ORIGINAL RESEARCH PAPER

Volume-8 | Issue-6 | June-2019 | PRINT ISSN No. 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

VENTILATOR ASSOCIATED PNEUMONIA IN ICU - INCIDENCE, ETIOLOGY AND ANTIBIOTIC SENSITIVITY PATTERNS OF THE ISOLATES

Anaesthesiology

Agarwal Ankit* Associate Professor, Deptt, of Anaesthesia & Critical Care, AIIMS Rishikesh *Corresponding Author

Singh DK Professor, Deptt, of Anaesthesia & Critical Care

Nath Gopal Professor, Department of Microbiology IMS, BHU

ABSTRACT

Background: Ventilator associated pneumonia is the most common infection in ICU in patients on mechanical ventilation with incidence between 7 to 47%.

Aims of the study: The aim of study was to determine incidence of VAP in an ICU of tertiary care hospital and to find out etiology and antibiotic sensitivity pattern of isolates.

Material and Methods: The study was conducted over a period of two years. Endotracheal aspirate was obtained from patients put on mechanical ventilation for >48h and presenting with pneumonia. Semiquantitative cultures were performed and VAP was diagnosed if the cfu was >105/ml. Antibiotic sensitivity was also performed by Kirby Bauer method.

Results: The overall incidence of VAP was found to be 32.63%. Acinetobacter sp was the commonest organism. All other organisms were multidrug resistant.

Conclusions: VAP continues to be major threat to patients. Since it is caused by multidrug resistant bacteria and there is no difference in etiology of early and late onset VAP, it seems that the bacteria come from hospital environment probably ventilator itself

KEYWORDS

Ventilator Associated Pneumonia, ICU, MDR organisms

INTRODUCTION

There is no universally accepted valid definition of ventilator associated pneumonia (VAP). However, centre for Disease Control & Prevention (CDC) has defined VAP as Pneumonia where patient is on mechanical ventilation for >2 days on the date of event, with day of ventilator placement being day1 and the ventilator was in place on the date of event or the day before(1). VAP is the single most common cause of morbidity & mortality in Intensive Care Unit (ICUs) and the incidence has been reported to vary between 6.6 – 47.05% (2, 3). In terms of per 1000 ventilation days the incidence has been found to be 13.6/1000 MV days by international nosocomial infection control consortium (INICC) data. However, the incidence of VAP is higher in Asian Countries and reported to range from 3.5 to 46 infection /1000 MV days(4). In India it was reported to be 40.1 VAP infection/1000 MV days by Mathai etal(5) and 39.59 infection/1000 MV days by Patil(6). VAP has sometimes been classified as early onset type i.e. pneumonia occurring within 4 days of MV and is considered to be caused by antibiotic sensitive bacteria with a better prognosis and late onset VAP occurring >4 days of MV and is supposed to be caused by multidrug resistant bacteria and associated with greater morbidity and mortality (7,8,9,10))

VAP may be caused by a variety of bacteria like Pseudomonas aeruginosa, Acinetobacter baumani, Klebsiella pneumonia, Escherichia coli and Staphylococcus aureus(11,12,13,14). Viral and fungal pathogens are rarely associated with VAP since most of the pathogens causing VAP are multi drug resistant(MDR), the present study was therefore undertaken to assess the incidence of VAP in ICU of a tertiary care hospital and to find out the bacteria responsible for it and their antibiotic sensitivity pattern.

MATERIALAND METHODS

This prospective study was conducted during April, 2011 to March 2013 in ICU of a tertiary care hospital. The patients were included in the study if they were on mv for more than 48 h and had clinical pulmonary infection score (CPIS)>6 (Table4).

Table 4 The Clinical Pulmonary Infection Score

Parameter	Result	Score
Temperature (˚C)	36.5 – 38.4	0
	38.5 – 38.9	1
	≤36 or ≥39	2
Leucocytes (cells/mm3)	4,000 or 11,000	0
	<4,000 of <11,000	1
	≥500 band cells	2
Tracheal secretions (subjective)	None	0
	Mild/nonpurulent	1
	Purulent	2
Radiographic findings on chest X-ray	No infiltrates	0
	Diffuse/patchy infiltrates	1
	Localised infiltrate	2
Culture results (respiratory sampling)	No/mild growth	0
	Moderate/florid grwoth	1
	Modeate /florid growth and pathogen consistant with Gram stain	2
Oxygenation status (PaO2, FiO2 ratio)	>240 or acute respiratory distress syndrome (ARDS)	0
	≤240 and absence of ADRS	2

They were excluded from the study if clinico-radiological findings were suggestive of pneumonia at the time of admission in ICU or condition other than pneumonia.

During the 2 years period a total 3670 patients were admitted in ICU and 1324 patients were put on mv and 808 of them were ventilated for more than 48 hours, 507 of them had been suspected to have developed VAP. Endotracheal secretions were collected using a 22 inch 12 F suction catheter, which was introduced in the endotracheal tube for approximately 10 inches. Secretions were aspirated gently and the catheter was withdrawn. 2ml of saline was pushed into it to flush the exudates in a sterile container. The samples were transported to microbiology laboratory within an hour. In the laboratory the samples were homogenized by vortexing for 1 min and semi quantitative cultures were made on blood agar, chocolate agar and MacConkey agar plates with 2mm loop which delivers about 25µl. The plates were incubated at 37˚C(BA and CA in candle jar) and were examined 24 hours and then after 48 hours of incubation. With this 2mm loop 250 colonies corresponded to10^5cfu/ml. Any growth well below this threshold was assumed to be due to contamination or colonization. All the significant growths were characterized by colony morphology, gram staining and detailed biochemical characterization following standard procedures(15). Antibiotic sensitivity testing was performed by Kirby Bauer method following CLSI guidelines(16).

RESULTS

Out of 507 who were clinically suspected to have developed VAP, 432 yielded bacteria growth on culture and a total of 562 bacterial isolates were found (more than one organism in some of the samples). Of the 432 cultures positive patients, 105(24.30 % had early onset VAP and 327(75.70 %) had late onset VAP and 301(69.67 %) were male and 131(30.33%) were females(Table–I). VAP was more common seen in elderly patients especially in the age group 61–70 years.

Table-I: Distribution of cases according to onset of VAP and sex

	Number		
	Male	Female	Total
Early onset	78 (74.28)	27 (25.72 %)	105 (24.30 %)
Late onset	221 (67.58 %)	107 (32.72 %)	327 (75.70 %)
Total	301 (69.67 %)	131 (30.33 %)	432 (100 %)

Table-II: Age wise distribution of VAP cases

Age group		
11 – 20	27	6.25 %
21 – 30	30	6.94%
31 – 40	41	9.50%
41 – 50	57	13.19%
51 – 60	47	10.88%
61 – 70	194	44.90%
>70	36	8.34%
	432	100.00 %

The bacteriological profile of the isolates is presented in Table II. It is to be noted that Acinetobactor is the single most common organized isolated in 32.92% cases. Klebsiella pneumonia was isolated from 32.06% cases followed by Pseudomonas aeruginosa (18.86%), Escherichia coli (10.50%) and Staphylococcus aureus (9.43%). Some other bacteria were also isolated from few patients only. In 302 patients only single bacteria was isolated while in 130 patients a mixed microflora was found. Same microorganism were isolated from early and late onset VAP cases (Table IV).

Table III: Bacteriological profile of VAP

Bacteria	No of isolates	Percentage
Acinetobacter spp	185	32.92
Klebsiella pneumonia	124	22.06
Pseudomonas aeruginosa	106	18.86
E. coli	59	10.50
Staphylococcus aureus	53	9.43
Others	35	6.23
Total	**562**	**100.00**

Others include Enterobacter sp.–9, Proteus sp–4 Serratia – 2, Stenotrophomonas maltophilia – 7, Streptococcus pyogenes – 3, CONS – 3, Diphtheroids – 2.

Table IV: Distribution of isolates in Early versus Late onset VAP

Bacteria	Early onset	Late onset	Total
Acinetobacter	41	144	195
Klebsiella	29	95	124
Pseudomonas	22	84	106
E. coli	13	46	59
Staphylococcus	14	39	53
Others	9	26	35

Table V: Early versus late onset VAP organisms

Antibiotic	Acinetobacter sp			Klebsiella pneumonia			Pseudomonas aeruginosa			Escherichia coli			Staphylococcus aureus		
	Early	Late	Total	Early	Late	Total	Early	Late	Total	Early	Late	Total	Early	Late	Total
	41	144	185	29	95	124	22	84	106	13	46	59	14	39	53
Amoxicillin	0	0	0	0	0	0	-	-	-	0	0	0	1 (7.1%)	3 (7.7%)	4 (7.5%)
Cefiroxime	0	0	0	-	-	-	-	-	-	2 (15.4%)	8 (17.4%)	10 (21.7%)	2 14.2%)	6 (15.4%)	8 (15.0%)
Ceftriaxone	3 (7.3%)	10 (6.9)	13 (7.0%)	2 (6.9%)	11 11.6%)	13 (10.5%)	0	0	0	3 (23.0%)	10 (21.7%)	13 (22.0%)	2 (14.2%)	6 (15.4%)	8 (15.0%)
Cefipime	8 (19.5%)	21 (14.6%)	25 (15.7%)	-	-	-	6 (27.2%)	19 (22.6%)	25 (23.6%)	4 (30.8%)	10 (21.7%)	14 (23.7%)	2 (14.2%)	8 (20.5%)	10 (18.9%)
Cefoperazone + sulbactum	32 (78.0%)	80 (55.6%)	112 (60.5%)	10 (34.5%)	25 (26.3%)	35 (28.5%)	17 (77.3%)	56 (66.7%)	73 (68.9%)	5 (38.4%)	20 (43.4%)	25 (42.4%)	4 (28.5%)	11 (28.2%)	45 (28.3%)
Ciprofloxin	6 (14.6%)	12 (8.3%)	18 (9.7%)	0	3 (3.2%)	3 (2.4%)	5 (22.7%)	19 (22.6%)	24 (22.6%)	3 (23.0%)	7 (15.2%)	10 (16.9%)	2 (14.2%)	6. (15.4%)	8 (15.1%)
Levofloxacin	6 (14.6%)	12 (8.3%)	18 (9.7%)	0	3 (3.2%)	3 (2.4%)	5 (22.7%)	19 (2.6%)	24 (22.6%)	3 (23.0%)	7 (15.2%)	10 (16.9%)	2 (14.2%)	6 (15.4%)	8 (15.1%)
Amikacin	9 (22.0%)	26 (18.0%)	35 (18.9%)	11 (37.9%)	31 (32.6%)	42 (33.9%)	10 (45.4%)	44 (52.4%)	54 (51.0%)	8 (61.6%)	20 (43.4%)	28 (47.5%)	6 (42.9%)	21 (53.9%)	27 (50.9%)
Gentamicin	6 (14.6%)	15 (10.5%)	21 (11.4%)	2 (6.9%)	7 (7.4%)	9 (7.3%)	7 (31.8%)	24 (28.6%)	31 (29.2%)	3 (23.0%)	9 (19.6%)	12 (20.3%)	5 (35.7%)	16 (41.0%)	21 (47.6%)
Aztreonem	-	-	-	-	-	-	20 (90.9%)	79.0 (94.0%)	99 (93.4%)	-	-	-	-	-	-
Piperacillin + Tozobactum	10 (24.4%)	28 (19.4%)	38 (20.5%)	7 (24.1%)	20 (21.0%)	37 (21.8%)	18 (81.8%)	73 (86.9%)	91 (85.8%)	10 (76.9%)	32 (69.6%)	42 (71.2%)	5 (35.7%)	12 (30.8%)	17 (32.1%)
Imipenem	38 (92.7%)	137 (95.1%)	175 (94.6%)	26 (89.7%)	88 (92.6%)	114 (91.9%)	20 (90.9%)	78 (92.9%)	98 (92.5%)	11 (84.6%)	42 (91.3%)	53 (89.8%)	11 (78.6%)	33 (84.8%)	44 (83.0%)
Meropenem	38 (92.7%)	137 (95.1%)	175 (94.6%)	26 (89.7%)	88 (92.6%)	114 (91.9%)	20 (90.9%)	78 (92.9%)	98 (92.5%)	11 (84.6%)	42 (91.3%)	53 (89.8%)	11 (79.6%)	33 (84.6%)	44 (83.0%)
Tigecycline	34 (83.0%)	132 (91.7%)	166 (89.7%)	12 (41.4%)	30 (31.6%)	42 (33.9%)	-	-	-	13 (100.0%)	45 (97.8%)	58 (98.3%)	14 (100.0%)	39 (100.0%)	53 (100.0%)
Colistin	41 (100.0 %)	144 (100.0%)	185 (100.0%)	22 (75.9%)	80 (84.2%)	102 (82.3%)	20 (90.9%)	75 (89.3%)	95 (89.6%)	13 (100.0%)	46 (97.8%)	59 (100.0%)	-	-	-
Cefoxitin	-	-	-	-	-	-	-	-	-	-	-	-	2 (14.2%)	6 (15.4%)	8 (15.1%)
Linezolid	-	-	-	-	-	-	-	-	-	-	-	-	14 (100.0%)	39 (100.0%)	53 (100.0%)
Teicoplanin	-	-	-	-	-	-	-	-	-	-	-	-	14 (100.0%)	39 (100.0%)	53 (100.0%)
Vencomycine	-	-	-	-	-	-	-	-	-	-	-	-	14 (100.0%)	39 (100.0%)	53 (100.0%)

The antibiotic susceptibility pattern of the major isolates has been presented in Table–V. It will be seen that majority of the strains of Acinetobacter were resistant to most of the antibiotics except imipenem, meropenem, tigecyeline and colistin. Similarly most of the Klebsiella pneumonia strains were resistant to many antibiotics except imipenem, meropenem and colistin. E.coli strains showed good susceptibility to imipenem (89.8 %) meropenem (89.8 %) tigecycline (98.3 %) and colistin (100 %). Many strains were also sensitive to piperacillin + Tazobactum (17.2 %), Amikacin (47.46 %) and Cefoperazone + Sulbactum (42.37 %).

All the strains of S. aurus were found to be sensitive to linezolid, vancomycin, tigecycline and teicoplanin and many were sensitive to Amikacin (50.9%), Gentamicin(47.6%), Piperacillin Tazobactum(32.1%), Cefoperazone sulbactum(28.3%), Imipenem(83.0%) meropenem (83.0%). A few strains were also sensitive to other antibiotics as well.

DISCUSSION

Ventilator associated pneumonia is defined as pneumonia that develops >48 hours of MV and is considered to be the major cause of health care associated infection.VAP has been mostly seen in elderly

males(17) and in this study also the most commonly affected group was 61 – 70 years (46.90 %) and males were more commonly affected(69.67 %) than females(30.33 %) Table I & II. Its prevalence has been reported to vary from 6.6% to 47.05%(2,3). In the present study also the overall incidence of VAP was found to be 32.63%(432 cases among 1324 on MV). However, if we look at the onset of VAP, the incidence was higher among late onset(36.01%) as against the 25.24% in early onset VAP. Though the incidence of VAP appears to be a little higher in our study, it might be due to the fact that most other studies have been reported form developed countries. Some Indian studies have also reported a much higher incidence(45.4%) of VAP. Dey Bairy 2007(18). The early onset VAP was seen in 24.30% whereas late onset VAP was found in 75.70% of the total VAP cases.

A rapid microbiological confirmation of VAP along with early institution of appropriate antibiotic treatment is required. Sometimes it becomes difficult in culture to differentiate colonizers/contaminates from pathogens(19). However, it can be done by doing quantitative or semi quantitative cultures, if the cfu was less than 10^5/ml it is regarded as colonizer/contaminants. Using the above criterion, 432 patients were confirmed to have VAP out of 507 clinically suspected VAP cases.

The most commonly isolated organism in our study was found to be Acinetobacter sp(185, 32.92%) followed by Klebsiella pneumoniae(124,22.06%), Pseudomonas aeruginosa (106, 18.86%) E. coli (59,10.50%), Staphylococcus aureus(53,9.43%) and others(35,6.23%) – Table III. Thus a total of 562 isolates were obtained from 432 cases. This is because in 130 patients the etiology of VAP was found to be polymicrobial as has been reported by others(5). Acinetobactor has been reported to be the commonest organism in VAP n several other studies(4,5,18,20) also. The universal stress protein A(UspA) and phospholipase D have been found to be the virulence factors for A. baumannii in animal experiments(20,21).

Klebsiella pneumoniae was the second common organism found in our study being responsible for 22.06 % of the VAP cases. A similar incidence of K. pneumoniae causing VAP has been found in many other studies(6,17). Besides the production of carbapenamases, K pneumonia has been shown to have several other virulence factors like K1, K2 antigen(22), hypoxia inducible factor 1α (HIF-1α) and high affinity iron chelating molecules like siderophores(23,24).

Pseudomonas aeruginosa was the next most common GNB causing VAP in our study was found responsible for 10.86% cases. Similar to other studies(5,6,25). Some virulence factors such as quorum sensing system type–III secretory protein and lipopolysacchardes of P. aeruginosa induce an immune response. The resultant secreted cytokines, and chemotactic and other inflammatory mediators induce severe lung injury which may contribute to development of VAP(26,27).

The incidence of VAP caused by E. coli was lowest among GNBs in this study with 10.50% cases being caused by it. A similarly lower rate of infection by E. coli has been reported by several other workers(5,6,17). It has been shown in mouse that deficiency of CD44 lead to lung injury(28) whereas deficiency of CD47 protects the lung tissue(29). The same mechanism may be responsible in man also.

Staphylococcus aureus was the single most important pathogen among Gram positives causing VAP. In our study it was found responsible for 9.43% cases only. Other studies too have found Staphylococcus aureus to be the commonest Gram positive cocci causing VAP with a variable incidence(5,6,17). However, Dey and Bairy 2007(18) did not get a single isolate of S. aureus. Various factors such as protein A, haemolysin, staphylokinase and toxic shock syndrome toxin have been shown to be necessary for invasive pulmonary infection(30).

Some other bacteria were also isolated from few patients of VAP(6.23%). These included, Enterobacter sp, Proteus, Serratia, Stenotrophomonas maltophila among Gram negative and Streptococcus pyogenes, CoNS and Diphtheroids amongst Gram positive. Since they were not isolated as a single organism, their role in VAP is very much doubted.

An attempt was made to classify all VAP cases into early onset (within 48 – 96 hours of mv) and late onset (occurring after 96h) of MV. It was seen that 105(24.30%) cases were early onset and 327(75.70%) were late onset. Other Indian studies have also reported a lower incidence of early onset VAP. Mathai etal 2016(5) have reported it to be 30.85% and Patil and Patil 2017(6) to be 17.56%. However, some studies show a much higher incidence of 47.7% for early onset VAP. It is believed that early onset VAP is caused by antibiotic sensitive community acquired bacteria which may be commensal in throat and the late onset is caused by drug resistant hospital flora(31). However, in the present study no such difference was observed in early and late onset groups and both the groups were caused by a few resistant hospital strains of bacteria. Many other workers have also reported the late onset VAP to be much more common than early onset VAP(5,6,18) and the GNB to be responsible for both early and late onset VAP (Dey and Bairy 2007(18) and Patil and Patil 2017(6). However, in a few studies, Gram positives like S. aureus, S. pneumoniae and GNB like Haemophilus, influnenzae have been found to be more common in early onset VAP(14,32,33).

Emergence of multidrug resistant (MDR) and pan drug resistant bacteria and the fact that no new antibiotic is in pipeline has worsened the situation in ICUs. In the present study also almost all the organisms (both Gram negative and Gram positive were multi drug resistant. (Table V). the only antibiotics which were effective against good number of isolates were colistin, imipenem, meropenem,tigecycline, Amikacin and Cefoperazone sulbactum for Gram negatives and Teicopplanin, Vancomycin, Linezolid, Tigecycline, Amikacin Erythromycin and cefoperazone sulbactum for Gram positive bacteria. Also it is to be noted that there was no appreciable difference in antibiotic sensitivity pattern of isolates of early onset and late onset VAP (Table VI). Drug resistance to several antibiotics have been shown by various workers in varying proportions (6,18,34). Empirical antibiotics for VAP should be started which will cover Gram negative bacilli, Pseudomonas and Staphylococcus aureus depending on the local antibiogram of the ICU. Once the culture sensitivity report is available, de-escalation must be done to reduce the emergence of resistance.

REFERENCES

1. http://www.cdc.gov/nhsn/pdfs/pscmanual/6/pscvapcurrent.pdf2019.
2. D.M. Kushara, C. da Cruz Enz. A.F.M. Avelar. M.A. S. Peterlini, M. da Luz and G. Pedreira. "Risk factors for ventilator associated pneumonia in infants and children: A crosssectional cohort study". Americal Journal of Critical Care, Vol 23, no 6. Pp 469-476, 214
3. M.F. Patira, G Chidini, L. Ughi et at. "Ventilator associated pneumonia in a Italian pediatric intensive care unit : A prospective study". World Journal of Pediatric, vol. 9, no. 4, pp 365- 368.
4. Chawla R. Epidemiology, etiology and diagnosis of hospital acquired pneumonia and ventilator associated pneumonia in Asian countries. Am J Infect Control 2008;36 4 supp: 593-100.
5. Ashu Sara Mathai, Atul Phillips, Rajesh Issac. Ventilator associated pneumonia : A persistent healthcare problem in Indian Intensive Care Units. Lung India2016; 33 (5) : 512 – 516.
6. Harsha V Patil, Virendra C Patil. Incidence, bacteriology and clinical outcome of ventilator associate pneumonia at tertiary care hospital. Pub Med 2017; 8: 46-55.
7. American Thoracic Society, Infectious Diseases Society of America. 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.
8. Hunter JD : Ventilator associated pneumonia. BMJ 2012; 344 (e 3325) : e 3325
9. Niederman MS, Craven DE. Guidelines for the management of adults with hospital acquired ventilator associated and healthcare associated pneumonia. Am J Respir Crit Care ed 2005; 171: 388-416.
10. Joseph NM, Sistla S, Dutt TK, Badhe AS, Parija SC. Ventilator associated pneumonia in a tertiary care hospital in India : incidence and risk factors. J Infant Dev Ctries 2009; 3: 771-7.
11. Chastre J, Fagon JY. Ventrilator associated pneumonia. Am J Respir Crit Care Med 2002; 165:867-903.
12. Celis R, Torres A, Gatell JM, Almela M, Rodriguez RR, Agusti VA. Nosocomial pneumonia: A multivariate analysis of risk and prognosis. Chest 1988;93:318-24.
13. Craven DE, Steger KA,. Epidemiology of nosocomial pneumonia : new perspectives on an old disease. Chest 1995;108:1S-16S.
14. Rello J, Torres A, Ricart M, Valles J. Gonzalez J, Artigas A, et al. Ventilator associated pneumonia by Staphylococcus aureus : Comparison of methicillin-resistant and methicillin-sensitive episodes. Am J Respir Crit Care Med 1994;150:1545-9.
15. Collie JG, Fraser AG, Marmion BP, Simmons A. (ed). Mackie & Mc Cartney;s Practical Medical Microbiology. 14th edition. Elsevier, 2006.
16. Clinical and Laboratory Standards Institute (CSI). Performance Standards for Antimicrobial Disk Susceptibility Test. Approved Standard- Eleventh Edition. CLSI Document M02-A11, 17th International Supplement M 100 – S22, Vol 32. Wayne Pennsylvania USA: Clinical and Laboratory Standards Institute, 2012.
17. Sonika Agarwal, Barnali Kakati, Nand Kishore, Sushant Khanduri, Mukta Singh. Colistin resistant in organisms causing ventilator associated pneumonia – Are we going into pre antibiotic era ?. Crit Care Shock 2018; 21: 78-87.
18. Arindam Dey, Indira Bairy. Incidence of multidrug resistant organisms causing ventilator associated pneumonia n a tertiary care hospital: A nine month's prospective study. Annals of Thoracic Medicine 2007; 2 (2) :52-57.
19. Rajasekhar TR, Anuradha K, Suhasini T, Lakshmi V. The role of quantitative cultures of non-bronchoscopic samples in ventilator associated pneumonia. Indian J Med Microbial 2006;24:107-13.
20. B.A. Almomani. A. McCullough, R. Gharaibeh, S. Samrah, and E Mahasneh. "Incidence and predictors of 14-day mortality in multidrug resistant Acinetobacter baumannii in ventilator associated pneumonia". The Journal of Infection in Developing Contries, vol 9, no. 12, pp 1323-1330, 2015.
21. A.C. Jacobs,I Hood, K.I. Boyd et al. "Inactivation of phospholipase D diminishes Acinetobacter baumannii pathogenesis,:" Infection and Immnity, vol 78, no. 5, pp 1952-1962., 2010.
22. L.K. Siu, K.M. Yeh, J.C. Lin, C.P. Fung and F.Y. Chung. "Klebsiella pneumonia liver abscess : a nee invasive syndrome ". The Lancer Infectious Disease, Vol 12, no. 11, pp 881 – 885, 2012

23. V.I. Holden. P. Breen, S. Houle, C.M. Cozois and M.A. Bachman. "Klebsiella pneumonia siderophores induced inflammation, bacterial dissemination and HIF-Iα stabilization during pneumonia", MBio, vol 7, no 5, Article ID e01397-16, 2016.
24. V.I. Holden and M.A. Bachman. "Diverging roles of bacterial siderphores during infection." Metallomics, vol 7, no 6, pp 986-995, 2015.
25. Dey A, Bairy I. Indicence of multidrug resistant organimsm causing ventilator associated pneumonia in a tertiary care hospital.: A nine month's prospective study. Ann Thorac Med 2007; 2:52-7.
26. S.L. Gellatly and R.E.W. Hancock. "Pseudomonas aeruginosa : new insights into pathogenesis and host defenses." Pathogens and Disease, vol 67, no 3, pp 159-173, 2013.
27. R.T. Sadikot, T.S. Blackwell , J.W. Christman and A.S. Prince/ " Pathogen host interactions in pseudomonas aeruginosa pneumonia." American Journal of Respiratory and Critical care Medicine vol 171, no11, pp 1209-1223.
28. Q. Wang, P Teder, N.P. Judd, P.W. Noble and C.M. Doerschuk "CD44 deficiency leads to enhanced Neutrophil migration and lung injury in Escherichia coli pneumonia in mice." The Americal Journal of Pathology, vol 161, no 6, pp 2219- 2228, 2002.
29. X. Su, M. Johansen, M.R. Looney, E.J. Brown and M.A. Mathay. "CD47 deficiency protects mice from lipopolysaccharide induced acute lung injury and Escherichia coli pneumonia." The Journal of Immunology, vol. 180, no. 10, pp 694 = 6953, 2008.
30 P. Recsei, B. Kreiswirth, M CYReilly, P, Schlievert, A. Gruss and R.P. Newick. " Regulation of a exoprotein gene expression in Staphylococcus aureus by agr". MGG Molecular & General Genetics, vol 202, no. 1, pp 58-61, 1986.
31. Charles P, Kali R, Easow JM, et al. Ventilator associated pneumonia, Australia Med L. 2014;7(8):334-344.
32. Combes A, Luyt CE, Fagon JY, Wolff M. Trouilles JL, Chastre J. Early predictors for infection recurrence and death in patient with ventilator associated pneumonia. Crit Care Med 20078;35:146-54.
33. American Thoracic Society; Infectious Diseases Society of America. 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.
34. Bhatia A, Kalra J, Kohli S, Kakati B and Kauhaik R. Antibiotic resistance patern in intensive care unit of a tertiary care hospital. Int J Basic Clin Pharmacol 2018;7:906-911.