Biosciences, Biotechnology Research Asia Vol. **8**(1), 195-203 (2011)

A Comparative Study of Ventilator-Associated Pneumonia and Ventilator Associated Tracheobronchitis: Incidence, Outcome, Risk Factors

K.V. YOGEESHA BABU, V.L. JAYASIMHA, K.G. BASAVARAJAPPA, ARUN KUMAR, K.G. RAGHU KUMAR, H.P. NIRANJAN and V. VIJAYANATH

Department of Microbiology, SS Institute of Medical Sciences and Research Centre, Jnanashankara, NH-4 Bypass road, Davangere - 577 005 (India).

(Received: March 18, 2011; Accepted: April 22, 2011)

ABSTRACT

Background

Ventilator associated tracheobronchitis (VAT) and Ventilator associated pneumonia (VAP) are common in endotracheally intubated and mechanically ventilated patients. Limited data available on review of literature regarding comparative studies of VAT and VAP from Indian subcontinent necessitated the present study.

Objectives

The present comparative study was conducted with an objective of determining incidence, etiology and associated risk factors of VAT and VAP.

Material and Methods

Consecutive non duplicated endotracheal aspirate cultures from 870 patients on ventilator for more than 48 hours were included in the present study. VAT and VAP were diagnosed with standard clinical and laboratory criteria. Patients receiving noninvasive pressure ventilation and patients with tracheostomy on ICU admission were excluded from the present study. Organism identification and antimicrobial susceptibility testing was done by standard laboratory procedures. Statistical analysis was done by Student "t" test and "z" test for proportions.

Results

Among 870 intubated patients, an incidence of 10.80%, 14.9% and 7.81% was observed for colonizers, Ventilator associated tracheobronchitis (VAT) and Ventilator associated pneumonia respectively. Mean ±SD duration of hospital stay was 12±2.1 and 16±11.2 days respectively for VAT and VAP without statistically significant difference in age and sex distribution. P. aeruginosa , K. pneumoniae and Acinetobacter baumanii were the most common pathogens of VAT and VAP. 20.35% (35/172) cases (VAT and VAP) were due to pan drug resistant isolates. Imipenem resistance of, 21.43%,33.3% and 44.82% among *P. aeruginosa, K. pneumoniae* and Acinetobacter baumanii respectively was observed . Sixteen antibiogram types of different pathogens with high resistance to Cefotaxime with no significant difference in antimicrobial susceptibility were observed among VAT and VAP pathogens. Crude mortality among VAP patients was higher 38.24% (26/68) than in VAT patients, 6.15% (8/130)($P < 0.001$). Association of Prior imipenem therapy, Septic shock, Steroid therapy and Diabetes mellitus with VAP was highly significant.

Conclusions

VAT and VAP continue to be major challenges to the critical care physicians caused by most common pathogens P. aeruginosa, K. pneumoniae and Acinetobacter baumanii. VAP results in higher crude mortality than VAT. VAT and VAP cases are caused by several distinct antibiogram types of most common pathogens emerging and persisting in the ICUs. Predisposing risk factors are more frequently associated with VAP than VAT. Knowledge of the important risk factors predisposing to VAP may prove to be useful in implementing simple and effective preventive measures including non-invasive ventilation, precaution during emergency intubation, minimizing the occurrence of re-intubation, avoidance of accidental extubations as far as possible.

Key words: Ventilator associated tracheobronchitis (VAT), Ventilator associated pneumoniae (VAP), Endotracheal aspirates, Predisposing risk factors,

INTRODUCTION

Nosocomial lower respiratory tract infections are the most common nosocomial infections in the intensive care unit (ICU)[1,2]. Ventilator associated tracheobronchitis (VAT) and ventilator associated pneumonia(VAP) are two consequences of patients on long term endotracheal intubation and mechanical ventilation. The incidence of VAT and VAP varies among different studies, depending on the definition, the type of hospital or ICU, the population studied, and the level of antibiotic exposure[3,4].

Several risk factors may predispose patients to either colonization of the respiratory tract with pathogenic microorganisms and/or aspiration of contaminated secretions. Knowledge of the incidence of VAP and their associated risk factors are imperative for development and use of more effective therapeutic and preventive measures[5].

Limited data available regarding incidence, etiology and predisposing risk factors of VAT and VAP from our tertiary care hospital necessitated the present study.

MATERIAL AND METHODS

This prospective observational study of one year duration was conducted in ICUs of our tertiary care hospital. All consecutive non-duplicated endotracheal aspirate specimens collected from intubated patients on ventilator for more than 48 hours were included in the present study. Patients receiving noninvasive pressure ventilation and patients with tracheostomy on ICU admission were excluded from the present study.

Ventilator associated tracheobronchitis was defined using all of the following criteria: fever (>38°C) with no other recognizable cause; new or increased sputum production; positive ($\geq 10^6$ colony-forming units/ml) endotracheal aspirate culture [4,5] , and no radiographic evidence of nosocomial pneumonia. Patients with abnormal chest radiograph at admission were excluded. For diagnosis of VAP new or progressive radiographic infiltrates with other criteria for VAT was required with significant colony count (10^6 cfu/ml). Isolation of micro-organisms with a colony count of less than 10^6 colony-forming units/ml was considered as colonization.

Endotracheal aspirates from patients were collected with a sterile catheter with mucus trap and processed according to standard laboratory procedures[6]. Susceptibility to Amikacin (Ak), Ciprofloxacin(CF), Gentamycin(G), Netilmycin(NT), Amoxycillin (AM), Amoxycilin-calvalunate(CAM), Cefotaxime (Ce), Ceftazidime(Ca), Cefaperazone (Cs), Cefpirome(CPM), Cefaperazone-Sulbactam (Cs+Sul), and Imipenem(I) was determined by Kirby-Bauer's disc diffusion method according to CLSI guidelines[7].

Predisposing risk factors were analyzed with Student "t" test and "z" test of proportions using SPSS windows software 13.

RESULTS

In the present study, 22.75% (198/870) patients presented with significant colony counts of different microorganisms (10^6 cfu/ml) from quantitative culture of endotracheal aspirate. An incidence of 10.80%, 14.9% and 7.81% was observed for colonizers, Ventilator associated tracheobronchitis (VAT) and Ventilator associated pneumonia respectively. Mean ±SD duration of hospital stay was 12±2.1 and 16±11.2 days respectively for VAT and VAP. There was no statistically significant difference in age and sex distribution in patients with VAT and VAP.

Most common pathogen of VAT was P. aeruginosa 52.3% (68/130) followed by K. pneumoniae 20.8% (27/130). Among 68 cases of VAP in the present study, 41.18 (28/68) were from early onset VAP and 58.82% (40/68) were late onset VAP. Most common pathogen among early onset VAP was Klebsiella pneumoniae 42.86% (12/28) followed by P. aeruginosa,21.43% (12/28). P. aeruginosa was the most common among late onset VAP, 60 %(24/40) followed by Acinetobacter baumanii 20% (8/40). Staphylococcus aureus was the only Gram positive bacteria causing VAP and VAT in the present study.

Significant difference in antimicrobial

resistance was not observed among micro organisms causing VAT and VAP. High degree of resistance to third generation Cephalosporins, especially with cefotaxime was observed among VAT and VAP pathogens. Ciprofloxacin, Netilmycin and Amikacin retained good susceptibility.

PAN drug resistant strain of P. aeruginosa PA-1 strain was responsible for 8 cases of VAP and VAT each. PA-2 was responsible for majority of cases of VAP (41.78%) and VAT (26.6%)

Pan drug resistant strain of K. pneumoniae KP-1 was responsible for 4 cases of VAP and 6 cases of VAT.

Table 1: Distribution of colonisers and vat pathogens from endotracheal aspirate cultures

Micro-organism	Colonisers	Pathogens	Total
Pseudomonas aeruginosa	34	68	102
Klebsiella pneumoniae	14	27	41
Acinetobacter baumanii	19	17	36
E. coli	4	8	12
Staphylococcus aureus	2	7	9
Others	21	3	24
Total	94	130	224

Table 2: Distribution of vat pathogesn among early and late onset vap

Micro-organism	Early onset vap	Late onset vap	Total
Pseudomonas aeruginosa	6	24	30
Klebsiella pneumoniae	12	6	18
Acinetobacter baumanii	4	8	12
E. coli	2	1	3
Staphylococcus aureus	2	1	3
Others	2	0	2
Total	28	40	68

Table 3: Antibiotic resistance (by percentage) of vat pathogens

Micro organism	Ak	G	Ce	Cs	Cs+Sul	Ca	CPM	AM	CAC	CF	Nt
Pseudomonas aeruginosa (68)	29	65	90	65	55	50	45	97	87	25	31
Klebsiella pneumoniae (27)	22	53	92	67	61	43	27	87	76	20	24
Acinetobacter baumanii (17)	24	70	96	38	31	49	36	91	84	22	26
E. coli (8)	21	42	61	32	23	18	12	31	27	14	22
Staphylococcus aureus (7)	43	44	33	33	24	45	31	20	12	14	21
Others (3)	20	41	31	45	33	25	17	31	23	13	14

Note: Amikacin (Ak), Ciprofloxacin(CF), Gentamycin(G), Netilmycin(NT),Amoxycillin(AM), Amoxycilin-calvalunate(CAM), Cefotaxime(Ce), Ceftazidime(Ca), Cefaperazone(Cs), Cefpirome(CPM), Cefaperazone-Sulbactam(Cs+Sul), and Imipenem(I)

Table 4: Antimicrobial resistance (percentage) pattern of VAP pathogens

Micro organism	Ak	G	Ce	Cs	Cs+Sul	Ca	CPM	AM	CAC	CF	Nt
Pseudomonas aeruginosa (30)	32	65	90	71	55	65	45	97	87	25	31
Klebsiella pneumoniae(18)	22	53	95	67	61	43	27	87	76	20	24
Acinetobacter baumanii (12)	24	70	96	38	31	69	36	91	89	22	26
E. Coli (3)	21	42	71	32	23	18	12	31	27	14	22
Staphylococcus aureus (3)	43	44	33	33	24	45	31	20	12	14	21
Others (2)	20	41	31	45	33	25	17	31	23	13	14

Note: Amikacin (Ak), Ciprofloxacin(CF), Gentamycin(G), Netilmycin(NT),Amoxycillin(AM), Amoxycilin-calvalunate(CAM), Cefotaxime(Ce), Ceftazidime(Ca), Cefaperazone(Cs), Cefpirome(CPM), Cefaperazone-Sulbactam(Cs+Sul), and Imipenem(I)

Table 5: Distribution of *P. aeruginosa* strains (antibiogram typing)

Strain of PA	Antibiogram	No of vat Caused by Particular strain	No of vap caused by particular strain	Total
1	R- Resistant to all	8	8	16
2	R- G,AM, CAC Ce, Cs, Cs+Sul,Ca S- CF, CPM, Ak,Nt,I	28	8	36
3	R- G, AM, CAM, Ce, CPM, Ca, Cs,Cs+Sul, IS- CF, Ak, Nt	2	3	5
4	R- , Cs, Cs+Sul, G, Ce, CPM, Nt, CF,AM,CAMS- Ak,I, Ca	18	4	22
5	R –Ak, , AM, Cs, Ca, Cs+Sul, Ce, Cz, Cip, GS-Nt,I,CPM	12	7	19

Note: Amikacin (Ak), Ciprofloxacin(CF), Gentamycin(G), Netilmycin(NT),Amoxycillin(AM), Amoxycilin-calvalunate(CAM), Cefotaxime(Ce), Ceftazidime(Ca), Cefaperazone(Cs), Cefpirome(CPM), Cefaperazone-Sulbactam(Cs+Sul), and Imipenem(I)

Table 6: Distribution of *K. pneumoniae* strains among vat and vap cases

Strain of PA	Antibiogram	No of vat Cases	No of vap Cases	Total
1	R- Resistant to all	6	4	10
2	R- G,AM, CAC Ce, Cs, Cs+Sul,Ca S- CF, CPM, Ak,Nt,I	11	6	17
3	R- G, AM, CAM, Ce, CPM, Ca, Cs,Cs+Sul, I S- CF, Ak, Nt	2	3	5
4	R- , Cs, Cs+Sul, G, Ce, CPM, Nt, CF,AM,CAM S- Ak,I, Ca	3	3	6
5	R -Ak, , AM, Cs, Ca, Cs+Sul, Ce, Cz, Cip, G S-Nt,I,CPM	2	1	3
6	R - Ak, G, Ce, Cs, Cs+Sul, Ca, CPM, AM, CAC, CF, Nt, S - I	3	1	4

Note: Amikacin (Ak), Ciprofloxacin(CF), Gentamycin(G), Netilmycin(NT),Amoxycillin(AM), Amoxycilin-calvalunate(CAM), Cefotaxime(Ce), Ceftazidime(Ca), Cefaperazone(Cs), Cefpirome(CPM), Cefaperazone-Sulbactam(Cs+Sul), and Imipenem(I)

Pan drug resistant strain of Acinetobacter baumanii AB-1 was responsible for 5 cases of VAP and 4 cases of VAT.

20.35% (35/172) cases (VAT and VAP) were due to pan drug resistant isolates of most common pathogens namely, P.aeruginosa, K. pneumoniae and A. baumanii. High degree of Imipenem resistance was observed, 21.43%,33.3% and 44.82% among P. aeruginosa, K. pneumoniae and Acinetobacter baumanii respectively. Distribution antibiogram types of strains is shown in Table5, 6, and 7. 92 isolates of VAT and 64 isolates of VAP were multidrug resistant (Resistant to 6 or more antibiotics)

Crude mortality among VAP patients was higher than VAT [38.24% (26/68) Vs 6.15% (8/130), P < 0.001 HS]. Duration of mechanical ventilation was significantly higher in VAP cases than in VAT. Association of Prior imipenem therapy, Septic shock, Steroid therapy and Diabetes mellitus with VAP was highly significant . Distribution of other risk factors is shown in Table 8.

Table 7: Distribution of acinetobacter baumanii strains among vat and vap cases (antibiogram typing)

Strain of PA	Antibiogram	No of vat Cases	No of vap Cases	Total
1	R- Resistant to all antibiotics	4	5	9
2	R - Ce,Cs, Ca , CPM, Cs+Sul, AM, CAC, G S- Ak,Nt,I, CF	8	2	10
3	R- I, Ce,Cs,Cs+Sul, AM, CAM, Ca, G, S- Ak, Nt, CPM	2	2	4
4	R -G, Ce, Cs, Cs+Sul, Ca, CPM, AM, CAC, CF, Nt S - I, Ak	2	2	4
5	R - Ak, G, Ce, Cs, Cs+Sul, AM, CAC, CF, Nt S - I, CPM, Nt	1	1	2

Note: Amikacin (Ak), Ciprofloxacin(CF), Gentamycin(G), Netilmycin(NT),Amoxycillin(AM), Amoxycilin-calvalunate(CAM), Cefotaxime(Ce), Ceftazidime(Ca), Cefaperazone(Cs), Cefpirome(CPM), Cefaperazone-Sulbactam(Cs+Sul), and Imipenem(I)

Table 8: Association of risk factors with VAT and VAP

Risk factor	VAT	VAP	P value
Prior antibiotic treatment	104	68	0.46 NS
Prior imipenem treatment	48	51	< 0.001 HS
Duration of mechanical ventilation	13.3±13.1	21.6±16	<0.001 HS
Septic shock	8	32	<0.001 HS
Ccf	10	16	<0.076 S
Copd	87	52	0.68 NS
Ards	34	29	0.14 NS
Respiratory failure	22	44	< 0.001 HS
Accidental extubation	92	50	0.67 NS
Reintubations	71	39	0.71 NS
Steroid therapy	21	38	<0.001 HS
Iv cannulation	115	68	0.36 NS
Diab etes mellitus	32	48	<0.001 HS
Malignancy	6	12	0.02 S
Mdr pathogens	92	64	O.17 NS

DISCUSSION

The present study reported high incidence of VAT and VAP. The incidence of VAT as reported by Nseir S *et.al.,* is 2.7% to 10%[7]. Kampf G *et.al.,* and Rello J *et.al.,* have reported an incidence of 2.7% to 3.7% for VAT among ICU patients[8,9].

Ventilator associated tracheobronchitis (VAT) represents an intermediate process between lower respiratory tract colonization and ventilator associated pneumonia (VAP). VAT is difficult to differentiate from colonization and VAP. New or persistent infiltrate on chest radiograph may be difficult to interpret in some critically ill patients. It is possible that significant number of VAT cases actually represent VAP with the "new or progressive infiltrate" not visible on poor quality portable chest radiographs.

VAP is the most frequent intensive-care-unit (ICU)-acquired infection, occurring in 9 to 24% of patients intubated for longer than 48 hours .Hina Gadani *et.al.,* have reported a high incidence of VAP of 37%.[12]. In recent studies, the reported incidence ranges from 15 to 30%[12.13]. Relatively low incidence of VAP in the present study in spite of high incidence of colonization and VAT is due to better nursing care and strict infection control measures. The present study has demonstrated that although colonization and VAT are inevitable consequences of endotracheal intubation and mechanical ventilation, VAP can be prevented with appropriate infection control measures.

Crude mortality among VAP patients was higher than VAT [8.24% (26/68) Vs 6.15% (8/130),P<0.001 HS). In the present study slightly higher mortality was reported in Late onset than early onset VAP (22.1% Vs 16.2%,Stastically not significant). Joseph et.al have reported almost similar mortality rates in early and late onset VAP. The mortality attributable to VAP has been reported to range between 0 and 50%. Studies across the world have provided different results when determining attributable mortality, in part because of very different populations (less-acute trauma patients, acute respiratory distress syndrome [ARDS] patients, and medical and surgical ICU patients) and in part as a result of variances in appropriate empirical medical therapy during the initial 2 days.

In the present study P. aeruginosa followed by A. baumanii were most common pathogens of late onset VAP and K. pneumoniae followed by P.aeruginosa in early onset VAP with a high incidence of MDR and pan drug resistant strains(PDR). Non-fermenters such as Pseudomonas spp. and Acinetobacter spp. were significantly associated with late-onset VAP as observed in other studies. [14,15] But in our study even in patients with early-onset VAP, P. aeruginosa was the second most common pathogen because most of them had risk factors for MDR pathogens.[14,15] American Thoracic Society guidelines supports the same reasoning by suggesting 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 MDR pathogens and should be treated similarly to patients with late-onset VAP[16].

Craven et.al. contend that VAT is a precursor of VAP much like cystitis as precursor for pyelonephritis, and propose that surveillance cultures of endotracheal aspirates should be monitored periodically and therapy initiated when quantitative culture results reach a certain level of positivity (VAT) in the setting of signs of systemic infection[17]. However this can be questioned, as microorganisms isolated from 32 out of 68 cultures from VAP cases were different from isolates from previous cultures of VAT or colonization, indicating other exogenous sources of pathogens.

In the present study there was no significant difference in antimicrobial susceptibility pattern in pathogens from VAT and VAP patients. Ciprofloxacin Netilmycin, Amikacin and Imipenem were found to be useful drugs. High degree of resistance was observed with Cefotaxime probably due to wide spread use of this antibiotic for prophylaxis. Similar and different findings of the other studies reflect the antimicrobial prescription policies, different strains of circulating micro organisms and various predisposing risk factors prevalent in the particular hospital.

High incidence of Imipenem resistance

among VAT and VAP pathogens in the present study necessitate further inquiry into the cause for the resistance, especially regarding Metallo- Beta-lactamase production.[18,19] Josepth et. al. have reported that VAP is increasingly associated with MDR pathogens with production of ESBL, AmpC β-lactamases and metallo -β-lactamases responsible for the multi-drug resistance of these pathogens. [20]

In the present study 16 VAP cases were due to Pan drug resistant isolates. Four each of K. pneumoniae and A. baumanii and 8 isolates of P. aeruginosa. Emergence , persistence and spread of Pan drug resistant isolates was due to widespread use of multiple broad spectrum antibiotics injudiciously. Clinicians were practically left with no option for treating VAP patients with PAN DRUG RESITANT infections resulting in poor prognosis of VAP patients.

Majority of the VAP cases were caused by 16 distinct antibiogram types of most common pathogesns (5 strains of P. aeruginosa, 6 of K. pneumoniae, 5 strains of A. baumanii). This study demonstrated emergence and persistence of several distinct MDR and Pan drug resistant strains of pathogens in hospital. Knowledge of the susceptibility pattern of the local pathogens should guide the choice of antibiotics, in addition to the likelihood of organisms (early- or late-onset VAP).

Increased duration of intubation and mechanical ventilation was significantly associated with VAP patients than VAT (21.6±16 Vs 13.3±13.1 , P < 0.001 HS). Whether this was a cause or effect of VAP could not be identified with certainty. Accidental extubations and reintubations were significantly associated with VAP than VAT in the present study.

The presence of endotracheal tube bypassing the innate immunity from nostril or mouth to carina was found to be the most important risk factor for colonization, VAT and VAP in the patients. Aspiration of contaminated oropharyngeal, gastric, or tracheal secretions around the cuffed endotracheal tube into the normally sterile lower respiratory tract results in most cases of nosocomial lower respiratory tract infections, as reported by Metheny NA et. al. Endotracheal tube biofilm formation plays an important role in sustaining tracheal colonization with frequent seeding of lower respiratory tract by MDR micro-organisms and also having an effect on late onset of nosocomial lower respiratory tract infections by MDR micro-organisms[20].

Reporting of accidental extubation as an independent risk factor in the present study suggests that extubation may be associated with increased rates of aspiration of infected upper airway secretions. Septic shock, steroid therapy, Diabetes mellitus, malignancy and respiratory failure necessitating intubation and mechanical ventilation were significantly associated with VAP patients. Other risk factors were more less equally distributed among VAT and VAP patients. (Table 8).

Although clinical observations (Predisposing factors) in the present study were quantitated and analyzed with some objectivity, judgments as to their association with VAT or VAP, by necessity were relatively subjective and to some extent arbitrary. Our analysis may not be having the power to identify all important VAP risk factors in this study population. Despite those limitations, the findings of this study signify several important risk factors of VAT and VAP in critically ill patients on mechanical ventilation requiring medical attention for implementing simple and effective preventive measures.

List of predisposing risk factors of VAP and VAT are innumerable as reported by several authors. Joseph *et.al.,* have reported impaired consciousness, reduced cough reflex, Supine head position, stress ulcer prophylaxis, surgery, burns, chronic renal failure, trauma, steroid therapy and duration of mechanical ventilation e" 5 days were documented as independent risk factors for the development of VAP.

Awareness of the independent risk factors of endotracheal colonization and VAT documented in this study may assist in identifying patients at higher risk for VAP, guide implementation of appropriate preventive measures, and modulate potential intervention measures during management.

To conclude, VAT and VAP continue to be a major challenges to the critical care physicians in India and are common nosocomial infections occurring in mechanically ventilated patients. P. aeruginosa , K. pneumoniae and Acinetobacter baumanii are the most common pathogens of VAT and VAP. Most of the VAP cases are caused by several distinct antibiogram types of most common pathogens emerging and persisting in the ICUs. Predisposing risk factors are more frequently associated with VAP than VAT. Knowledge of the important risk factors predisposing to VAP may prove to be useful in implementing simple and effective preventive measures including non-invasive ventilation, precaution during emergency intubation, minimizing the occurrence of re-intubation, avoidance of accidental extubations as far as possible.

ACKNOWLEDGEMENTS

We duly acknowledge the statistical analysis done by Mrs. Rajashree Patil

REFERENCES

1. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas- Chanoin MH *et. al*., The prevalence of nosocomial infection in intensive care units in Europe.Results of the European Prevalence of Infection in IntensiveCare (EPIC) Study. EPIC International Advisory Committee**.** *JAMA*, **274:** 639-644 (1995)..
2. Torres A, El-Ebiary M, Rano A. Respiratory infectious complications in the intensive care unit. *Clin Chest Med* 1999; **20**: 287-301.
3. Davis KA, Ventilator-associated pneumonia: a review. *J Intensive Care Med* **21**: 211-226 (2006).
4. 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* **171**: 388-416 (2005) .
5. Ibrahim EH, Tracy L, Hill C, Fraser VJ, Kollef MH. The occurrence of ventilator-associated pneumonia in a community hospital: risk factors and clinical outcomes. *Chest* **120**: 555-561 (2001).
6. Collee TG, Diguid JP, Fraser AG. Mackie and Mc Cartney practical Medical Microbiology. 14th ed. Edinburg: Churchill Livingstone (2006).
7. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing, 7th Informational Supplement (M100-517), Wayne, PA: Clinical Laboratory Standards (2007).
8. Kampf G, Wischnewski N, Schulgen G, Schumacher M, Daschner F. Prevalence and risk factors for nosocomial lower respiratory tract infections in German hospitals. *J Clin Epidemiol*, **51**: 495-502 (1998).
9. Rello J, Ausina V, Castella J, Net A, Prats G. Nosocomial respiratory tract infections in multiple trauma patients. *Chest*, **102**: 525-529 (1992).
10. Niederman MS, Craven DE, Bonten MJ. American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA). Guideline for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med,* **171**: 388-416 (2005).
11. John Dallas and Marin Kollef. VAT vs VAP : Are We Heading Toward Clarity or Confusion?. Chest **135**: 252-255 (2009).
12. Klompas M. Does this patient have ventilator-associated pneumonia. *JAMA*; **297**: 1583-1593 (2007).
13. Palmer LB, Smaldone GC, Simon S, *et al.,* Tracheal aspirates in long-term mechanically ventilated patients: a human model of Gram negative infection and inflammation. Chest, **108**: 1326-1332 (1995).
14. Bonten MJ, Bergmans DC, Ambergen AW, *et al*., Risk factors for pneumonia, and colonization of respiratory tract and stomach in mechanically ventilated ICU patients. *Am J Respir Crit Care Med*, **154**: 1339-1346 (1996).

15. Singh N, Rogers P, Atwood CW, Wagner MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. *Am J Respir Crit CareMed,* **162**: 505-511 (2000).
16. Adair CG, Gorman SP, Feron BM, et al. Implications of endotracheal tube biofilm for ventilator-associated pneumonia. *Intensive Care Med*, **25**: 1072-1076 (1999).
17. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **165**: 867-903 (2002).
18. Noyal Mariya Joseph, Sujatha Sistla, Tarun Kumar Dutt, Ashok Shankar Badhe3, Subhash Chandra Parija. Ventilator-associated pneumonia in a tertiary care hospital in India: incidence and risk factors., *J Infect Dev Ctries* 2009; **3**(10): 771-777.
19. Nseir S, Di Pompeo C, Pronnier P, Beague S, Onimus T, Saulnier F *et. al.,* Nosocomial tracheobronchitis in mechanically ventilated patients: incidence, aetiology and outcome**.** *Eur Respir J* **20**: 1483-1489 (2002).
20. Metheny NA, Clouse RE, Chang YH, *et al.,* Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors. *Crit Care Med,* **34**: 1007-1015 (2006).