteria.

The MIC breakpoints for Meropenem against *Acinetobacter* :4 - susceptible, 8 - intermediate and 16 - resistant (Clinical and Laboratory Standards Institute, 2013).

Results and Discussion

The total number of patients selected for the study was 100, out of which 68% were males and 32% were females.

The highest incidence was seen in the age group of 41-60 years (44%) followed by 61-80 years (38%), 21-40 years (12%) and 81-100 years(6%).

The incidence of *Acinetobacter* causing Ventilator associated pneumonia was found to be 31%.

Among the 31 patients with *Acinetobacter* VAP, 74.19% were males and 25.81% were females.

The highest incidence was recorded in the 61-80 years age group (41.94%) followed by 41-60 years age group (35.48%), 21-40 years (12.91) and 81-100 years (9.68%). *Acinetobacter baumannii* was the causative agent in early onset VAP in 32.26% of cases and in late onset VAP in 67.74% of cases.

The maximum incidence was found in patients diagnosed with multisystem involvement (38.71%), Central nervous system disorders (35.48%), Kidney disorders (16.13%), Cardiovascular disorders (3.23%) and Others (poisoning, carcinoma, road traffic accidents) in 6.45% of cases. Diabetes was associated with *Acinetobacter* VAP in 16.13% of cases, Hypertension in 29.03%, both diabetes and hypertension in 29.03% and no comorbidities in 25.81% of cases.

Acinetobacter baumannii was isolated as a single organism in 16.13% of early onset VAP and 35.48% of late onset VAP. It was isolated with other organisms, *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Staphylococcus aureus* in 16.13% of early onset VAP and 32.26% of late onset VAP.

In the case of early onset VAP, maximum resistance was observed to Amikacin, Cotrimoxazole and Ciprofloxacin followed by Ceftazidime, Ceftriazone. Among Carbapenems, 50% resistance to Imipenem and 60% to Meropenem were noted. All the isolates were sensitive to Colistin.

In late onset VAP, maximum resistance was noted among Cotrimoxazole, Amikacin and Ciprofloxacin. Imipenem resistance was noted in 61.9 % of isolates and Meropenem resistance in 57.14%. None of the isolates were resistant to Colistin.

The biofilm estimation by microtitre plate method showed 54.84% of isolates to be strongly adherent, 32.26% of isolates to be moderately adherent, 6.45% to be weakly adherent and 6.45% of isolates were non adherent.

Minimum inhibitory concentration determination by micro broth dilution method showed that 12 isolates (38.71%) were sensitive and 19 isolates (61.29%) were resistant. Compared to disk diffusion method, MIC testing identified one more resistant isolate. Ventilator associated pneumonia is the most important nosocomial infection in the Intensive care unit. It leads to increased

mortality and associated with increased duration of mechanical ventilation and hospital stay (Chaari *et al.,* 2013).

Acinetobacter baumannii is a significant cause of nosocomial pneumonia especially in intubated patients. Its capacity to survive adverse environmental conditions and upregulate resistance determinants has made it a successful pathogen in hospitals (Cisneros-Herreros *et al.,* 2005).

The present study was done at a tertiary care hospital to know the incidence, characteristics and antibiotic sensitivity pattern of *Acinetobacter baumannii* involved ventilator associated pneumonia.

The total number of patients selected for the study was 100 after applying the inclusion and exclusion criteria, out of which 68% were males and 32% were females.

The highest incidence was seen in the age group of 41-60 years (44%) followed by 61-80 years (38%), 21-40 years (12%) and 81-100 years(6%).

Incidence of VAP

The incidence of *Acinetobacter* causing Ventilator associated pneumonia was found to be 31%.

The present study was on par with similar studies by *Ebrahimi et al.,* and *Japoni et al.,* but a study by *Bagheri Nesami et al.,* showed a higher incidence of 57.83%

Gender distribution of *Acinetobacter* VAP cases

Among the 31 patients with *Acinetobacter* VAP, 74.19% were males and 25.81% were females.

In similar studies, higher incidence was noted in males which were comparable to our study.

Age distribution of *Acinetobacter* VAP cases

The highest incidence was recorded in the 61-80 years age group (41.94%) followed by 41-60 years age group (35.48%), 21-40 years (12.91) and 81-100 years (9.68%).

Baraibar et al., in their study observed 12.5% of VAP cases above 60 years. The mean age was 47.8 ± 21.7 years for *Acinetobacter* VAP group according to a study by *Di Bonita et al.,* The mean± SD age of these patients was 59.18:±:18.72 years in a study by (Baraibar *et al.,* 1997).

Hortal et al., has reported old age as a risk factor for ventilator associated pneumonia in his study.

This is because of their immunocompromised state and the mucociliary clearance efficiency is also decreased (Hortal *et al.,* 2009).

Critically ill patients have impaired phagocytosis and behave as immunosuppressed even before the emergence of nosocomial infection.

This is due to the actions of the anaphylatoxin, C5a, which impairs neutrophil phagocytic activity (Morris *et al.,* 2009).

Recently, a combined dysfunction of T-cells, monocytes and neutrophils has been noted to predict nosocomial infection (Morris *et al.,* 2013).

Also *Acinetobacter baumannii* affects the immunocompromised and the chronically ill patients which accounts for the reason cases > 60 years were involved (Al-Anazi *et al.,* 2012).

Fig.1

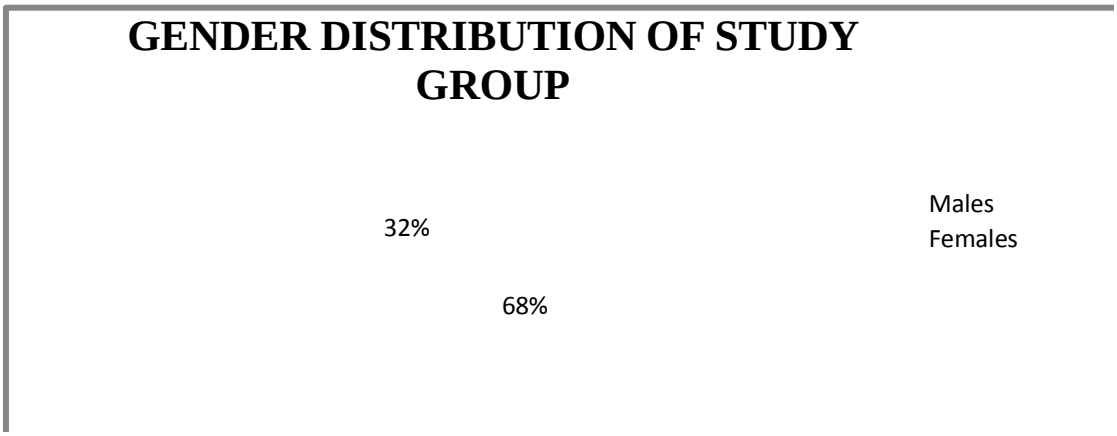
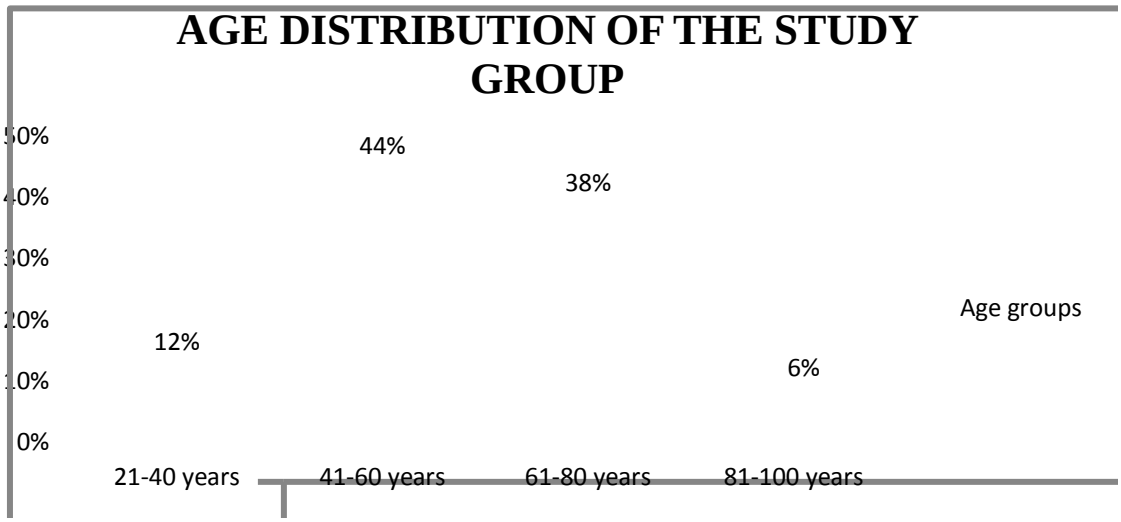


Fig.2



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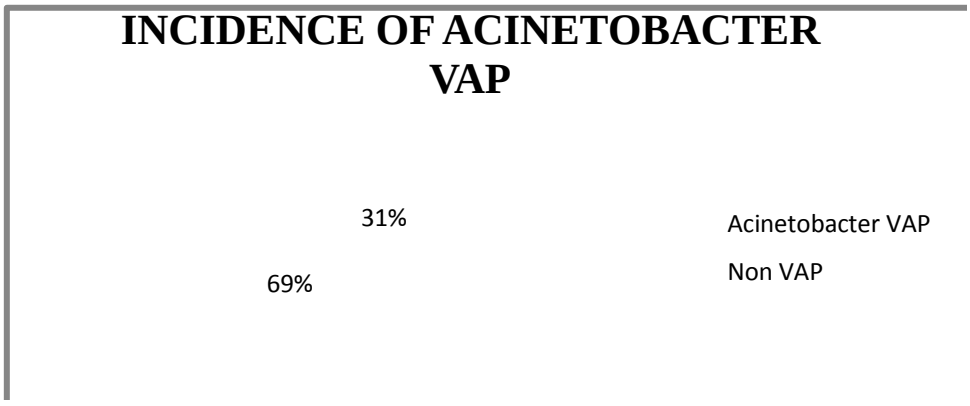

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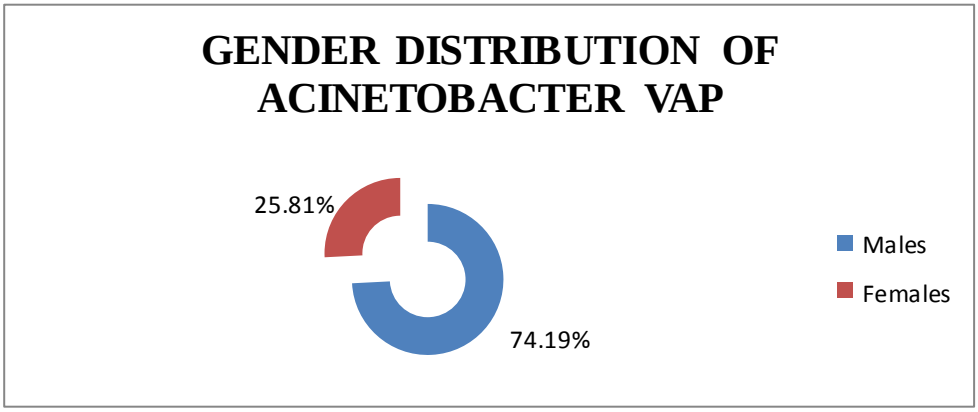

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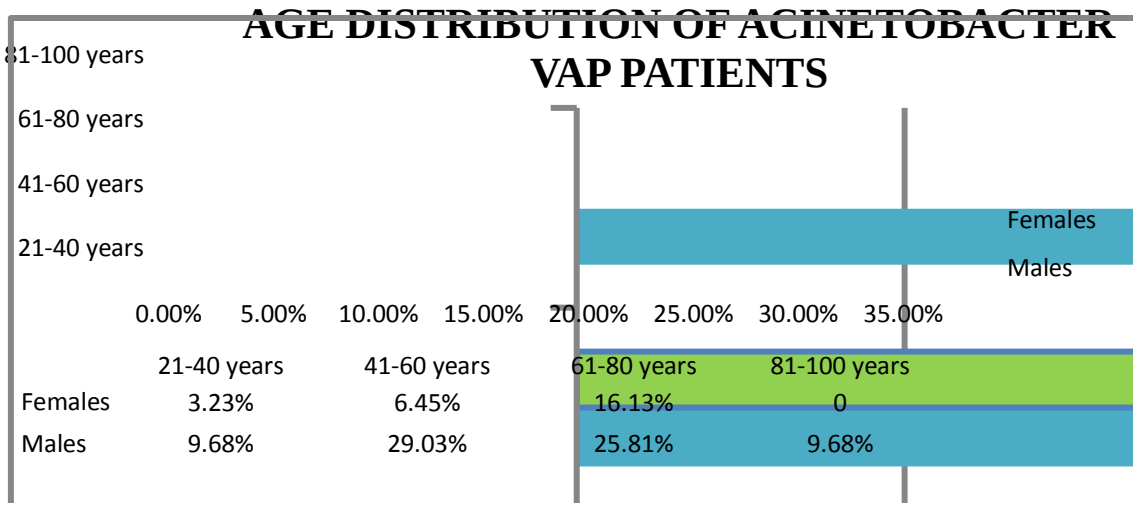

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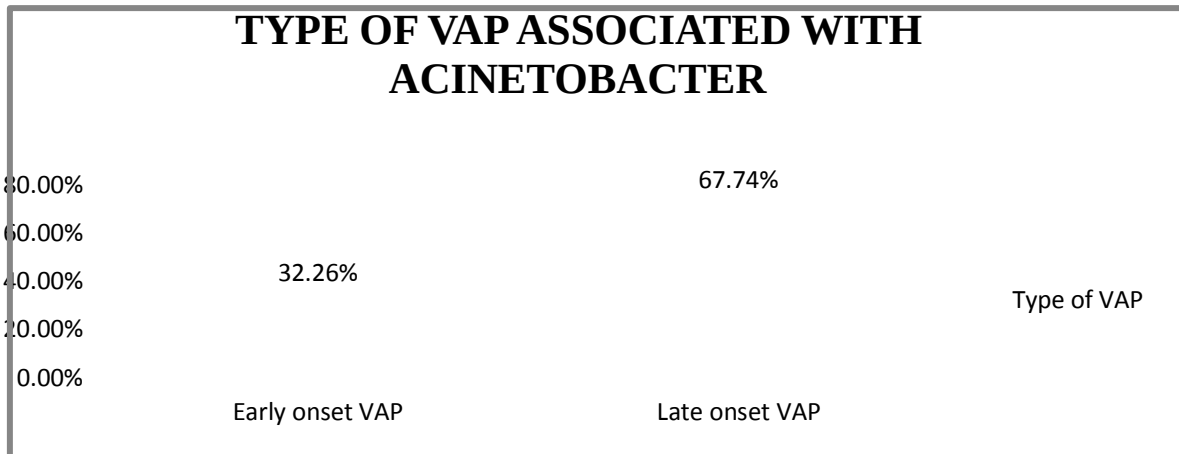

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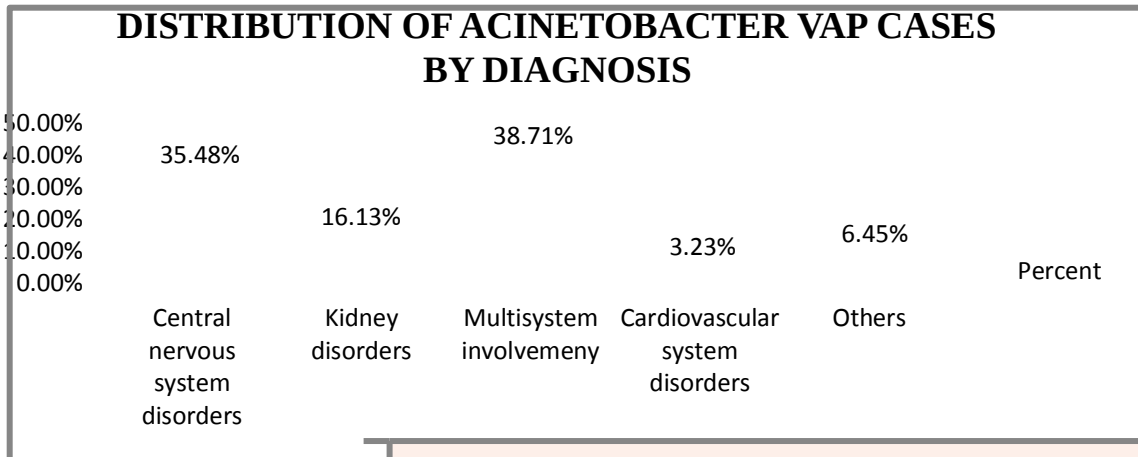

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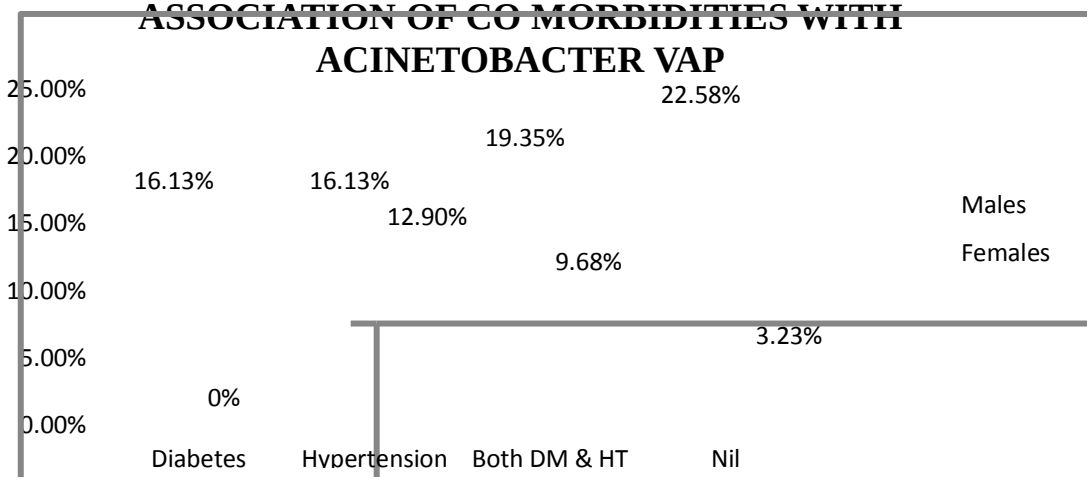

Fig.9

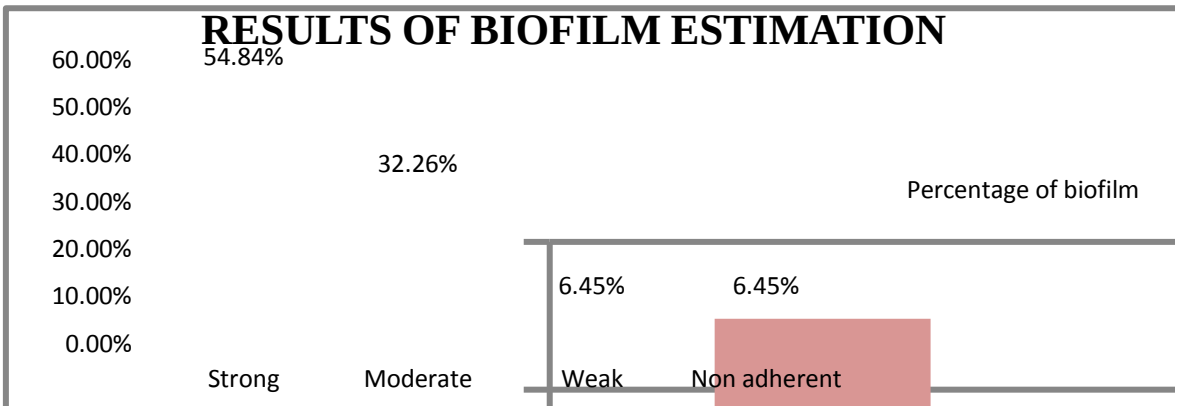

Table.1 Association of *Acinetobacter* VAP to microbial etiology

Type of VAP	Monomicrobial		Polymicrobial	
	N	%	N	%
***Acinetobacter* early onset VAP**	5	16.13%	5	16.13%
***Acinetobacter* late onset VAP**	11	35.48%	10	32.26%
Total	16	51.61%	15	48.39%

Table.2 Antimicrobial resistance in *Acinetobacter baumannii*

Antibiotics	Early onset VAP		Late onset VAP	
	N=10	**%**	**N=21**	**%**
Ceftazidime (30µg)	7	70%	17	80.95%
Ceftriaxone (30µg)	7	70%	16	76.19%
Cefepime (30µg)	6	60%	14	71.43%
Cefoperazone Sulbactam (75/30µg)	5	50%	16	76.19%
Piperacillin Tazobactam (100/10 µg),	6	60%	15	71.43%
Amikacin (30µg)	8	80%	18	85.71%
Ciprofloxacin (5µg)	8	80%	18	85.71%
Cotrimoxazole (1.25/23.75 µg)	8	80%	19	90.48%
Imipenem (10 µg)	5	50%	13	61.9%
Meropenem (10 µg)	6	60%	12	57.14%
Tigecycline (15µg)	2	20%	5	23.81%
Colistin (10µg)	0	0	0	0

Table.3 MIC Testing of meropenem by broth microdilution method

Organisms	0.25	0.5	1	2	4	8	16	32
ATCC *Escherichia coli*	-	S	-	-	-	-	-	-
Acinetobacter baumannii	-	-	7	5	-	-	16	3

Table.4 Outcomes of *Acinetobacter baumannii* infection in early and late onset VAP

OUTCOME	EARLY ONSET VAP	LATE ONSET VAP
Ventilator days	8.1 ± 4.43 days	11.62 ± 3.69 days
ICU days	9.9 ± 5.22 days	12.81 ± 3.83 days
Hospital days	13.6 ± 8.36 days	17.24± 9.77 days

Interpretation of biofilm production by microtitre plate method

S. No	OD Value	Biofilm
1.	OD < ODc	Non-adherent
2.	ODc<OD< 2ODc	Weak
3.	2ODc<OD<4ODc	Moderate
4.	> 4 ODc	Strong

Preparation of dilutions of antimicrobial agents

Step	Concentration(µg/ml)	Volume (ml)	CAMHB (ml)	Final concentration(µg/ml)
1	512	1	1	256
2	512	1	3	128
3	512	1	7	64
4	64	1	1	32
5	64	1	3	16
6	64	1	7	8
7	8	1	1	4
8	8	1	3	2
9	8	1	7	1
10	1	1	1	0.5
11	1	1	3	0.25
12	1	1	7	0.125

Incidence of VAP

Author	Incidence	Reference
Shete et al.,	11.3%	(17)
Baraibar et al.,	8.1%	(18)
Ebrahimi et al.,	35%	(19)
Japoni et al.,	34.5%	(20)
Bagheri-Nesami et al.,	57.83%	(21)
Present study	31%	

Gender Distribution of *Acinetobacter* VAP cases

Author	Males	Females	Reference
Tsakiridou et al.,	55%	45%	(22)
Baraibar et al.,	66.2%	33.8%	(18)
Castro et al.,	65.4%	34.6%	(23)
Present study	74.19%	25.81%	

Type of VAP

Acinetobacter baumannii was the causative agent in early onset VAP in 32.26% of cases and in late onset VAP in 67.74% of cases.

Ina study by *El- Saed et al.,* 26.5% of late onset VAP was due to *Acinetobacter baumannii* and early onset VAP was caused by *Haemophilus* spp and *Streptococcus pneumoniae*. But in our study, *Acinetobacter baumannii* was the causative agent in both types of VAP (El-Saed *et al.,* 2013).

In another study, *Acinetobacter* caused early onset VAP in 25.93% of cases and late onset VAP in 74.07% of cases which is similar to our study (Sabrina *et al.,* 2015).

Diagnosis of VAP patients

The maximum incidence was found in patients diagnosed with multisystem involvement (38.71%), Central nervous system disorders (35.48%), Kidney disorders (16.13%), Cardiovascular disorders (3.23%) and Others (poisoning, carcinoma, road traffic accidents) in 6.45% of cases.

Baraibar et al., identified cardiac arrest, ARDS, coma, heart disease, head trauma and neurosurgery as the triggers favouring *Acinetobacter* ventilator associated pneumonia (Baraibar *et al.,* 1997).

In a study by *Tsakiridou et al.,* Cardiac disorders-5%, Neurologic disorders-18%, Respiratory failure-41%, Head trauma-9%, were the underlying disorders in *Acinetobacter* VAP patients (Tsakiridou *et al.,* 2014). *Shete et al.,* identified head trauma (28.57%), cerebral haemorrhage (14.29%) and COPD (57.14%) as the associated clinical conditions in *Acinetobacter* VAP patients (Shete *et al.,* 2010). *Ergul et al.,* identified chronic disorders and neurological disorders as the risk factors for the development of VAP (Ergul *et al.,* 2017). This is because in neurological disorders there is loss of swallowing reflex and pooling of secretions which is a pre requisite for VAP (Vijai *et al.,* 2016).

Association of co-morbidities with VAP

Diabetes was associated with *Acinetobacter* VAP in 16.13% of cases, Hypertension in 29.03%, both diabetes and hypertension in 29.03% and no comorbidities in 25.81% of cases. In a study by *Di Bonita et al.,* diabetes was associated with *Acinetobacter* VAP in 20% of cases and Hypertension in 50% of cases (Di Bonito *et al.,* 2012). *Whiles et al.,* found that the presence of comorbidities in any patients admitted in ICU led to increased stay in the ICU and hospital (Bristol *et al.,* 2016).

Acinetobacter baumannii was isolated as a single organism in 16.13% of early onset VAP and 35.48% of late onset VAP. It was isolated with other organisms, *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Staphylococcus aureus* in 16.13% of early onset VAP and 32.26% of late onset VAP.

Antimicrobial susceptibility of *Acinetobacter baumannii* isolates in early and late onset VAP

In the case of early onset VAP, maximum resistance was observed to Amikacin, Cotrimoxazole and Ciprofloxacin followed by Ceftazidime, Ceftriazone. Among Carbapenems, 50% resistance to Imipenem and 60% to Meropenem were noted. All the isolates were sensitive to Colistin.

In a study by *Shete et al.,* maximum resistance was observed to third generation Cephalosporins, Amikacin and Cefepime but

all the isolates were sensitive to carbapenems (Shete *et al.,* 2010).

In late onset VAP, maximum resistance was noted among Cotrimoxazole, Amikacin and Ciprofloxacin. Imipenem resistance was noted in 61.9 % of isolates and Meropenem resistance in 57.14%. None of the isolates were resistant to Colistin.

Safari et al., documented 94% resistance to Meropenem and 85% resistance to Imipenem among *Acinetobacter baumannii* isolated from patients in ICU wards (Safari *et al.,* 2013).

Hasani et al., reported 100% resistance to Carbapenems and documented that Tigecycline and Colistin were the spare drugs to treat *Acinetobacter* VAP patients (Hasanin *et al.,* 2016).

Multi drug resistance (MDR) is defined as resistance to at least one antimicrobial agent in three or more antimicrobial categories, extremely drug resistant (XDR), resistant to all antibiotics tested except one, Pan drug resistant (PDR), resistant to all antibiotics tested (Magiorakos *et al.,* 2012). In the present study, 26(83.87%) isolates were multidrug resistant. In a study by *Nowak et al.,* 32% (of isolates were MDR, 34% were XDR and 31% were PDR. Fortunately in our study, none of the isolates were XDR or PDR (Nowak *et al.,* 2017).

Biofilm production by *Acinetobacter* isolates

Bacterial biofilms have a role in the pathogenesis of VAP. They are aggregates of bacteria within an extrameric polymeric substance. Their determination is important because they are involved in microbial persistence and relase of VAP (Gil-Perotin *et al.,* 2012). The biofilm estimation by microtitre plate method showed 54.84% of isolates to be strongly adherent, 32.26% of isolates to be moderately adherent, 6.45% to be weakly adherent and 6.45% of isolates were non adherent. In a study by *Rao et al.,* 62% of *Acinetobacter* VAP isolates were strong biofilm producers (Rao *et al.,* 2008). In a study by *Mulla Summaiya et al.,* 60% of *Acinetobacter* VAP isolates were strong biofilm producers, 13.33% were moderate biofilm producers and 26.67% were weak biofilm producers (Summaiya and Urmi, 2012).

MIC testing of *Acinetobacter* isolates

Antimicrobial susceptibility testing is done in the laboratory for detection of anti -microbial resistance and to select the optimum antibiotic for treatment.

It can be done by Kirby Bauer's disk diffusion method but it is less sensitive. So Minimum inhibitory concentration testing (MIC) by microbroth dilution method was done for Meropenem which was widely used in our ICU for treatment of *Acinetobacter* VAP. The results showed that 12 isolates (38.71%) were sensitive and 19 isolates (61.29%) were resistant. Compared to disk diffusion method, MIC testing identified one more resistant isolate (Reller *et al.,* 2009).

Outcome of *Acinetobacter* VAP

The ventilator days was found to be 8.1 ± 4.43 days in early onset VAP and 11.62 ± 3.69 days in Late onset VAP.

The length of ICU stay was found to be 9.9 ± 5.22 days in early onset VAP and 12.81 ± 3.83 days in Late onset VAP.

The total hospital stay was 13.6 ± 8.36 days in early onset VAP and 17.24± 9.77 days in Late onset VAP.

The median Ventilation days was 7(6–11) and the Length of ICU stay 15(11–34) in a study by (Hasanin *et al.,* 2016).

The mean ICU stay was 25 ± 17 days in a study by (Tsakiridou *et al.,* 2014).

Mortality

The mortality rate in case of early onset VAP caused by *Acinetobacter* was 30% and 38.1% in the late onset VAP. Similar studies on *Acinetobacter* VAP had mortality rates of 54% by (Gurjar *et al.,* 2013) 68% by (Tsakiridou *et al.,* 2014) and 53.3% by (Hasanin *et al.,* 2016). Ventilator associated pneumonia is a common nosocomial infection in the ICU. It leads to increased mortality and increased health care costs. And when VAP is caused by MDR *Acinetobacter*, the effects are more pronounced. The prevention of VAP should be collaborative effort by the infection control team, ICU physicians and the nursing care team The preventive strategies of VAP include following the ventilator care bundles which comprises elevation of the head end of the bed, daily sedation holidays, early possible extubation, peptic ulcer and deep venous thrombosis prophylaxis.

Strict infection control measures, antibiotic stewardship programs, frequent ICU surveillance and antimicrobial resistance tracking are essential to eliminate dangerous MDR *Acinetobacter* infections in the ICU (Wip and Napolitano, 2009; Keyt *et al.,* 2014).

Source of funding: None

Conflict of interest: None

Acknowledgement

The author would like to thank Dr. Radha Madhavan for her valued support and suggestions and the ICU staff team for the immense help.

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How to cite this article:

Nanthini Devi, P. and Gomathi, S. 2018. Multi Drug Resistant *Acinetobacter* Ventilator Associated Pneumonia in a Tertiary Care Hospital. *Int.J.Curr.Microbiol.App.Sci.* 7(04): 1448-1463. doi: https://doi.org/10.20546/ijcmas.2018.704.164