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VENTILATOR-ASSOCIATED PNEUMONIA IN THE INTENSIVE CARE UNIT OF SURGICAL EMERGENCY TEACHING HOSPITAL IN SULAIMANI CITY

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ABSTRACT

Ventilator-associated pneumonia (VAP) is a common nosocomial infection with high mortality in intensive care units. The aim of this study was to determine the prevalence of VAP in Sulaimani Surgical Emergency Teaching Hospital, and examine the frequency of pathogens with their susceptibility patterns. A group of 152 patients on mechanical ventilation and a control group of 65 patients were selected from the Intensive care unit of Sulaimani Surgical Emergency Teaching Hospital/Iraq over a period of one year (from October 2019 to February 2020). Both groups were followed for the development of pneumonia. Culturing, identification and susceptibility testing of pathogens was performed at the Microbiology Department of Public Health Laboratory. The incidence of VAP was 80.9% in the ventilated patient group. Males had a higher incidence than females (ratio 3:1), and patients between 30-40 years were the most affected age group, having been admitted predominantly after traffic accidents. Among pathogens, gram-negative bacteria were the most frequent causative agents (93.3%), notably *Acinetobacter baumannii* (43.3%). Among Gram-positive bacteria only, *Staphylococcus aureus* was frequently present (17.8%). Acquired resistance was exceedingly high, especially in the non-fermenting group of gram-negatives. The incidence of VAP is very high among ICU patients in Sulaimani city predominantly affecting males in the 31-40 year age group. VAP is mostly caused by gram-negative infections (especially *Acinetobacter baumannii*); gram positives are not uncommon, including methicillin-sensitive *staph. aureus* as most common agent of VAP**.** Multidrug resistant bacteria are common and account for near 40% of all VAP agents.

1. Introduction

Ventilator-associated pneumonia (VAP) is defined as lower-respiratory tract infection after 48 hours of intubation and mechanical ventilation without the presence of prior significant pleura-pulmonary involvement [(1)]. VAP is the most common intensive care unit (ICU)-acquired nosocomial infection and is associated with prolonged hospital stay, increased morbidity, and mortality and management costs.

Therefore, potential functional, mechanical and pharmacological measures to prevent VAP have been frequently investigated [(2)]. In diagnostics, besides the clinical symptoms and radiological signs, the microbiological identification of the causative agent is the most fundamental [(3)].

Culturing and sensitivity testing is indispensable since multidrug resistance is common and often requires the use of last resort antibiotics such as carbapenems, polymyxins or glycylcyclines. On some occasions, mixed infections involving viruses or fungi can mean an increase in management modalities [(4)].

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Indicative criteria of VAP include the presence of a new or persistent chest X-ray infiltrate with at least one of the following: purulent secretions, temperature above 38 °C, leukocyte count exceeding 10,000/µl, and isolation of an etiologic agent from specimen obtained by end tracheal aspirate, bronchoalveolar lavage, protected specimen brush, or biopsy [5, 6]. Hemoptysis typically occurs and it is not limited to cases of tuberculosis and lung abscess [3, 7].

Endotracheal aspirate (ETA) uses a closed or open suction system to collect a sample from the tracheo-bronchial tree for quantitative culture without camera guidance. Patients with endotracheal tubes can undergo diverse sampling procedures through sterile catheters, then cultures from the distal airways can be collected either by blind protected brushes or by blind mini-lavage. These procedures have a sensitivity and specificity of 80% when compared to postmortem lung histology and cultures [8, 9]. Bronchoscopic broncho-alveolar lavage excels at targeting a specific area of the lung, but is also more invasive, expensive and has a higher prerequisite in terms of the competence level of personnel[10].

In this study, we aimed to investigate the incidence of VAP in the ICU of the Emergency Hospital in Sulaimani city and characterize the frequency of different pathogens causing VAP and their antibiotic sensitivity patterns. Additionally, we tried to clarify significant demographic relations of VAP with gender, age and underlying illnesses.

2. Methods

In this prospective study, we randomly chose patients on ventilators admitted to the ICU of Sulaimani Emergency Teaching Hospital between October 2019 and February 2020. A total of 152 inpatients on mechanical ventilation were included in the ventilator study group and followed for the development of VAP. Patients were eligible for enrollment if they developed pneumonia after 48 hours of ICU admission, intubation and mechanical ventilation, with intact chest wall and diaphragm.

Patients with signs and symptoms of chest infection at a time of intubation and during the first 48 hours of mechanical ventilation were excluded. Additionally, patients with foreign body inhalation and penetrating lung injury were also ruled out. The control group consisted of 65 randomized patients admitted to our ICU who did not undergo mechanical ventilation, and were followed for development of Hospital-Acquired Pneumonia (HAP). The diagnosis of pneumonia was based on symptoms (fever, cough, dyspnea, productive pulmonary secretion), detection of inflammatory markers (leukocyte count, erythrocyte sedimentation rate, C-reactive protein, and procalcitonin), chest X-ray or CT, and microbiological culturing.

The specimen collection was performed wearing personal protective equipment under aseptic circumstances. From the study group endotracheal aspirates (ETA) and broncho-alveolar lavages (BAL) were obtained through the endotracheal or tracheostomy tube. From the control group, sputum samples and deep pharyngeal aspirates were collected.

For most of the specimens, prolonged storage was not necessary since the laboratory processed them upon receipt. In a few exceptional circumstances (like holidays), the storage conditions were transport swab with preserving media or thioglycolate broth kept in fridge at 4-8 ˚C. After receiving specimens, they were inoculated on Columbia sheep blood (Ibn Al-Betar Research Center, Iraq) and MacConkey agar (Lab M Ltd., UK) for atmospheric air culture, and on chocolate agar for 5% CO_2 incubation for 24 hours at 37 °C.

Cultured plates were then examined for visible growth. Isolate identification was performed with Vitek-II system (bioMérieux SA, France) or the semi-automated API system (bioMérieux SA, France). Antimicrobial sensitivity testing and evaluation was done with either Vitek-II system or using the manual disk diffusion method (Kirby-Bauer method) and interpreted according to clinical and laboratory standards institute (CLSI) recommendations. Methicillin resistant *Staphylococcus aureus* was detected with cefoxitine (30 µg/disc) sensitivity testing.

3. Results

ìThe incidence of VAP was very high among the patients of the ventilator study group: 123 of 152 patients developed VAP (80.9%) in the ICU. From the 123 VAP cases 104 (84.5%) were successfully cultured positive for bacterial pathogens. Culture negative VAP cases might originate from prior antibiotic administration, the presence of fastidious and atypical microorganisms, or viral infections 48 hours after admission. Two cases (1.6%) proved to be of fungal etiology (both were *Candida* species). Polymicrobial infection was present in 0.98% (12/123) of VAP and it was 1.2% (12/104) in VAP with culture positive. In the control group, 21 of the involved 65 patients, developed pneumonia contributing to a HAP incidence of 32.3%, but only 15 of them had a culture positive sample. The differences between the group of patients on ventilators and the control group was statistically significant ($p<0.05$). The VAP mostly developed in the 31-40 year (27.9%) age range while in the control group, pneumonia was mostly in the 51-60 year (33.3%) age group (table 1). Males were predominant in both VAP group and in control group, 76.9% vs. 66.7% respectively.

Age group	Patient groups		Total
	Control (%)	VAP (%)	
0-10 years	1 (6.7)	6 (5.8)	7 (5.9)
11-20	2 (13.3)	10 (9.6)	12 (10.1)
21-30	1 (6.7)	23 (22.1)	24 (20.2)
31-40	3 (20)	29 (27.9)	32 (26.9)
41-50	1 (6.7)	11 (10.6)	12 (10.1)
51-60	5 (33.3)	7 (6.7)	12 (10.1)
61-70	1 (6.7)	10 (9.6)	11 (9.2)
71-80	1 (6.7)	7 (6.7)	8 (6.7)
81+	-	1 (1.0)	1 (0.8)
Total	15 (100)	104 (100)	119 (100)

Table 1. Age distribution of VAP and control group in culture positive cases

Pathologies associated with the VAP group were mainly of traumatic origin (60.5%), and due to various underlying medical conditions in the control group (53.3%) (Table 2).

	Pathology groups	Frequency (%)		
		Control group	VAP group	Total
1	Traffic accident, Fall from height	4 (26.7)	54 (51.9)	58 (48.7)
2	Bullet injury, explosion blast, stab, shrapnel, Suicide attempt	0 (0)	9 (8.7)	9 (7.6)
3	Gastrointestinal obstruction, perforation, etc. Urinary tract complication	3 (20)	13 (12.5)	16 (13.4)
4	Orthopedic complications (amputation, fixation, prosthetic surgery)	0 (0)	1 (1)	1 (0.8)
5	Gynecological complication	0 (0)	2 (1.9)	2 (1.7)
6	Pediatric diseases	0 (0)	1 (1)	1 (0.8)
7	Medical conditions (stroke, Guillain-Barre, myasthenia, hematology, oncology, etc.)	8 (53.3)	24 (23.1)	32 (26.9)
	Total	15 (100)	104 (100)	119 (100)

Table 2. Distribution of VAP and control group in culture positive cases according to their ICU admission pathology

The elaboration of VAP patient samples revealed a gram-negative dominance (82.2% of isolates in VAP patient samples), represented by 15 different bacterial species. *Acinetobacter baumannii* had the highest prevalence in both patient groups (38.1% of all VAP), figure (1). *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli* were the four consecutive pathogens, with 15.3%, 10.2%, 8.5% and 6.8% respectively, shown table 3.

Interestingly, while *Staphylococcus aureus* was a common finding (15.3% in the VAP and 13.3% in the control group), none of the 20 isolates proved to be methicillin-resistant according to CLSI criteria [11].

Bacterial groups			Isolated bacteria	Count	Percentage
Control group isolates n=15	Gram – 11 (73.3%)	1	*Acinetobacter baumannii*	4	26.7 %
		2	*Klebsiella pneumoniae*	4	26.7 %
		3	*Escherichia coli*	2	13.3 %
		4	*Pseudomonas aeruginosa*	1	6.7 %
	Gram + 4 (26.7%)	5	*Staphylococcus aureus*	2	13.3 %
		6	*Staphylococcus epidermidis*	2	13.3 %
VAP group isolates n=118	Gram – 97 (82.2%)	1	*Acinetobacter baumannii*	45	38.1 %
		2	*Klebsiella pneumoniae*	12	10.2 %
		3	*Pseudomonas aeruginosa*	10	8.5 %
		4	*Escherichia coli*	8	6.8 %
		5	*Burkholderia cepacia*	4	3.4 %
		6	*Rhizobium radiobacter*	3	2.5 %
		7	*Pantoea sp.*	3	2.5 %
		8	*Enterobacter cloacae*	2	1.7 %
		9	*Pseudomonas luteola*	2	1.7 %
		10	*Citrobacter braakii*	2	1.7 %
		11	*Raoultella ornithinolytica*	2	1.7 %
		12	*Serratia marcescens*	1	0.8 %
		13	*Proteus sp.*	1	0.8 %
		14	*Pseudomonas fluorescens*	1	0.8 %
		15	*Shewanella putrefaciens*	1	0.8 %
	Gram + 21 (17.8%)	16	*Staphylococcus aureus*	18	15.3%
		17	*Streptococcus* group-B	1	0.8 %
		18	*Enterococcus faecalis*	1	0.8 %
		19	*Staphylococcus epidermidis*	1	0.8 %

Table 3. Bacterial identification results of the isolates in culture positive cases of VAP patients and the control group.

Figure 1. Colonies of *Acinetobacter baumannii* (often nicknamed as Iraqibacter (11) on MacConkey (left plate) and Columbia sheep blood agar (right plate)

The results in the VAP patient group showed that tigecycline was the most effective in vitro antibiotic (96.6% sensitivity rates among the tested bacteria); especially against multidrug-resistant (MDR) Acinetobacter baumannii and Klebsiella pneumoniae (detailed in Table 4 and 5). Acquired resistance against β-lactams among the VAP isolates was formidable, only 2.3%-21.1% of the tested isolates proved to be sensitive to different aminopenicillins (lowest: ampicillin, highest: ticarcillin-clavulanate), albeit third and fourth generation cephalosporins performed marginally better with 22.1% and 20.0% sensitivity rate respectively. Carbapenems showed insufficient overall activity; (ertapenem 81.8%, meropenem 52.6% and imipenem 37.5%) due to the reduced efficacy against most glucose non-fermenting Gram-negatives e. g. Acinetobacter and Pseudomonas species.

	Antibiotic agent	piperacillin + tazobactam	Ceftazidime	Cefepime	Meropenem	Imipenem	Gentamicin	Amikacin	Tobramycin	Ciprofloxacin	Levofloxacin	Moxifloxacin	Tigecycline	Cotrimoxazole	Colistin
	Bacteria	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %
Non-fermenter Gram-negative rods	*Acinetobacter baumannii*				0/2 0%	1/25 4%	4/30 13.3%	1/1 100%	1/13 7.7%	0/26 0%	2/24 8.3%	2/17 11.8%	23/23 100%	0/35 0%	23/23 100%
	Pseudomonas aeruginosa	2/6 33.3%	2/8 25%	2/8 25%	2/7 28.6%	4/6 66.7%	4/8 50%	5/8 62.5%	3/7 42.9%	2/8 25%	0/4 0%	1/3 33.3%			
	Pseudomonas luteola		1/2 50%	1/2 50%	0/1 0%	2/2 100%	0/2 0%	2/2 100%		1/2 50%					
	Pseudomonas fluorescens		1/1 100%	1/1 100%	1/1 100%	1/1 100%	1/1 100%	1/1 100%		1/1 100%					
	Burkholderia cepacia	1/1 100%	1/1 100%			4/4 100%				0/1 0%				0/3 0%	
	Rhizobium radiobacter		1/1 100%			3/3 100%	0/1 0%	1/3 33.3%		0/3 0%				0/2 0%	
	Shewanella putrifaciens					1/1 100%		1/1 100%		1/1 100%					

Table 4. The frequency (and percentage) of sensitive isolates to the listed antibiotics among the non-fermenter gram-negative bacteria isolated from the VAP patient group

	Antibiotic agent	Amoxicillin +clavulanate	Piperacillin +tazobactam	Cefotaxime	Ceftazidime	Cefepime	Meropenem	Imipenem	Ertapenem	Gentamicin	Ciprofloxacin	Chloramphenicol	Cotrimoxazole	Tigecycline	Aztreonam
	Bacteria	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %	COUNT %
Enterobacteriaceae	*Klebsiella pneumoniae*	1/2 50%	1/1 100%	1/2 50%	3/7 42.9%	2/8 25%	1/7 14.3%	5/6 83.3%	3/4 75%	1/7 14.3%	0/2 60%	0/3 0%	2/9 22.2%	4/4 100%	0/3 0%
	Escherichia coli	2/2 100%	2/3 66.7%	2/2 100%	1/2 50%	1/5 20%	4/6 66.7%	5/5 100%	2/2 100%	4/4 100%	2/8 25%	2/3 66.7%	3/4 75%	4/4 100%	0/4 0%
	Enterobacter cloacae					2/2 100%	2/2 100%	2/2 100%			1/1 100%	2/2 100%		2/2 100%	2/2 100%
	Citrobacter braakii			0/1 0%			2/2 100%	2/2 100%		0/1 0%	1/2 50%		0/2 0%		
	Serratia marcescens			1/1 100%	1/1 100%		1/1 100%	1/1 100%	1/1 100%	1/1 100%	1/1 100%		1/1 100%		
	Proteus sp.	1/1 100%	0/1 0%	0/1 0%	0/1 0%	0/1 0%	0/1 0%		1/1 100%	1/1 100%	1/1 100%		0/1 0%		
	Pantoea sp.				1/1 100%	1/2 50%	1/1 100%	1/1 100%	0/1 0%	1/3 33.3%	0/3 0%	0/1 0%	1/1 100%		0/1 0%
	Raoultella terrigena						1/1 100%	1/1 100%	1/1 100%		1/1 100%			1/1 100%	

Table 5. Number (and percentage) of sensitive isolates to the listed agents among the *Enterobacteriaceae* family isolated from the VAP patient group

Regarding fluoroquinolones, moxifloxacin attained the highest sensitivity rate (50%), while ciprofloxacin and levofloxacin performed poorly (35% for both).

Amikacin was rarely investigated but showed a quite consistent activity (74.4%). In the control group the most effective antibiotics were (with 100% susceptibility among the targeted bacteria) amikacin, minocycline, trimethoprim-sulfamethoxazole, clindamycin, quinupristin-dalfoprsitin, and linezolid.

4. Discussion

Ventilator-associated pneumonia is considered a significant risk factor for increasing mortality, prolonging ICU stay and increasing the financial burden on hospitals. The incidence of VAP in this study was 81% among ICU patients (123 VAPs out of 152 patients), higher than in most other studies (15-37%) performed in similar geoeconomical regions [12-16]. We suspect that the most important contributing factor to this is the over-representation of critically ill trauma patients and the high patient-to-nurse ratio (which might have adversely affected the quality of care given to the patients) in our ICU. However, identifying the precise reason for this is important for the future.

Most VAP patients are in the 31-40 year age grou. Typically, they were involved in trauma and surgical emergencies. A study performed by Blot S., et al reported that ventilator-associated pneumonia did not occur more frequently among the elderly, but associated mortality in these patients was higher (54). A study taken in India showed that mean age of VAP patients was 34 years which is consistent with our findings [14].

The higher ratio for males (3:1) distinct in both patient groups also originates mainly in social, religious and physical differences between the two genders, since males are more frequently involved in construction work and traffic accidents (these two being responsible for 49% of total admissions in our study), or get traumatized during military and social conflicts [17]. Pediatric and gynecologic conditions were uncommon in both groups because patients with such aliments are more likely to be admitted to pediatric and maternity hospitals respectively, instead of emergency hospitals.

The gram-negative pathogens were present in almost all of the VAP cases, and *Acinetobacter baumannii* had the highest prevalence in both patient groups (38.1% of all VAP and 26.7% of all HAP). Other studies in comparable geopolitical environments found similar results [18, 19]. Interestingly, while *Staphylococcus aureus* was common, none of the 20 isolates proved to be methicillin-resistant. With regard to antibiotics, we found that tigecycline had the best overall *in vitro* activity (96.6% sensitivity rate among the tested strains), but is a questionable option since it's *in vivo* effectiveness and pharmacokinetics in pneumonia are not very well established. Amikacin also showed considerable inhibitory activity (74.4%), making it a good candidate for combinational therapy.

Some of the above mentioned studies obtained different data, many of them reporting *Pseudomonas aeruginosa* as the most frequent bacteria up to 55% in VAP (14), usually followed by *Acinetobacter baumannii* (33%) [20-22].

In a prospective study performed on 813 mechanically ventilated ICU patients in Novi Sad - Republic of Serbia, VAP was diagnosed in 115 patients. In 82 cases the pathogen was successfully cultured and *Acinetobacter baumannii* was the most prevalent bacteria (65%) showing sensitivity to only 1 or 2 antibiotic groups in about 90% of the cases. The investigators also reported that more than 86% of the *Klebsiella pneumoniae* isolates were resistant to cefepime (interpreted according to EUCAST guidelines), and the mortality rate was 68%, which is in agreement with the literature [6].

Although colistin, tigecycline and some carbapenems are reasonable choices for empiric treatment of VAP patients in our ICU, the use of these last resort antimicrobials should be limited for infections proven to be sensitive exclusively to them, and followed by culturing to avoid emergence of resistance during therapy. Aminopenicillins, cephalosporins, and quinolones have lost purpose in empiric VAP treatment. Amikacin and other aminoglycosides might be considered in combinational therapy for their good synergistic potential. The intimidating amount of infections caused by multi-resistant pathogens demonstrates that we have entered a dark era of antibiotics, and a change in antimicrobial restriction policy is mandatory but already too late.

5. Conclusions

The incidence of VAP is very high among ICU patients in Sulaimani city predominantly affecting males in the 31-40 year age group. VAP is mostly caused by gram-negative infections (especially *Acinetobacter baumannii*); gram positives are not uncommon, including methicillin-sensitive *staph. aureus* as most common agent of VAP**.** Multidrug resistant bacteria are common and account for nearly 40% of all VAP agents. Colistin, tigecycline and some carbapenems are reasonable choices for empiric treatment of VAP patients in our ICU, while aminopenicillins, cephalosporins, and quinolones have lost purpose in empiric VAP treatment.

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