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Research Article

Ventilator-Associated Pneumonia: Microbiology, Antibiotic Resistance, Changing Trends, and Clinical Implications from the 10-Year Experience of a Single Center

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Abstract

Objectives: This study aimed to determine how ventilator - associated pneumonia (VAP) frequency, and antibiotic susceptibilities are affected by the changes in the intensive care unit (ICU) conditions in adult patients.

Methods: In this retrospective study, 457 VAP patients diagnosed in the ICUs of a training hospital between 2008 and 2017 were analyzed. Alterations in VAP rates during this period were evaluated.

Results: Our results indicated that the improvement of physical conditions, and VAP prevention measures yielded a remarkable decline in the rates of VAP. VAP rates (cases per 1000 ventilator-days) decreased significantly between before 2013 and 2013-2017 periods (from 16.1 to 7.1; p<0.0000001). A total of 504 VAP episodes developed and 569 microorganisms were identified. The most frequent microorganisms were *Acinetobacter baumanii* (33.7%), *Pseudomonas aeruginosa* (31.6%), *Klebsiella pneumonia* (12%). The resistances against sulbactam-ampicillin, imipenem, and meropenem were increased significantly after 2013. (p=0.002, p<0.001, p=0.001; respectively.) There was a noteworthy surge in resistances against colistin (p=0.010) in Gram - negative bacteria and teicoplanin in Gram - positive bacteria (p=0.044).

Conclusion: The study shows that the rates of VAP can be decreased with collaboration with other disciplines, adherence to preventative measures and continue education of healthcare workers.

Keywords: Antibiotic resistance, etiology, rate, ventilator - associated pneumonia

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Healthcare-related infections (HCRI) are among the most important health problems affecting hospitalized patients that increase morbidity and mortality, treatment costs and prolong hospital stay in our country as in the rest of the world. These infections occur 5-10 times more frequently in intensive care units (ICU). Factors such as age, immune status, underlying diseases and nutritional status of the patient as well as the number of patients, ar-

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chitectural structure of the ICU, adherence to disinfection and sterilization measures, and the non-compliance with the aseptic and isolation procedures may be responsible for this higher incidence. Ventilator - associated pneumonia (VAP) takes the first place among HCRI's.[1, 2] It has been defined as pneumonia seen within 48 hours in individuals who received ventilation support with the aid of the endotracheal tube or tracheostomy.[3]

Ventilator - associated pneumonia may present with higher rates of mortality and morbidity in ICU patients devoid of any symptoms of pneumonia before or following intubation. It is a serious complication of a mechanical ventilator, and it may differ from nosocomial pneumonia. The incidence of ventilator - associated pneumonia differs according to the types and conditions of ICUs.[1, 2] This study aimed to determine VAP frequency during the study period, relevant factors, and antibiotic susceptibilities which are affected by the changes in ICU conditions.

Methods

Study Design

In this retrospective study, we aimed to investigate the factors isolated by ventilator-associated pneumonia rates in a training hospital between 2008-2017 and the resistance of these isolated agents to various antibiotics.

Ventilator-associated pneumonia (VAP) was defined as pneumonia that developed more than 48 hours after endotracheal intubation. Our definitions for HAP and VAP were consistent with those used for these diagnoses by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA).[3]

Microbiological Study

All the samples were transported to the Microbiology laboratory. Gram stain preparations were made from all tracheal and bronchoalveolar lavage fluid samples and examined first under low power (×10 objectives) to determine the presence and type of cells in the specimen and then observed under oil immersion field (×100 objective).[4] All the samples were inoculated on blood agar, MacConkey agar and Chocolate agar. Semi-quantitative cultures were done.[5] Growth >105 CFU/ml was taken as the cut-off threshold for ETAs while growth >104 CFU/ml was taken as the cut-off for BALs.[6] Samples showing growth less than these thresholds were assumed to be due to colonization. In case of significant growth, the isolated colonies were subjected to gram stain and biochemical tests for identification. Identification was carried out according to standard biochemical tests.[7] We have been working with BD Phoenix automated system (*Phoenix 100, Becton Dickinson, BD Diagnostic Systems, Franklin Lakes, New Jersey, USA*) since 2012. CLSI criteria were used to determine antibiotic susceptibility until 2016, but it has been replaced with EUCAST criteria as January 2016.

In our hospital, active surveillance of the hospital infections is routinely performed by a team of two infectious diseases specialists and four infection control nurses by reviewing daily patient visits and electronic patient files and interviewing with the treating physicians in the ICUs. The infection control team provides regular training to health care workers about the importance of prevention of healthcare-related infections, hand hygiene, and other infection control practices. Between 2008 and 2017, the data of the ICU patients (number of patients, ventilator use in days, number of VAP cases, the frequency of ventilator use, the frequency of ventilator use per 100 patients and frequency of VAP in 1000 days) were investigated. Changes in these parameters were inquired particularly after 2010 and 2013. In 2010, a new ICU (ICU ward 1) was opened in our institution with improved physical conditions and new health care workers who are trained in the prevention of hospital infection. Physical conditions of the other old ICU (ICU ward 2) were improved in 2012. In 2013, a new medical professional team consisting of a new anesthesiology physician and infectious diseases physician were assigned, and a more strict consultation mechanism was introduced for healthcare-related infections. Patients were evaluated for VAP and other health care related infections by the new physician team on a daily basis. Additional VAP preventative measures such as daily assessment of weaning, monitorization of endotracheal cuff pressure, elevation of bed heads (30–45º), implementation of routine oral care with chlorhexidine were started. All of these precautions were recorded in the patient files but were not observed directly by the health providers.

Statistical Analysis

Descriptive variables are expressed as mean and standard deviation for quantitative variables and as number and percent for categorical variables. Comparison of groups regarding numerical variables is carried out by students or Mann Whitney u tests. Chi-square test was employed to evaluate the significance of the difference between categorical variables. The alterations of variables across a time course are presented as line graphs, and interpretation is made concerning the clinical relevance. VAP ratio results were presented as the rate ratio (IRR) and 95% confidence interval (CI) with accompanying p values. The level of significance was set at $p<0.05$.

Analysis of data was performed by using Statistical Package for Social Sciences (*SPSS Inc., Chicago, IL, USA*) version 21.

Ethical Approval

The necessary permission for the study was obtained from the hospital Ethics Committee (Decision no: 2018-4).

Results

Table 1 demonstrates VAP events, VAP rates per 100 patients and per 1000 ventilation days between 2008 and 2017. VAP rates were 23.7 per 100 patients and 17.3 per 1000 ventilation days in 2008. Since 2008, VAP rates have been gradually declined. There was a decline in the year 2010. In 2010, a new ICU was opened in our institution and new health care workers were assigned. Although the physical conditions of the old ICU were improved in 2012, there was an increase in the VAP rate in 2012-2013.

Table 1. Distribution of number of ventilator - associated pneumonias (VAP)

Year	Percent of ventilator use (%)	VAP rate per 100 patients	VAP rate per 1000 ventilator days
2008	0.90	23.47	17.23
2009	0.94	21.77	14.94
2010	0.82	21.60	19.35
2011	0.68	16.95	16.75
2012	0.73	13.28	13.06
2013	0.73	17.07	15.36
2014	0.81	15.98	7.80
2015	0.80	8.85	4.83
2016	0.77	9.59	3.96
2017	0.76	8.08	4.15

VAP: Ventilator- associated pneumonia.

VAP rates were 17.7 per 100 patients and 15.36 per 1000 ventilation days in 2013. There was a remarkable decline in the numbers of VAP patients, VAP rates per 100 patients and per 1000 ventilation days after the year 2013. A new medical professional team, a more strict infectious diseases consultation mechanism and preventative measures such as elevation of bed heads and implementation of routine oral care with chlorhexidine were started. After these regulations, the VAP rate continued to fall. Results were shown in figure 1. Significant differences in the VAP rates (cases per 1000 ventilator-days) between 2008-2012 and 2013-2017 periods occurred (from 16.1 to 7.1; p<0.0000001, rate ratio: 2.267, confidence interval: 1.887-2.731). Results were shown in Table 2.

A total of 457 patients (281 males, 61.5%; 176 females, 38.5%) with an average age of 64.11±18.12 were diagnosed with VAP in the ICUs in our hospital (Table 3). Patients who were diagnosed with VAP in and after 2010 were

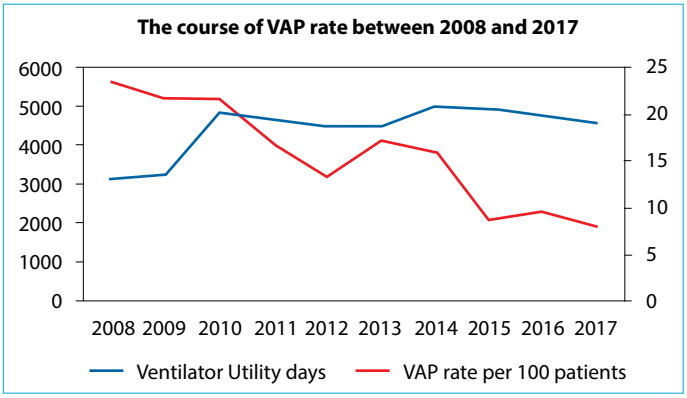

Figure 1. The course of VAP rate between 2008 and 2017.

Table 2. VAP rates categorized by intensive care units

	Before 2013	2013-2017	P	Rate ratios (%95 CI lower and upper bound)
ICU ward 1				
VAP rate *	19.45	7.5	<0.0000001	2.573
No of VAP events	115	103		(1.972-3.361)
Ventilator-days	5912	13625		
ICU ward 2				
VAP rate *	15.5	6.57	<0.0000001	2.289
No of VAP events	219	67		(1.748-3.027)
Ventilator-days	14548	10188		
Total				
VAP rate *	16.1	7.1	<0.0000001	2.267
No of VAP events	334	170		(1.887-2.731)
Ventilator-days	20640	23813		

VAP: Ventilator - associated pneumonia.

significantly older than the patients who were diagnosed before 2010 (57.74±17.74 vs. 66.31±17.62; p<0.001). Similarly, the average age of VAP patients diagnosed in and after 2013 was higher than that before 2013 (62.56±18.07 vs. 68.54±17.14; p<0.001). There was a remarkable increase in the number of women diagnosed with VAP after 2013 (p<0.001).

Pathogen type was identified in the vast majority (452, 98.9%) of our patients and Gram-negative microorganisms were detected in 430 (95.6%) of our series. A single pathogen was isolated in 396 (86.4%) of VAP patients, whereas mixed pathogens were observed in 57 (12.5%) of cases.

A total of 504 VAP cases were diagnosed and 569 microorganisms were identified. The microorganism could not be isolated in six (1.2%) of VAP cases. The most frequent microorganisms detected in patients diagnosed with VAP were *Acinetobacter baumanii* (192, 33.7%), *Pseudomonas aeruginosa* (180, 31.6%), *Klebsiella pneumonia* (68, 12%), and *Staphylococcus aureus* (34, 6%) (Table 4).

As shown in Table 5, the antibiotic resistances most commonly occurs for ceftriaxone (481, 92.3%), sulbactam ampicillin (462, 88%), ceftazidime (342, 65.3%), cefepime (303, 58.2%) and ciprofloxacin (297, 56.1%). We noted that resistance against imipenem and meropenem were significantly increased after 2010 (p<0.001). Antibiotic sensitivity was highest for linezolid (35, 97.2%), vancomycin (34, 97.2%), teicoplanin (34, 94.4%) in Gram-positive bacteria. Antibiotic sensitivity was highest for colistin (421, 93.6%) and amikacin (314, 60.3%) in Gram-negative bacteria. After 2013, there was an increase in the number of VAPs associated with single pathogens (p=0.001). The resistances against sulbactam-ampicillin, imipenem, and meropenem were increased significantly after 2013 (p=0.002, p<0.001, p=0.001) respectively. Moreover, there was a noteworthy

Table 3. An overview of number of ventilator - associated pneumonia (VAP) cases and events

	Number of cases (n=457)	
	Number	**Percent (%)**
Year		
2008	48	10.5
2009	44	9.6
2010	82	17.9
2011	75	16.4
2012	52	11.4
2013	63	13.8
2014	35	7.7
2015	20	4.4
2016	19	4.2
2017	19	4.2
Gender		
Male	281	61.5
Female	176	38.5
ICU ward		
1	200	43.8
2	257	56.2
Age (years)	64.11±18.12	

ICU: intensive care unit.

Table 4. The distribution of microorganisms isolated in our VAP series

Microorganism	**Number**	**Percent (%)**
Acinetobacter baumannii	192	33.7
Acinetobacter lwoffi	2	0.4
Burkholderia cepacia	1	0.2
Candida parapsilosis	2	0.4
Citrobacter freundii	4	0.7
Enterobacter aerogenes	4	0.7
Enterobacter cloacae	15	2.6
Escherichia coli	24	4.2
Klebsiella oxytoca	1	0.2
Klebsiella pneumoniae	68	12.0
Morganella morgannii	1	0.2
Pneumococci	1	0.2
Proteus mirabillis	22	3.9
Pseudomonas aeruginosa	180	31.6
Stenotrophomonas maltophilia	6	1.1
Serratia marcessens	6	1.1
Staphylococcus aureus	34	6.0
Unidentified	6	1.1

Table 5. Antibiotic resistance and sensitivity profile of microorganisms isolated in VAP patients

Antibiotics	**Resistant**		**Sensitive**	
	n	**%**	**n**	**%**
Sulbactam ampicillin	462	88.0	63	12.0
Piperacilin-Tazobactam	304	58.3	217	41.7
Ceftriaxone	481	92.3	40	7.7
Ceftazidim	342	65.3	182	34.7
Cefepim	303	58.2	218	41.8
Imipenem	260	49.6	264	50.4
Meropenem	262	50.0	262	50.0
Gentamicin	236	45.4	284	54.6
Amikacin	207	39.7	314	60.3
Ciprofloxacin	297	56.1	232	43.9
Colistin	29	6.4	421	93.6
Methicillin	20	57.1	15	42.9
Vancomycine	1	2.8	35	97.2
Teicoplanin	2	5.6	34	94.4
Linezolid	1	2.8	35	97.2

surge in resistances against colistin (p=0.010) in Gram-negative bacteria and teicoplanin in Gram-positive bacteria (p=0.044). Of the VAP cases (53.8%) died.

Discussion

This study was carried out to investigate the changes in the rates and characteristics of VAP after implementation of rehabilitative measures in ICU. Our results indicated that improvement of physical conditions, as well as the establishment of a closer collaboration between other disciplines such as infectious diseases, adherence to antisepsis precautions and employment of a stable and experienced ICU team, are important measures to decrease the rates of VAP. The decline in the number of VAP patients became more obvious after the assignment of stable and experienced personnel, strict adherence to VAP preventative measures and the onset of closer collaboration with the infectious diseases department.

Microbiologically, we observed that *P. aeruginosa* and *A. baumannii* strains were responsible for 65.3% of VAP cases. *Pseudomonas aeruginosa*, *Acinetobacter baumannii, Enterobacteriaceae* and *S. aureus* have been frequently implicated in previous studies. In the literature, the microorganisms which were isolated from patients with VAP vary depending on the duration of mechanical ventilation and ICU stay, previous antibiotic history and underlying diseases of the patients.[8–10] According to the National Hospital Infections Surveillance Network (UHESA) 2017 Agent Distribution and Antibiotic Resistance Summary Report, non-fermentative Gram-negative bacilli is isolated in 66.5% of cases. Of these *A. baumannii* strains were 44.4% and P.aeruginosa strains were 16.3%. *Enterobacteriaceae* family in 26.2% of cases and Gram-positive bacteria in 5% of VAP isolates. Gram-negative bacteria were more common in ventilatory associated pneumonia in Turkish hospitals.[11]

In recent years, increased rates of VAP caused by multidrug resistance Gram-negative bacteria has been a major treatment problem for a physician. The majority of microorganisms were resistant to ceftriaxone, ampicillin-sulbactam, ceftazidime, and piperacillin-tazobactam. Many countries are seeing resistance to several antibiotics (ceftriaxone, piperacillin, carbapenems, aminoglycosides, and fluoroquinolones etc).[9–13] According to the National Hospital Infections Surveillance Network (UHESA) 2017 Agent Distribution and Antibiotic Resistance Summary Report, the resistance status of the agents isolated from the VAP cases are listed in the report: for meropenem and colistin resistance in the *A. baumannii* strains, it was 97.3% and 4.3%, respectively, while for P.aeruginosa strains it was 61.3% and 3.8% respectively. Ceftriaxone, meropenem and colistin resistance in *K.pneumoniae* strains were 84.9, 62.6% and 26.2%, respectively. Resistance rates of oxacillin, vancomycin, teicoplanin, linezolid and daptomycin for *S. aureus* strains were 50.8%, 0%, 6.8%, 2.3% and 9.9% respectively.[11] In recent years resistance to carbapenem and colistin in nosocomial Gram-negative pathogens and teicoplanin, linezolid, daptomycin resistance in nosocomial Gram-positive pathogens have grown in Turkey. Based on local surveillance data, each center should make its own therapeutic choice for empiric antimicrobial therapy. The use of appropriate empiric antimicrobial therapy is likely to reduce microbiologic failure and improve clinical outcomes.

VAP preventing program is essential for ICUs. The vast majority of ICUs have implemented ventilator bundles for prevention. Bundle constituents vary from hospital to hospital, but most include a core set of common interventions such as the head of the bed elevation, oral care with chlorhexidine, daily sedative interruptions, thromboembolism prophylaxis, and stress ulcer prophylaxis.[14] Several studies evaluated the efficacy of VAP prevention bundle in the literature. Daniel et al.[15] prospectively evaluated patients and their prevention measures consisted of daily assessments of sedation, daily assessment for extubation, elevation of the head of the bed, and oral care with chlorhexidine. The education of clinical teams was performed. They reported a decrease in VAP incidence from 6.9 to 1.0/1000 ventilation days (p=0.0002) after the implementation of the VAP prevention bundle. Marini et al.[16] Conducted a prospective study, their VAP prevention bundle comprised of elevation of the head of the bed, daily assessments of sedation and extubation, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, daily oral care with chlorhexidine, the use of an endotracheal tubes with subglottic suctioning, and the control of cuff pressure. They reported a decrease in VAP rates from 4.0 to 0.8/1000 ventilation days. Eom et al.[17] conducted a prospective study in adult intensive care units of 6 university hospitals. Their ventilator bundle included the head of the bed elevation, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis, and oral decontamination with chlorhexidine 0.12%. They reported an implementation of the VAP bundle reduced the VAP rate from a mean of 4.08 cases per 1.000 ventilator-days to 1.16 cases per 1.000 ventilator-days. Effective implementation is as essential as creating ICUs VAP bundle. Best practices include continuing education of health care providers, making necessary arrangements for compliance to VAP bundle, and providing regular feedback on process measure performance and outcome rates.

The main limitations of the present study involve retrospective design, and data confined to the experience of a

single center. Thus, interpretation of our findings and extrapolation of our results to larger populations must be made cautiously. Further prospective, controlled, multicentric studies may provide more reliable information on the course, pathogenesis and changing trends of VAPs in the adult population.

Conclusion

To conclude, VAP is a critically important problem for ICUs and VAP preventing program is essential. Bundle constituents vary from hospital to hospital, but the effective implementation is as essential as creating VAP bundle. Best practices include continuing the education of health care providers, making necessary arrangements for compliance to VAP bundle, and providing regular feedback on process measure performance and outcome rates.

Disclosures

Ethics Committee Approval: University of Health Science Izmir Bozyaka Training and Research Hospital Ethic Commitee, dare. 28.08.2018, Decision no: 2018-4.

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Conflict of Interest: None declared.

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