Original article:

Ventilator Associated Pneumonia a challenge in intensive care unit acquired infection

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Abstract

Background: Ventilator-Associated Pneumonia (VAP) is one of the frequent intensive-care-unit (ICU)-acquired infection. The aetiology of VAP varies with patients' profiles and ICU settings. Due to the increasing incidence of multidrug-resistant organisms in ICUs, early and correct diagnosis of VAP is an urgent challenge for an optimal antibiotic treatment. The aim of the study was to assess the incidence of VAP in different patients by various organisms to create a database of the causative agents of VAP, their drug resistance profile in that area. ***Methodology:*** A prospective study was done over a period of 12 months in a rural tertiary care hospital enrolling patients undergoing mechanical ventilation (MV) for >48 h. Samples were collected from patients with suspected VAP, cultures were performed on all samples. VAP was diagnosed by the growth of significant pathogens. Combination disk method, EDTA disk synergy (EDS) test and cefoxitin double disc synergy test were performed for the detection of different patterns of drug resistance. ***Results:*** Culture positive cases were 52.29% of total. *Acinetobacter spp, Klebsiella pneumoniae* and *Staphylococcus aureus* were most frequent pathogen in early-onset VAP, while *Pseudomonas* spp. and *Acinetobacter spp*. dominated the list of pathogens responsible for late-onset VAP. Prior antibiotic therapy and hospitalization of five days or more were independent risk factors for VAP by MDR pathogens. ***Conclusions:*** This study highlighted high incidence of VAP in our setup. Production of ESBL, AmpC beta-lactamases and metallo beta-lactamases were responsible for the multi-drug resistance of the pathogens causing VAP, implicating the injudicious use of antimicrobial therapy. Combined approaches of rotational antibiotic therapy and education programs might be beneficial to fight against these MDR pathogens to decrease the incidence of VAP.

Keywords: Ventilator-Associated Pneumonia; drug resistance; *Staphylococcus aureus*

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Introduction

Patients admitted in the intensive care unit (ICU) are at risk for dying not only from their illness but from added insults such as nosocomial infections (NI) also. Pneumonia is the second commonest NI in critically ill patients, after UTI, affecting 27% of all critically ill patients[1]. Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring more than 48 hours after endotracheal intubation and initiation of mechanical ventilation (MV) including pneumonia developing even after extubation[2]. VAP is the most frequent intensive-care-unit (ICU) acquired infection, occurring in 9 to 24% of patients intubated for longer than 48 hours[3,4]. Early-onset VAP, occurring during the first four days of mechanical ventilation (MV), usually is less severe, associated with a better prognosis, and is more likely to be caused by lesser resistant strains of bacteria. Late-onset VAP, develops five or more days after initiation of MV, is caused by multidrug-resistant

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(MDR) pathogens and is associated with higher degree of morbidity and mortality[5]. Diagnosing VAP requires a high clinical suspicion combined with bedside examination, radiographic examination, and microbiologic analysis of respiratory secretions. Reasonable clinical criteria for the suspicion of VAP include a new and persistent (>48h) or progressive radiographic infiltrate plus two of the following: temperature of >38°C or <36°C, blood leukocyte count of >10,000 cells/ml or <5,000 cells/ml, purulent tracheal secretions, and gas exchange degradation[1]. Aggressive surveillance is vital in understanding local factors leading to VAP and the microbiologic milieu of a given unit. VAP may be caused by a wide spectrum of bacterial pathogens, which may be polymicrobial and are rarely due to viral or fungal pathogens in immunocompetent hosts[2,7] Common pathogens include aerobic gram-negative bacilli, such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae* and *Acinetobacter* species. Infections due to gram-positive cocci, such as *Staphylococcus aureus*, are more common in patients with diabetes mellitus and head trauma[7]. The frequency of specific MDR pathogens causing VAP may vary by hospital, patient population, exposure to antibiotics, type of ICU patient and changes over time, emphasizing the need for timely local surveillance data[7]. Detection of the causative organism is crucial for the diagnosis of VAP. This is done by collecting the lower respiratory tract sample either by invasive (protected specimen brush [PSB] or broncho-alveolar lavage [BAL]) or noninvasive (endotracheal aspirate [ETA]) techniques and culturing quantitatively or semi-quantitatively. The major difficulty of this approach is in obtaining samples from the lower respiratory tract - mainly because of its probable contamination with the upper airway flora, which may result in misinterpretation of cultures [8]. The American Thoracic Society (ATS) guidelines recommend that quantitative cultures can be performed on ETA or samples collected either bronchoscopically or nonbronchoscopically [9]. Reliance on semi-quantitative cultures, which may not reliably separate true pathogens from colonizers, can lead to either more or broader-spectrum antibiotic therapy than with a quantitative approach. On the other hand, there are many studies which compared the diagnostic value of quantitative cultures of bronchoscopic and nonbronchoscopic samples in VAP. No technique could consistently be shown to achieve a superior diagnostic yield as compared with another. Another advantage in terms of cost – lower respiratory tract sample collection through endotracheal tube is much less expensive compared to BAL or PSB and hence is widely preferable in most of the hospital settings. Judicious antibiotic usage is essential, as resistant organisms continue to plague intensive care units and critically ill patients. Pseudomonas spp., Acinetobacter spp. and even Enterobacteriaceae are quite often multidrug-resistant due to production of extended spectrum beta (β)-lactamases (ESBL), AmpC β-lactamases (AmpC) or metallo-β-lactamases (MBL)[9]. The aetiological agents of VAP vary with different patient populations and types of ICUs[2]. Therefore, the local microbial flora causing VAP needs to be studied in each setting to guide more effective and rational utilization of antimicrobial agents. The objectives of this study were to determine the prevalence and risk factors of MDR pathogens among our VAP patients and to determine their antibiotic susceptibility pattern as well as detect the presence of ESBL, AmpC β-lactamases, carbapenemases and metallobetalactamases in these VAP pathogens.

Material and Methods

This study was a prospective observational one conducted in the intensive care units (ICU) and in the Dept. of Microbiology of Burdwan Medical College & Hospital which is a medical College in Burdwan District, West Bengal, from Jan 2012 to December 2012. This study was approved by the institutional Ethical committee. The ICU is comprised of 12 well-spaced beds and patients were either admitted directly to the ICU or transferred from other departments. During 12 months study period a total 113 patients who were intubated and received mechanical ventilation in the ICU were reviewed prospectively. Among them four patients were found to develop pneumonia within 48 hours of initiation of MV and hence excluded from study. So, remaining 109 patients were included in the study. Age, sex and the clinical parameters of the patients including the provisional diagnoses were noted from the institutional clinical notes, bedside clinical charts. Details of antibiotic history, steroid usage, previous surgery, chronic debilitating condition if any, level of consciousness etc. have also taken into account. Diagnosis of VAP was done on the basis of clinical and micrbiological criteria and confirmed by positive bacteriological culture of the samples obtained from the patients viz. Endotracheal aspirate, tracheostomy suction yielding $\geq 10^5$ cfu/mL. Collected samples

were mechanically liquefied and homogenized by vortexing for 1 min and then serially diluted in 0.9% sterile saline solution with final dilutions of 10^{-2}, 10^{-3} and 10^{-4}. The samples were then plated on sheep blood agar (SBA), chocolate agar (CA), MacConkey agar (MA) by using 4 mm Nichrome wire loop (Hi-media, Mumbai, India), which holds 0.01 ml of solution. All plates were then incubated overnight at 37°C at 37°C in 5% CO_2 incubator. All plates were checked for growth overnight and then after 24 and 48 h of incubation. For definite diagnosis of VAP in this study, quantitative culture threshold was considered as 10^5 cfu/ml. Growth of any number of organism below this level was considered to be due to colonization or contamination and therefore not processed further[7]. Bacterial isolates were identified using conventional biochemical battery of tests namely sugar fermentation test, indole production, MR-VP,Citrate utilization, Urease production, TSI-test,PPA, amino acid decarboxylation tests , Oxidase tests etc. Following this anitimicrobial susceptibility testing (AST) was performed by Kirby-Bauer disc-diffusion technique. Selection of battery of antimicrobials was done following the guideline of CLSI document 2011[11] for *Enterobacteriaceae, Pseudomonas spp, Acinetobacter, Staphylococcus aureus*. Detection of methicillin resistance in Staphylococcus aureus has been done by using cefoxitin (30mcg) disc in Muller Hinton agar plate (MHA). ESBL production by enterobacteria has been confirmed by combination disc test using Cefotaxime alone & Cefotaxime-clavulenic acid and Ceftazidimealone & Ceftazidime- clavulenic acid discs. Any increase in 'zone of inhibition' diameter by ≥5mm around the disc containing Clavulenic acid in comparison to the original disc (Cefotaxime/ Ceftazidime) is indicative of ESBL production by the test isolate. AmpC detection was performed by both screening test by Cefoxitin (30mcg) disc followed by phenotypic confirmatory test i.e. cefoxitin-cloxacillin double disc synergy test (CC-DDS). This test is based on the inhibitory effect of cloxacillin on AmpC. Disks containing either 30 µg of cefoxitin and 30 µg of cefoxitin plus 200 µg of cloxacillin were procured for the present study. The screen positive isolates were inoculated on Mueller-Hinton agar using McFarland 0.5, followed and incubated at 35°C for 16 to 18 h. A difference in the cefoxitin-cloxacillin inhibition zones minus the cefoxitin alone zones of ≥4 mm was considered indicative for AmpC production. Amp C detection for *Citrobacter fruendii* is not done because of the the fact that it produces chromosomally encoded Amp C[12]. Detection of metallo-β-lactamases (MBL) has been done by EDTA disk synergy test (EDS) using both meropenem and ceftazidime discs. Appearance of an expanded zone of inhibition between meropenem or ceftazidime and EDTA discs was interpreted as positive for MBL production.

Results:

A total 203 patients were admitted in the ICU of the institution in the above mentioned study period (one year) and 109 patients were enrolled for the study according to the inclusion criteria. Quantitative culture results were significant ($\geq 10^5$ cfu/ml) for pathogenic organisms causing VAP in 57 (52.29%) patients. Fifty-two (47.71%) patients did not have VAP, and they served as non-VAP control group. Patients developing VAP within 96 h of MV were categorized as having 'early-onset VAP,' and those having it after 96 h were classified as 'late-onset VAP.' Out of these 57 cases, 21(36.84%) were categorized under the early-onset group and the remaining 36 (63.16%) under the late-onset group. The incidence of VAP increased with the duration of MV. The median duration of MV in non-VAP group was 3.6 days as against 15.5 days in patients with VAP ($P<0.05$) [Mann-Whitney test].

The clinical spectrum of the patients as evident from Table 1 shows that highest number of VAP cases occur in the setting of post operative MV (12/57) followed by CRF/ARF/DM/HTN/IHD cases (11/57), road traffic accident, malignancy ,organophosphate poisioning, CVA, acute pancreatitis, FUO, cirrhosis of liver and malaria. *Acinetobacter spp.* was the commonest organism (n=20) to be isolated from clinical samples in the VAP cases (culture positive cases) followed by *Pseudomonas aeruginosa* (14), *Klebsiella pneumonia (10), Staphylococcus aureus (6), Proteus mirabilis (3),Citrobacter spp. (2)* and *Enterobacter spp. (n=2)* in this study, respectively. Early onset cases were found to be caused by *Acinetobacter spp, Klebsiella pneumoniae* and *Staphylococcus aureus* mainly where as *Pseudomonas spp.* and *Acinetobacter spp.* caused late onset VAP with maximum frequency followed by other organisms isolated in the study. The antimicrobial susceptibility/ resistance pattern has been depicted in the table: 1.

Table 1: Pattern of antimicrobial susceptibility/ resistance

Disease	Patients with suspected VAP (n=109)	Culture positive VAP (n=57)
OP Poisoning	14	06
Road Traffic Accidents	16	08
Malaria	05	01
Malignancy	10	06
CVA	06	05
Post Operative Patients	27	12
CRF/ARF/DM/HTN/ IHD	16	11
Acute Pancreatitis	08	03
FUO	03	02
Liver Abscess/ Cirrhosis	04	03

OP - Organophosphorus, CRF - Chronic renal failure, ARF – Acute renal failure, DM - Diabetes mellitus, HTN - Hypertension, IHD - Ischemic heart disease, FUO – Fever of unknown origin

Cent percent of the *Staphylococcus aureus* isolates were found to be MRSA strains isolated from early onset VAP. None of the *Acinetobacter* spp. causing early-onset VAP were polymyxin B resistant, while, 20% resistance to polymyxin B was observed among *Acinetobacter* spp. associated with late-onset VAP. However, all *Pseudomonas spp.* isolates were sensitive to polymyxin B. ESBL production has been rampant among the *Enterobacteriaceae* isolated in this study, which forecasts bad days for infection control in intensive care units. In the present study, 100% of *Klebsiella spp., Enterobacter spp* and *Citrobacter fruendii* each was ESBL producer. Where as 66.6% of the *Proteus mirabilis* (n=3) isolates were ESBL producers. Metallobetamase production has been seen among most of the isolates of *Acinetobacter spp.(60%),Pseudomonas spp.(57.1%), Klebsiella pneumoniae(80%).* However, *Proteus mirabilis (33.3%)*, *Citrobacter spp.* (50%) and *Enterobacter spp* (50%) shows metallo-betalactamase production with somehow lower pace .

Amp-C betalactamase production has been observed with diverse frequency. All the isolates of *Enterobacter spp.* are Amp-C producer here. Whereas, 60% of the *Klebsiella pneumonia* and 33.3% of the *Proteus mirabilis* isolates in this study are Amp-C betalactamase producers (Table 3).

Table 3: Pattern of Antimicrobial resistance in the study

Antibiotic Resistance pattern	Percentage of the isolates involved (%)	
ESBLs	*Klebsiella pneumoniae*	100
	Proteus mirabilis	66.6
	Citrobacter fruendii	100
	Enterobacter spp.	100
Metallo-betalactamases	*Acinetobacter spp.*	60
	Pseudomonas spp.	57.1
	Klebsiella pneumoniae	83.3
	Proteus mirabilis	33.3
	Citrobacter fruendii	50
Amp-C beta-lactamse	*Enterobacter spp.*	100
	Klebsiella pneumoniae	60
	Proteus mirabilis	33.3

The overall AST profile shows that for *Acinetobacter spp* the effective antimicrobials of choice would be Polymyxin B (20%), Tigecycline(30%), Cefepime(40%), Amikacin (50%),Levofloxacin(50%). Rest of the antimicrobials have a resistance pattern above 50% of the total isolates.

All the isolates of *Pseudomonas spp.* are susceptible to Polymyxin B. But nine out of 14 isolates are resistant to amikacin, tobramycin and cefepime each. 12 isolates are resistant to gentamicin and Pip-tazo each. Six and ten isolates of *Pseudomonas spp.* are resistant ceftazidime and cefoperazone respectively. Fluoroquinolones are also no longer the choice against *Pseudomonas spp.*as evident from Table-2.

Table 2: Bacteria isolated from clinical samples from suspected VAP cases with susceptibility pattern

Antibiotics/ Group of Antibiotics: resistance pattern	Bacteria isolated from samples						
	Acinetobacter spp. **(n=20)**	***Pseudomonas spp.*** **(n=14)**	***Klebsiella Pneumoniae*** **(n=10)**	***Proteus mirabilis*** **(n=3)**	***Staph. aureus*** **(n=6)**	***Citrobacter fruendi*** **(n=2)**	***Enterobacter spp.*** ***(n=2)***
ESBL producer (%)	-	-	100(10)	66.6(2)	--	100 (2)	100 (2)
Amikacin (%)	50(10)	64.28(9)	50(5)	0	--	0	50(1)
Gentamicin (%)	60(12)	85.7(12)	60(6)	66.6(2)	33.3(2)	50(1)	100(2)
Tobramycin (%)	60(12)	64.28 (9)	50(5)	33.3(1)	-	-	-
Ciprofloxacin (%)	80(16)	92.8(13)	100 (10)	100(3)	83.3(5)	100(2)	100(2)
Levofloxacin (%)	50(10)	71.5 (10)	70(7)	100(3)	66.6(4)	50(1)	00
Cefepime (%)	40(8)	64.28 (9)	40 (4)	66.6(2)	--	50(1)	00
Ceftazidime (%)	80(16)	42.9 (6)	100(10)	66.6(2)	--	100(2)	100(2)
Cefoperazone (%)	90(18)	71.5 (10)	--	--	--	--	--
Cefoxitin (%)	--	--	60 (6)	33.3(1)	83.3(5)	100(2)	100(2)
Imipenem (%)	60(12)	57.1 (8)	80(8)	33.3(1)	--	50(1)	50(1)
Meropenem (%)	60(12)	71.5 (10)	80 (8)	100(3)	--	50(1)	50(1)
Polymyxyn B (%)	20(4)	00	10(1)	00	--	00	00
Tigecycline (%)	30(6)	--	50(5)	00	33.3(2)	50 (1)	50(1)
Vancomycin (%)		--	--	--	00	--	--
Linezolid (%)		--	--	--	16.6(1)	--	--
Teicoplanin (%)		--	--	--	00	--	--
Pip-Tazo (%)	80(16)	85.7(12)	80 (8)	100(3)	--	50(1)	100(2)

- Values against each antimicrobial agent indicate percentage of susceptibility of the particular organism to that aimicrobial agent in this current study.
- Values against ESBL producers indicate percentage of isolates of the particular organism producing ESBL.
- Figures in the parentheses indicate number of the isolates of the respective organism

50% of the *Klebsiella pneumonia*e and *Enterobacter spp.* isolates show resistance to amikacin,whereas, none of the *Citrobacter fruendii and Preoteus* isolates are resistant to thia drug. Levofloxacin was considered to be ineffective against seven, all of three and one isolates of *Klebsiella pneumonia*, *Proteus mirabilis* and *Citrobacter fruendii* respectively. Both the isolates of *Enterobacter spp.*are susceptible to it. Cefepime experienced a lower resistance pattern by the *Enterobacterial* isolates. All the *Enterobacterial*

isolates in this study when tested against Polymyxin B were sensitive except one *Klebsiella pneumonia* isolate.

Tigecycline was ineffective against five (out of ten), one (out of three) and one (out of two) isolates of *Klebsiella pneumonia*, *Citrobacter fruendii* and *Enterobacter spp* respectively. All of three *Proteus* isolates are sensitive to Tigecycline. Pip-tazo was also ineffective against most of the organism in this study.

Out of six *Staphylococcus aureus* isolates five were Meticillin resistant. These isolates are fully susceptible to Vancomycin, Teicoplanin and fairly so to linezolid (1 isolate resistant) and tigecycline (2 isolates resistant) .However, *Staphylococcus aureus* in the present study is highly resistant to ciprofloxacin (83.3%) and levofloxacin (66.6%) but not so towards gentamicin (33.3%).

Discussion

The incidence of culture positive VAP in our setting was 52.29 %. In the era of advanced diagnosis and early management of possible complications, the incidence should have to be lower. As found in some recent studies the incidences are reported to be low[7,13]. The high incidence in our study may be due to a higher number of cases (i.e., 57) and lack of adequate nursing staff which may have adversely affected the quality of care given to the patients. Another factor in our study was a high number of post operative cases and chronic debilitating illness cases admitted in ICU that required prolonged ventilation, which was proved to be risk factor for VAP. But in contrast to some other studies where organophosphate poisoning was the commonest background cause [13] , here highest number of VAP cases were emerged from the background of post-operative illness (12 out of 57) and chronic debilitating illness e.g.- CRF/ ARF/DM/HTN/IHD(11 out of 57). This finding is in accordance with the study of Peter George et al. who found chronic debilitating illness viz. Diabetes mellitus, hypertension as the most frequent causes for development of VAP in their study[14]. Other conditions requiring prolonged MV have also found to be serious causes for precipitation of VAP.

Multidrug resistant organisms are increasing in our ICUs. Earlier studies have shown that Pseudomonas is the most common organism[15]. In the present study multidrug resistant *Acinetobacter spp*. became the commonest pathogen followed by *P. aeruginosa*, and *K.pneumoniae* to cause VAP. This emphasizes the need to treat the cases of VAP with second-line antibiotics effective against these MDR pathogens. The findings also warrant the needs for stringent preventive measures for VAP, as the treatment of an established VAP becomes very expensive. Non-fermenters such as *Pseudomonas* spp. and *Acinetobacter* spp. were significantly associated with late-onset VAP as it was seen by other workers [16,17]. But in the present study patients with early-onset VAP had *Acinetobacter* spp. as the commonest pathogen. Besides *Acinetobacter* spp. the other common pathogens for early -onset VAP were *K.pneumoniae and S.aureus* (all 5 isolates were MRSA), here. This is in contrast to what obtained by Parija et al. as they found MRSA mostly in late-onset VAP cases[18]. Late-onset VAP was associated with higher rates of infection with polymyxin- B resistant MDR *Acinetobacter spp*., but the resistance of the non-fermenters to the other antibiotics was almost the same in both early- and late-onset VAP as found in the study. In fact all the polymyxin- B resistant isolates of *Acinetobacter* spp have been confronted in late- onset VAP cases. Most of the early-onset VAP cases had the history such as prior antibiotic therapy and current hospitalization for five days or more. That could be the reason for the almost similar AST patterns of the isolates from late-onset and early-onset VAP. The American Thoracic Society guidelines support the same reasoning by saying that patients with early-onset VAP who have received prior antibiotics or who have had prior hospitalization within the past 90 days are at greater risk for colonization and infection with drug resistant pathogens and should be treated similarly to patients with late-onset VAP [5].

100% of the *K.pneumoniae, C.fruendii, Enterobacter spp.* isolates were ESBL producers in this study. One out of the three isolates of P*roteus mirabilis* was non-ESBL. In a similar type of study by Parija et al,at JIPMER, Pondicherry, they found ESBL produced by 50% and 67% of *E. coli* and *K. pneumoniae* respectively, in their study. The high degree of drug resistance in our study may be indicative of poor infection control measures and a need of thorough revision of the institutional antimicrobial policy. Likewise, metallo-betalactamases (MBL) production have been observed in all of the gram-negative pathogen encountered in the study except *Enterobacter spp.* Klebsiella spp. was associated with maximum production of MBL(83.3%) followed by *Pseudomonas spp., Acinetobacter spp. Citrobacter spp., Proteus mirabilis.* The finding is not similar to what observed by Dwivedi M. Et al.[19]. In another study by Goel V et al, they have found MBLs production by 47.06% of *Pseudomonas aeruginosa*

and 62.96% of *Acinetobacter baumannii* isolates[20]. Amp-C production was maximum by *Enterobacter spp.* (100 %) followed by *Klebsiella spp.*(60%) and *Proteus mirabilis(33.3%)*. High frequency of AmpC production (73% of total isolates) was also encountered in another Indian stydy by Mutthuswami et al. from Coimbatore[21]. But low frequency of Amp-C production (33.3% among *Enterobacteriaceae*) has been observed by Parija et al[18]. From the present study, the need for judicious selection of patients for antibiotic therapy is emphasized. The prophylactic use of antibiotics is not recommended, and exposure to antibiotics is a significant risk factor for colonization and infection with nosocomial multidrug-resistant pathogens as observed by other authors[2,22]. The rational use of appropriate antibiotics may reduce patient colonization and subsequent development of VAP. Likewise, unnecessary prolonged hospital stay of the patients should be avoided as far as possible. But it may not be feasible in most situations due to patients' condition.

As the study was conducted in a resource-limited setting, only small number of patients with VAP in a single center were studied, which could be considered a limitation of our study. In addition, we recognize that the findings of this study may not necessarily reflect the situations in other similar centers in India. Hence, we suggest further multi-centered studies with larger patient numbers to confirm our findings, in particular the high incidence of MDR pathogens.

Conclusion

In conclusion, VAP is associated with MDR pathogens. Production of ESBL, AmpC β-lactamases and metallo β-lactamases were responsible for the multi-drug resistance of these pathogens. Here, knowledge of the incidence of pathogens and susceptibility pattern of them could guide the choice of antibiotics, in addition to the likelihood of organisms (early- or late-onset VAP). Judicious use of antibiotics can reduce the burden of drug resistance to the vulnerable patient population of ICU.

Conflict of interest: None declared

Referrences:

1. Steven M. Koenig and Jonathon D. Truwit, Ventilator-Associated Pneumonia: Diagnosis, Treatment, and Prevention. *Clin Microbiol Rev*. 2006 October; **19**(4): 637–657.
2. Chastre J and Fagon JY Ventilator-associated pneumonia. *Am J Respir Crit Care* Med 2002;**165:** 867-903.
3. Morehead RS and Pinto SJ Ventilator-associated pneumonia. *Arch Intern Med* 2000;160: 1926-36.
4. Joseph NM, Sistla S, Dutta TK, Badhe AS, Parija SC Ventilator-associated pneumonia in a tertiary care hospital in India: incidence and risk factors. *J Infect Dev Ctries* 2009**; 3:** 771-7.
5. Niederman MS and Craven DE Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171: 388-416.
6. Crowen DE, Steger KA. Epidemiology of nosocomial pneumonia:new eperspectives on an old disease**.Chest**. 1995;**108:** 1S-16S
7. Arindam Dey and Indira Bairy ; Incidence of multidrug-resistant organisms causing ventilator-associated pneumonia in a tertiary care hospital: A nine months' prospective study; Ann Thorac Med. 2007 Apr-Jun; **2**(2): 52–57.
8. Anuradha K, Suhasini T, LakshmiV, The role of non-bronchoscopic samples in ventilator-associated – pneumonia. *Indian J Med Microbiol*.2006; **24**: 107-13
9. Bradford PA Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev* 2001 **14:** 933-951.

10. American thorasic society;Infectious Disease society of America; Guidelines for managements of Adults with Hospital acquired, Ventillator associated, Healthcare associated pneumonia. *Am J Respir Crit Care Med*;2005:171:388-416[PbMed]
11. Clinical and Laboratory Standards Institute.Performance standards for antimicrobial susceptibility testing ; Twenty First Informational Supplement. (M100-S21);CLS Document.Pensylvania,Wayne ,Pa,USA.2011.
12. Jacoby G. A. *2009.* AmpC beta-lactamases. *Clin. Microbiol. Rev. 22:161–182*
13. Hina Gadani, Arun Vyas, and Akhya Kumar Kar, A study of ventilator-associated pneumonia: Incidence, outcome, risk factors and measures to be taken for prevention ; *Indian J Anaesth*. 2010 Nov-Dec**; 54(6): 535–540.**
14. George P and Aequiera A. Antimicrobial sensitivity pattern among organisms which were isolated from the endotracheal aspirates of patients with ventilator associated pneumonia. Journal of Clinical and Diagnostic Research [serial online] 2010 December [cited: 2013 Mar 3]; 4:3400-3404.
15. Rakshith P, Nagar V S, Deshpande A K. Incidence, clinical outcome and risk stratification of VAP- A prospective cohort study. Indian J of Crit Care Med. 2005; **9:** 211-6.
16. Craven DE. Epidemiology of ventilator-associated pneumonia. Chest 2000 117: 186S-187S.
17. Rello J, Ollendorf DA, Oster G, Vera-Llonch M, Bellm L, Redman R Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest* 2002; **122**: 2115-2121.
18. Joseph NM, Sistla S, Dutta TK, Badhe AS, Rasitha D, Parija SC, Ventilator-associated pneumonia in a tertiary care hospital in India: role of multi-drug resistant pathogens. *J Infect Dev Ctries* 2010**; 4**(4):218-225.
19. Dwivedi M, Mishra A, Azim A, Singh RK, Baronia AK, Prasad KN, Dhole TN, Dwivedi UN; Ventilator-associated pneumonia caused by carbapenem-resistant Enterobacteriaceae carrying multiple metallo-beta-lactamase genes. *Indian J Pathol Microbiol.* 2009 Jul-Sep**;52(**3):339-42. doi: 10.4103/0377-4929.54988.
20. Goel V, Hogade SA, Karadesai S G. Ventilator associated pneumonia in a medical intensive care unit: Microbial aetiology, susceptibility patterns of isolated microorganisms and outcome. *Indian J Anaesth* 2012;**56**:558-62
21. Muthusamy D, Appalaraju Boppe. Journal of Clinical and Diagnostic Research [serial online] 2012 August [cited: 2013 May 28 **]; 6**:970-973.
22. Alp E, Voss A (2006) Ventilator associated pneumonia and infection control. *Ann Clin Microbiol Antimicrob* 5: 7.