IJABR

International Journal of Advanced Biotechnology and Research (IJABR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-10, Issue-1, 2019, pp85-93
http://www.bipublication.com

Research Article

Evaluation of Empirical Therapy in Ventilator Associated Pneumonia in ICU in a tertiary care hospital

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[Received: 20/12/2018; Accepted: 12/01/2019; Published: 13/01/2019]

ABSTRACT

Ventilator Associated Pneumonia is one of the common and fatal among Nosocomial infections that requires in time, appropriate and adequate antibiotic therapy. Mortality rates are greater in patients with ventilator associated pneumonia; the chances of mortality are maximum in bed ridden immunocompromised patients in ICU.

Objective: The objective of this study was the evaluation of Empirical therapy in suspected VAP cases in ICU patients.

Methods: This was a prospective study involving 58 patients on mechanical ventilation with suspected VAP in a tertiary care hospital.The method involved pathogen identification, Antibiotic Sensitivity testing, hepatic, renal and hematological profiles and monitoring of Arterial blood gases of the patient. Pathogens from tracheal aspirates of the patients were subjected to commonly used antibiotics for their antibiograms. The prescribed antibiotics were evaluated by routine culture/sensitivity testing of tracheal aspirates and each patient was followed up to be assessed for the treatment progress. Effect of Antibiotic was evaluated for seven days by maintaining the record of the vital parameters of patients such as Temperature of the patient, PaO2, effect on leukocyte count, and from evaluation of LFTs and RFTs of the patient and chest radiograph obtained at the seventh day and keeping in view the overall disease status of the patient. Other outcomes were the mortality in these patients and the impact of inadequate empirical therapy on patient mortality. Also, to study the contribution of various risk factors upon VAP prognosis.

Results: The microbial flora and their resistancepattern is a matter of great concern for adopting the strict infection control measures, hospital wise antibiotic policy formulation to reduce morbidity, mortality and to prevent the emergence of resistant pathogens.

Most of the patients remained febrile. Changes were observed in the level of liver functional enzymes and in the values of renal functional tests. Leucocytes count in most of the patients remained either less than 4000 or greater than 11000 indicating persistence of infection. High mortality was observed in patients suspected for VAP. Major factor that caused patients mortality was the treatment failure due to inadequate antibiotics, utilization of irrational combinations of already resistant antibiotics.

Cross contamination, unhygienic practices by health personnel's and lack of adequate guidelines for antibiotic utilization in the ICU were the important contributors for development of VAP and other lower respiratory tract nosocomial infections. Methicillin sensitive *Staphylococcus aureus* and *E.coli* were found to be the most common pathogens involved. Empirical antibiotic therapy was found inappropriate in 53.4% of cases.

Conclusions: In this study, there was a high incidence of infection with resistant bacteria and inappropriate initial antibiotic therapy. Treatment failure due to inadequate antibiotics caused most mortality. Organ deterioration was also found to contribute to overall mortality in mechanically ventilated patients.

Keywords: ICU: Intensive care unit, VAP: Ventilator associated Pneumonia, PaO2: Partial pressure oxygen, LFT: Liver functional test, RFT: Renal Functional test.

INTRODUCTION:

Ventilator associated pneumonia is a nosocomial infection occurring with high frequency in bedridden patients upon mechanical ventilation (Japoni et al., 2011; Park, 2005)[15, 20]. It is not present at the time of admission but develops after 48hrs of intubation (Young and Ridley, 1999; Chaster, 2005; Park, 2005; Shaikh et al., 2008; Chandler and Hunter, 2009) [23, 4, 20, 19, 6]. There is no golden standard yet for its diagnosis but any patient upon mechanical ventilation greater than 48hrs could be suspected for VAP (Chandler and Hunter, 2009) [6]. Most of the antibiotics prescribed in the intensive care settings are mostly for nosocomial lower respiratory tract infections (Goldstein et al., 2006; Chastre et al., 2006) [12, 5]. Antibiotic selection widely depends upon the pathogen identified and culture sensitivity reports (Joost et al., 2010) [14]. At this point there is a need for larger, well designed clinical studies. Usually in early onset VAP most of the bacteria are sensitive to most antibiotics (Chandler and Hunter, 2009) [6] but delay in treatment or inadequate treatment increases the chances of emergence of MDR pathogens and thus complicates the treatment (Kollef and Fraser, 2001; Park, 2005) [16, 20]. Further the emergence of MDR pathogens is more in ICU patients which are immunocomprimised (Fridkin and Gaynes, 1999) [11]. Late onset VAP mostly involves MDR pathogens which are difficult to treat and increases the mortality rate (Aarts et al., 2008) [1]. Identification of Pathogen helps to choose more effective antibiotic and sensitivity testing helps to choose the targeted antibiotic thus allowing efficient management (Michel et al., 2005) [17]. Risk factors involved are the duration of mechanical ventilation, handling of the patient by nurses and health care personnels, history of frequent antibiotic usage – all of these are independent risk factors associated with VAP (Chastre, 2005)[4]. Usually increased mortality is observed in severely ill patients (Eachempati et al., 2009; Chandler and Hunter, 2009) [10, 6]. The Ventilator associated pneumonia has been poorly studied in Pakistan, but is likely to be significant problem, with resulting increased morbidity and mortality in the intensive care unit population. Less work has been done in our country to assess the frequency and etiology of nosocomial lower respiratory tract infections in patients admitted to intensive care unit as the causes are many and may vary by hospital, patient population, and type of ICU (Joseph et al., 2010) [13], thus emphasizing the need for timely, local surveillance data (Chastre, 2005; Park, 2005) [4, 20]. The study was designed to fulfill the following objectives:

1- To isolate and identify the bacterial pathogens from ventilator-associated infections in Surgical ICU patients.
2- To determine the antibiotic susceptibilities of bacterial isolates invitro and the trends in antibiotic resistance developed by pathogens from ventilator-associated infections.
3- To assess the associated risk factors
4- To evaluate the extent of organ deterioration.

METHOD:

A prospective study was performed to evaluate the resistance pattern of bacterial pathogens in ICU patients suspected for VAP to commonly used antibiotics. The method involved pathogen identification, Antibiotic Sensitivity testing, hepatic, renal and hematological profiles and monitoring of Arterial blood gases of the patient and frequent culturing of tracheal aspirates to

evaluate the response for antibiotic therapy provided. Pathogens from tracheal aspirates of the patients were subjected to commonly used antibiotics for their antibiograms. Effect of antibiotic was evaluated for seven days by recording the parameters of patients such as Temperature of the patient, PaO2/FiO2 ratio, effect on leukocyte count, and monitoring of LFTs and RFTs of the patient for the possible organ deterioration. Other outcomes were the mortality in these patients and risk factors that result in overall high mortality among VAP patients.

A total of 90 morbid samples of tracheal aspirates were collected with the help of a trained physician. This process was performed on the day-one of the insertion of endotracheal tube. These specimens were collected with sterilized disposable Nelton catheters attached to the aspirator. The specimens were immediately transferred to the microbiological laboratory and subjected to bacteriological examination. The collected samples were cultured to check the evidence of any previous bacterial infection. The patients having negative results on the basis of their initial cultures were further included for the study and the cases with positive cultures were excluded from the study.A second sample was collected after 48 hours of mechanical ventilation for suspected VAP cases. After seven days of the second sample a third sample was taken to further assess the response of antibiotic therapy and there outcome. Isolation of microbes was achieved by agar plate inoculation method. Identification and confirmation of respiratory tract isolates were performed following the standard protocols as per Bergey's Manual of Determinative Bacteriology, basic parameters for identification of bacteria were based on morphological colonial characteristics, microscopic features and biochemical profiles.

Antibiotic susceptibility profiles were determined by Disc Diffusion Method (Barry, 1991) [2] following the guidelines of National Committee for Clinical Laboratory Standards. (NCCLs, 1994; NCCLs, 2001) [18]. Antibiotic sensitivity was performed against different antibiotics used in the intensive care setting: Piperacillin+Tazobactam, Amoxycillin+Clavulanic acid, Meropenem, Ceftriaxone Sodium, Cefuroxime, Cefipime, Gentamicin, Amikacin, Tetracycline, Doxicyclin, Ciprofloxacin, Sparfloxacin, Moxifloxacin, Clarithromycin, Co-trimoxazole. The antibiotic susceptibility pattern of all the bacterial pathogens was determined by Kirby-Bauer Disc Diffusion Technique (Barry, 1991) [2].

To assess the safety of empirical medication provided the liver and renal functional tests were performed for each patient on the day of admission in ICU and on the last day of the treatment follow-up to access the possible liver and renal damage or change in the liver and renal functional status of these immunosuppressed patients.

RESULTS:

From a total of 90 samples, 58 were found positive for the isolation of bacterial pathogens of VAP. The incidence density of VAP among the patients admitted to ICU was found to be 64%. Patients were suspected for nosocomial lower respiratory tract infection considering Clinical Pulmonary infectious score chart. Out of 58 patients, 5(8.6%) had CPIS 6, 41(70.7%) had CPIS 6-8 and 12(20.7%) had CPIS 9-10 which were found consistent for the diagnosis of pneumonia.

Microbiological analysis of endotracheal samples from the patients suffering from ventilator-associated pneumonia revealed the presence of various types of bacteria. Of the 90 endotracheal samples, 58 (65%) samples were culture positive and remaining 32 (35%) samples were culture negative. A total of 58 bacterial pathogens were recovered from these culture positive samples.On bacteriological examination 18(31%) isolates of Methicillin Sensitive Staphylococcus aureus, 3(5.2%) isolates of Methicillin Resistant Staphylococcus aureus, 2(3.4%) isolates of Streptococcus, 9(15.5%) isolates of Pseudomonas, 5(8.6%) isolates of Acinetobacter, 5(8.6%)

isolates of Klebsiella, 12(20.7%) isolates of Escherichia, 2(3.4%) isolates of Enterobacter and 2(3.4%) isolates of Proteus were characterized.

Table 1: Pathogens Isolates of VAP No. of culture positive cases =58

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	MSSA	18	31.0	31.0	31.0
	MRSA	3	5.2	5.2	36.2
	E.Coli	12	20.7	20.7	56.9
	Pseudomonas Spp.	9	15.5	15.5	72.4
	Klebsiella Spp.	5	8.6	8.6	81.0
	Acinetobacter spp.	5	8.6	8.6	89.7
	Streptococci spp.	2	3.4	3.4	93.1
	Enterobacter spp.	2	3.4	3.4	96.6
	Proteus spp.				
	9.00	2	3.4	3.4	100.0
	Total	58	100.0	100.0	

Frequency of VAP In-relation to Age

Out of 58 patients, 10.3% were of the age group ≤ 20, 31% of the age group 21-30, 13.8% were of age between 31-40, 17.2% were between 41-50 and 27.6% were of age group > 50. (Fig. 1)

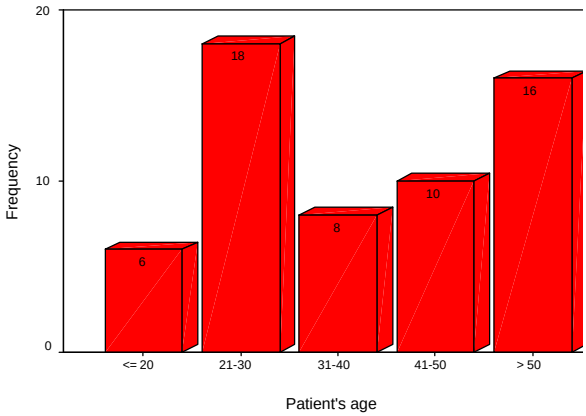

Fig 1: Frequency of Patients in Relation to Age

Frequency of VAP In-relation to Gender

Among selected patients 69% were males and 31% were females. (Fig.2)

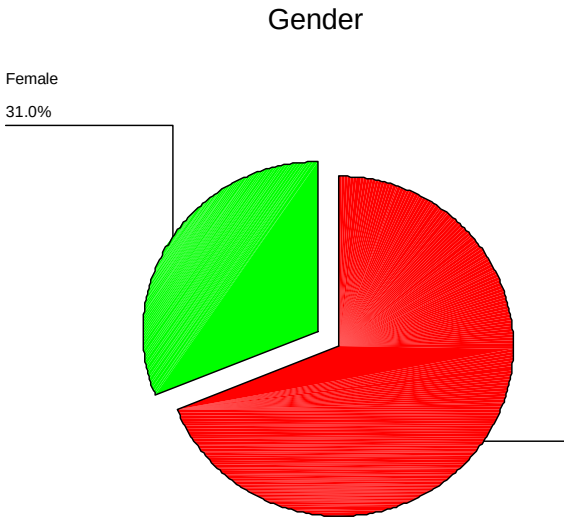

Fig 2: Frequency of Patients in Relation to Gender

Previous Exposure to Antibiotics Regarding previous exposure to antibiotics (within 3 months) it was inferred that the previous exposure to these antibiotics was found to be the most important contributing factor for the emergence of most resistant bacteria as causative agents of life-threatening VAP. Of the 58 patients, 30 (51.7%) had received Augmentin and 12 (20.7%) Clarithromycin, 8 (13.8%) Cephalexin, 5 (8.6%) Ceftazidime and 3 (5.2%) patients had received Flagyl.(Fig. 3)

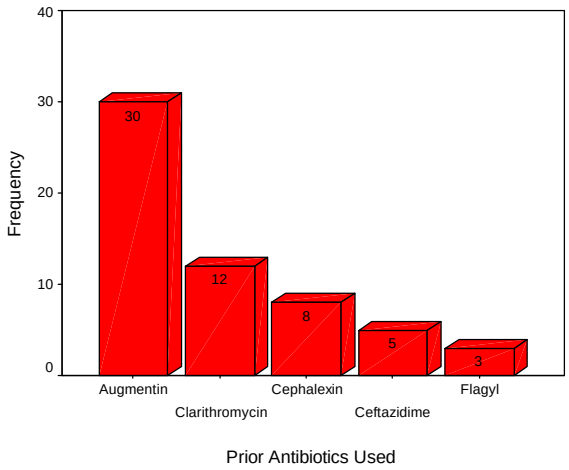

Fig 3: Frequency of Patients in Relation to Prior Exposure to Antibiotics

Antimicrobial Sensitivity Patterns:

These etiological agents of nosocomial infection were subjected to sensitivity testing for their antibiotic susceptibility patterns.

Antibiogram of MSSA & MRSA:

MSSA showed maximum resistance to Meropenem(77.8%) but was found highly sensitive to Tazocin, Fucidin and Linezolid. MRSA being multiple drug resistant pathogen showed complete resistance to most antibiotics such as Augmentin, Ceftazidime, Cefeperazone, Meropenem and Amikacin but was found sensitive to Tazocin, Tobramycin, Moxifloxacin, Fucidin, Linezolid, Tigecyclin and Vancomycin.

Antibiogram of Streptococci: Streptococci isolates showed maximum resistance to Ampicillin, erythromycin, Ciprofloxacin, and Fucidin but were highly sensitive to Meropenem, moxifloxacin, Linezolid and Tigecyclin.

Antibiogram of Pseudomonas Isolates: Pseudomonas isolates showed maximum resistance to Ceftriaxone, Ceftazidime, Cefotaxime, and Sparfloxacin. High sensitivity was observed for Tazocin, Imipenem, Cefipime& Amikacin.

Antibiogram of Klebsiella:

Kleibsiella showed maximum resistance to Augmentin, Cefotaxime, Sparfloxacin and Co-trimoxazole. High sensitivity was found for Tazocin, Tobramycin and Tigecyclin.

Antibiogram of Acinetobacter:

Acinetobacter isolates, another MDR pathogen resistant to many antibiotics thus presented great problems in antibiotic selection. Acinetobacter isolates were found highly resistant to Augmentin, Cefotaxime, Cefuroxime, Cefeperazone and Ciprofloxacin. High sensitivity was observed for Tazocin, Tigecyclin, Doxicyclin and Amikacin.

Antibiogram of E. Coli:

E.coli showed complete resistance to Augmentin, maximum resistance to Cefotaxime and moxifloxacin but were found highly sensitive for Tazocin, Sparfloxacin, Meropenem and Tigecyclin.

Antibiogram of Enterobacter:

Enterobacter isolates were showed maximum resistance against Augmentin, Ampicillin and Cefeperazone but was found sensitive against Ceftriaxone, Ceftazidime and Cefipime and showed maximum sensitivity for Meropenem and Tigecyclin.

Antibiogram of Proteus:

All Proteus isolates were highly resistant to Augmentin, Ciprofloxacin, Moxifloxacin and Sparfloxacin but showed sensitivity against Cefuroxime, Ceftriaxone, Cefeperazone, Cefipime, Tobramycin and Amikacin.

Table 2: Percentage Resistance of VAP Isolates

	MSSA (18)	MRSA (3)	Streptoc occi (2)	Pseudo monas (9)	Kleibsi ella (5)	Acineto Bacter (5)	E.Coli (12)	Entero Bacter (2)	Proteu s (2)
Ampicillin	16.6%	-	99.9%	-	-	-	-	99.9%	-
Cefuroxime	-	33.3%	50%	-	-	60%	-	-	50%
Cefotaxime	11.1%	-	-	44.4%	80%	60%	83.3%	50%	-
Ceftriaxone	-	-	-	66.6%	60%	-	41.6%	-	50%
Cefoperazone	5.5%	99.9%	50%	33.3%	40%	60%	-	99.9%	50%
Ceftazidime	44.4%	99.9%	-	55.5%	-	-	16.6%	50%	-
Cefipime	-	-	-	22.2%	-	40%	-	50%	50%
Erythromycin	-	66.6%	99.9%	-	-	-	-	-	-
Clarithromycin	11.1%	33.3%	50%	-	-	-	-	-	-
Augmentin	11.1%	99.9%	50%	-	80%	80%	99.9%	99.9%	99.9%
Imipenem	-	-	-	22.2%	-	-	-	-	-
Meropenem	77.7%	-	0%	-	-	-	16.6%	0%	-
Amikacin	16.6%	99.9%	50%	22.2%	40%	20%	8.3%	50%	50%
Tobramycin	27.7%	0%	50%	44.4%	20%	-	50%	-	50%
Tazocin	0%	0%	-	22.2%	20%	20%	16.6%	50%	-
Ciprofloxacin	16.6%	33.3%	99.9%	55.5%	60%	60%	-	50%	99.9%
Moxifloxacin	22.2%	0%	0%	-	40%	-	-	-	99.9%
Sparfloxacin	5.5%	66.6%	50%	77.7%	80%	20%	-	50%	99.9%
Fucidin	0%	0%	99.9%	-	-	-	-	-	-
Linezolid	0%	0%	0%	-	-	-	-	-	-
Co-trimoxazole	11.1%	-	-	-	80%	-	-	-	-
Vancomycin	16.6%	0%	-	-	-	-	-	-	-
Tetracyclin	-		50%	-	-	-	-	-	-
Doxicyclin	-	-	-	-	-	20%	-	-	-
Tigecyclin	-	0%	0%	-	0%	20%	-	0%	-

The identification of local Flora and finding their sensitivity patterns help in better selection of antibiotics for empirical therapy and a better response in patients helpful to reduce morbidity and mortality and emergence of more resistant pathogens (DiCocco and Croce, 2009).

Mortality Rate Among VAP Patients

High mortality rate was observed in ICU patients having nosocomial pneumonia. Of the total 58 patients, 26 (65 %) male patients and 14 (35 %) female patients were died during the study period. Thus the mortality rate was found to be 69.0 % among the patients diagnosed with VAP.(Fig. 4)

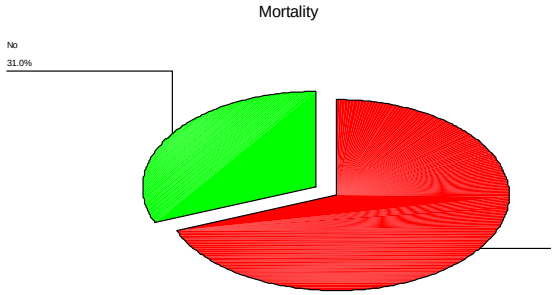

Fig 4: Mortality Rate Among VAP Patients

Evaluation of Organ Deterioration:

Frequency Distribution According to Liver Deterioration

Liver functional tests and renal functional tests were performed to assess the extent of organ deterioration in ICU patients. 32.8% have no liver deterioration, 36.2% showed mild deterioration, 22.4% had moderate deterioration and 8.6 % displayed severe deterioration. (Fig. 5)

Frequency Distribution According to Renal Deterioration

75.9% had no renal deterioration, 10.3% showed mild deterioration, 5.2% had moderate deterioration and 8.6% had severe deterioration.(Fig. 6)

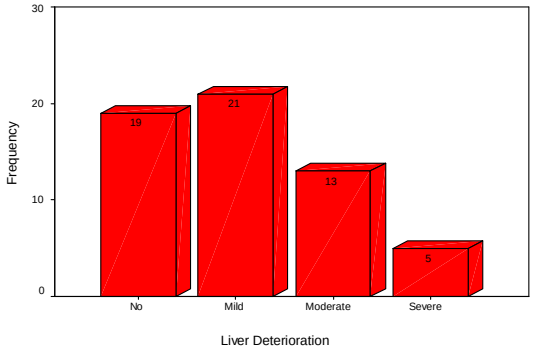

Fig 5: Frequency Distribution According to Liver Deterioration

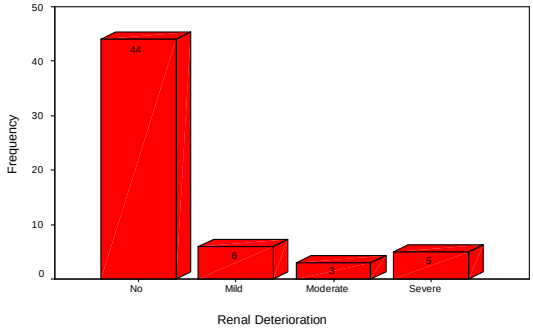

Fig 6: Frequency Distribution According to Liver Deterioration

DISCUSSION:

Microbial Patterns:

The pathogenic bacteria most frequently isolated from the patients were MSSA (Methicillin Sensitive Staphylococcus aureus) (18; 31%), E.coli (12; 20.7%), Pseudomonas isolates (9; 15.5%), Acinetobacter (5; 8.6%) and Streptococci (5; 8.6%). Other organisms isolated were MRSA (Methicillin Resistant Staphylococcus aureus) (3, 5.2%), Streptococci (2, 3.4%), Enterobacter (2, 3.4%) and Proteus (2, 3.4%). MRSA was isolated from comatose patients with multiple neuronal damage. MSSA was the most dominant pathogen isolated. A comprehensive study conducted by Park (2005) [20] revealed Pseudomonas aeruginosa as the most dominant pathogen isolated in VAP patients which in our study is the third most common pathogen isolated. Another study on Pathogens isolated from nosocomial infections reported Staphylococcus aureus as the leading pathogen isolated which is consistent with our study (Fridkin and Gaynes, 1999) [11]. Increased E.coli isolation has been reported by various studies in VAP patients as oropharyngeal aspiration is the most frequent route of entrance of these organisms into the lower respiratory tract which in our study is the second leading bacteria isolated (Ewig*et al.*, 1999) [8]. All the isolated bacteria in our study are consistent with those reported in different studies on microbiology of ventilator associated pneumonia (Park, 2005; Fradkin and Gaynes, 1999; Japoni et al., 2011) [20, 11, 15].

Antimicrobial Sensitivity Patterns:

These etiological agents of nosocomial infection were subjected to sensitivity testing for their antibiotic susceptibility patterns. MSSA showed maximum resistance to Meropenem (77.8%) but was found highly sensitive to Tazocin, Fucidin and Linezolid similar to the results reported by Vitkauskiene et al (2003) [22].

MRSA being multiple drug resistant pathogen showed complete resistance to most antibiotics such as Augmentin, Ceftazidime, Cefeperazone,

Meropenem and Amikacin but was found sensitive to Tazocin, Tobramycin, Moxifloxacin, Fucidin, Linezolid, Tigecyclin and Vancomycin. Fridkin and Gaynes (1999) [11] also explained the similar increase resistance for various antibiotics for both MSSA and MRSA and recommended Vancomycin as the suitable antimicrobial to treat MRSA infections.

Streptococci isolates showed maximum resistance to Ampicillin, erythromycin, Ciprofloxacin, and Fucidin but were highly sensitive to Meropenem, moxifloxacin, Linezolid and Tigecyclin. Streptococci still persist Intermediate sensitivity against various Beta-lactam antibiotics which was also reported by Park (2005) [20].

The increased in-vitro sensitivity of gram positive bacteria for linezolid has also been reported by different studies. Japoni*et al* (2011) [15] report 100% invitro sensitivity of Gram +ve bacteria for Linezolid and 94% sensitivity for Vancomycin which are consistent with our results.

Pseudomonas isolates showed maximum resistance to Ceftriaxone, Ceftazidime, Cefotaxime, and Sparfloxacin. Increased resistance for Fluroquinolones has also been reported by Fridkin and Gaynes (1999), Kollef and Fraser (2001) [11, 16]. High sensitivity was observed for Tazocin, Imipenem, Cefipime& Amikacin. This high sensitivity for Piperacillin-tazobactam has also been reported in various studies such as by Pfaller*et al* (2001), Bonten*et al* (1999), Kollef and Fraser (2001), Fridkin and Gaynes (1999). [21, 16, 11]

CONCLUSION:

The present study documents declining in vitro antibiotic susceptibility and development of resistance among virulent bacterial pathogens of ventilator-associated pneumonia (VAP). These bacteria developed increased resistance against commonly used antibiotics including Augmentin, Tetracycline, Ceftazidime, Ceftriaxone, Gentamicin, Erythromycin and Ciprofloxacin. The study also evidenced the emergence of resistant strains against relatively less commonly used antibiotics as was observed for Tazocin, Tobramycin, Moxifloxacin, Fucidin, Linezolid, Tigecyclin, Vancomycin, Imipenem, Cefipime and Amikacin. Clinical diagnosis of VAP yet remained a difficult task to be taken and no single technique is able to declare confirm diagnosis and multi-interventional approaches are involved making use of radiological and microbiological techniques, strict monitoring of patients vitals. Evaluation of initial antibiotic therapy (empiric therapy) is significantly important for reduction in morbidity and high mortality rate among VAP patients. It could be evaluated by the no delay in culture/sensitivity testing and routine practice of culturing of tracheal aspirates. Evaluation of possible organ deterioration that occurs in immune-suppressed patients of ICU is vital as organ deterioration; along with inadequate antibiotics is also an important contributor in patient's mortality and also essential for antibiotic dose adjustment in patients with hepatic and renal impairments.

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