

Risk Factor Analysis of Pan-drug Resistant *Acinetobacter baumannii*-induced Ventilator-associated Pneumonia in ICU

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Zheng *et al.*: Drug resistant bacteria-induced ventilator-associated pneumonia

This study was to investigate the risk factors of ventilator-associated pneumonia caused by pan-drug resistant *Acinetobacter baumannii* in intensive care unit so as to provide related basis for clinical prevention. A total of 105 intensive care unit patients, who were treated with ventilator over 48 h in the First Affiliated Hospital of Anhui Medical University and developed *Acinetobacter baumannii*-induced ventilator-associated pneumonia from January to September 2017 were enrolled in this study, including 70 cases with pan-drug resistant *Acinetobacter baumannii* infection served as the pan-drug resistant group and 35 cases with non-pan-drug resistant *Acinetobacter baumannii* infection served as the control group. The univariate analysis and logistic regression method were used to explore the risk factors of ventilator-associated pneumonia caused by pan-drug resistant *Acinetobacter baumannii*. The result of univariate analysis showed that the risk factors of pan-drug resistant *Acinetobacter baumannii*-induced ventilator-associated pneumonia included tracheotomy, enteral nutrition, the use of carbapenems and use of more than 3 antibiotics before infection. Logistic regression analysis showed that enteral nutrition and the use of carbapenems were independent risk factors of pan-drug resistant *Acinetobacter baumannii*-induced ventilator-associated pneumonia. In conclusion, enteral malnutrition and the use of carbapenems were the two significant risk factors for pan-drug resistant *Acinetobacter baumannii*-induced ventilator-associated pneumonia, which are necessary to take active preventive measures in clinical practice.

Key words: Intensive care unit, pan-drug resistant *Acinetobacter baumannii*, ventilator-associated pneumonia, logistic regression analysis, risk factors

Acinetobacter baumannii is widely found in water, soil, hospital environment and human skin. It is a kind of conditional pathogenic bacteria, but with the application of broad-spectrum antibiotics and glucocorticoids as well as the extensive development of invasive medical procedures, *A. baumannii* has become the main pathogen of nosocomial infection, especially as an important pathogen of ventilator-associated pneumonia (VAP). According to the monitoring data of nosocomial infection in the USA and domestic survey analysis on the common pathogenic bacteria of hospital infection, *A. baumannii* infection ranks fourth among all nosocomial infections. In fact, *A. baumannii* infection is most commonly seen in lungs and becomes an important pathogen of hospital-acquired pneumonia (HAP), especially of VAP^[1]. The rate of acquisition drug resistances of *A. baumannii* has increased year after year with the

emergence of multidrug resistant and even pan-resistant strains, which seriously threaten human health and became a major problem demanding prompt solution in clinical practices^[2]. In recent years, extensive use of antibiotics has become a major contributing factor for the increased resistance acquired by *A. baumannii*. The pan-drug resistant *A. baumannii* (PDRAB) is increasing, especially in the intensive care unit (ICU) severe burns wards^[3]. PDRAB is almost resistant to all commonly used antibiotics and is easy to cause nosocomial outbreak through cross infection, which a great difficulty to treat the infection^[4,5]. At present, there are few investigations on the clinical features and risk factors of PDRAB-induced VAP in ICU wards. The study was mainly aimed to perform prospective monitoring on the ICU patients treated on the ventilator over 48 h in the First Affiliated Hospital of Anhui Medical University from January to September 2017 to

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explore the risk factors of PDRAB-induced VAP so as to provide relevant basis for prevention of the infection. A total of 105 ICU patients, who were treated on ventilator over 48 h in this hospital and developed *A. baumannii*-induced VAP from January to September 2017 were enrolled in this study, including 70 cases with PDRAB infection served as the PDR group and 35 cases with non-PDRAB infection served as the control group. All patients participated in the study have signed the informed consent form. With combination of relevant literature and clinical practices, possible risk factors of PDRAB-induced VAP were screened out followed by the development of questionnaire, the patients treated with ventilator over 48 h were prospectively monitored by ICU doctor, and the information of the incidence of PDRAB induced VAP was recorded followed by statistical analysis. VAP diagnosis was implemented according to diagnostic criteria for nosocomial infection issued by Ministry of Health, People's Republic of China, there is new or persistent or progressive infiltration in the chest X-ray film with more than 3 indices, which were, fever with rectal temperature was over 38° or under 35°;

white blood cell count >10×10⁹/l with Gram's staining there were over 10 white blood cells at each high magnification; the culture of endotracheal aspiration was positive. The data were analyzed on SPSS 21 software, the count data were checked by X² test and the measurement data t test. The logistic regression was used for multivariate analysis, p<0.05 suggested that there was difference of statistical significance. A total of 105 ICU patients were enrolled in this study, including 70 cases with PDRAB infection served as the PDR group and 35 cases with non-PDRAB infection served as the control group. There were no statistically significant differences between the 2 groups in general information such as the gender, age, APACHE II, GCS score, ventilation time, mechanical ventilation time before positive culture, mixed infection, fungal infection and smoking history, as shown in Table 1. The univariate analysis showed that the risk factors of PDRAB-induced VAP included tracheotomy, enteral nutrition, the use of carbapenems and the use of more than 3 antibiotics before infection, as shown in Table 2. The logistic regression analysis was conducted on the 4 factors of statistical significance

TABLE 1: COMPARISON OF GENERAL DATA BETWEEN THE TWO GROUPS

Group	n	male	Age (y)	APACHE II	GCS	ventilation time (d)	ventilation time before positive culture (d)	mixed infection	fungal infection	smoking history
PDR group	70	36	57.5±7.5	23.4±1.7	9.6±1.7	21.8±4.6	8.2±1.2	7	9	23
Control group	35	19	57.3±6.8	23.2±1.9	9.5±1.5	21.4±3.7	8.3±1.1	4	6	11
t/X ²		0.076	0.652	0.187	0.057	0.673	0.096	0.051	0.35	0.022
P		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

TABLE 2: UNIVARIATE ANALYSIS ON RISK FACTORS OF PDRAB-INDUCED VAP

Variable	PDRAB group (n=70)	Control group (n=35)	X ²	P
Associated disease				
Diabetes	7	4	0.051	>0.05
Cardiovascular diseases	15	8	0.028	>0.05
Lung diseases	16	9	0.015	>0.05
Invasive operation				
Central venous catheterization	57	29	0.032	>0.05
Catheter	64	31	0.221	>0.05
Racheotomy	40	11	6.176	<0.05
Enteral nutrition	56	16	12.727	<0.05
Hormone use	41	20	0.02	>0.05
Antacid use	64	31	0.221	>0.05
Antibiotic use				
Piperacillin-tazobactam	34	16	0.076	>0.05
Third-generation cephalosporin	33	16	0.019	>0.05
carbapenems	36	7	9.531	<0.05
Use of more than 3 antibiotics before infection	43	10	10.077	<0.05

by univariate analysis and the results showed that enteral nutrition as well as the the use of carbapenems were independent risk factors of PDRAB-induced VAP, as shown in Table 3. VAP, one of HAP, refers to the pneumonia occurring since 48 h after mechanical ventilation. It is a common and serious complication in the process of mechanical ventilation. Once the patients have VAP, they are prone to difficulty of extubation, thereby prolonging the duration of hospitalization with increased expenses and even threatening the patients to death. Due to the specialty in pathogenic bacteria, diagnosis, treatment and higher mortality, VAP has attracted widespread attention in recent years. It has certain local and epidemiological characteristics and its occurrence is closely related to potential diseases, past use of antibiotics, transmission routes and source of pathogenic bacteria. Pathogenic spectrum varies from region to region^[6,7]. 90 % of the pathogenic bacteria were bacterial infections, and the infection rate of Gram-negative bacteria was higher. Generally, old patients have more severe underlying disease, low resistance and long hospital stay, and some patients may have lower immunity due to the use of immunosuppressants and hormones^[8,9]. Invasive procedures like endotracheal intubation make damages to local defense mechanism, leading to the condition that the pathogens in the upper respiratory tract are prone to spreading to the lower respiratory tract. In addition, the wide application of broad-spectrum antibiotics also leads to elevated infection rate of resistant opportunistic pathogens, flora imbalance and increased fungal infection^[10]. The therapy of VAP included, treatment of primary diseases, prevention of risk factors, nutritional support and immunological-support treatment along with application of reasonable antibiotics, the most important in this regard. At early stage, the correct use of antibiotics can reduce the mortality in patients. Because the diagnosis of VAP is difficult, patients highly suspected with VAP can be timely treated with empirical antibiotics simultaneously with bacterial cultures and drug sensitivity test. With the transition of pathogenic bacteria and the emergence of multiple antibiotic resistant strains, the choice of antibiotics for VAP treatment is also changing^[11]. *A. baumannii* has become an important clinical

pathogen and is characterized by fast obtaining, resistance spreading, multi and widespread-drug resistance. PDRAB has been worldwide epidemic and became a global challenge in the field of anti-infective therapy^[12]. MDRAB is defined to be resistant to at least 3 of such agents as cephalosporins against *Pseudomonas*, carbapenem antibiotics against *Pseudomonas*, complex preparation containing 13-lactamase inhibitors, fluoroquinolones and aminoglycosides^[13]. Extensively-drug resistant *A. baumannii* refers to the strains sensitive to only 1 or 2 types with potential anti-acinetobacter activity, commonly including tigecycline and colistin. *A. baumannii* infection is more commonly seen in critically ill patients and often accompanied by other bacterial infections or fungal infections, leading to high mortality in patients^[14]. In this study, the comparison of subjects' general data between the PDR group and the control group showed no statistically significant difference in gender, age, APACHE II, GCS score, ventilation time, mechanical ventilation time before positive culture, mixed infection, fungal infection and smoking history, suggesting that there is no obvious difference in general epidemiological characteristics between PDRAB-induced VAP patients and non-PDRAB induced VAP patients. According to the survey, PDRAB-induced VAP is related to tracheotomy and enteral nutrition with the latter being an independent risk factor. It is possibly because these invasive procedures destroy human normal defense mechanisms and therefore increase the chance of bacterial infection. When the enteral nutrition is retained in gastric tube, the stomach shows reflex inhibition with a delay of gastric emptying, likely to cause mis-inhalation and increase the chance of pulmonary infection. Besides, operation error, inadequate aseptic technique and unqualified sterilization in the process will also increase the incidence of infection in patients. The survey also showed that the number of antibiotics used before infection in the two groups was statistically different, indicating that the choice of multiple antibiotics may be an important factor of PDRAB infection. A related study has also shown that the infection of *A. baumannii* is related to the use of carbapenem antibiotics^[15]. And it

TABLE 3: LOGISTIC REGRESSION ANALYSIS ON RISK FACTORS OF PDRAB-INDUCED VAP

Variable	B	SE	Wald X ²	OR (95 % CI)	P
Tracheotomy (with vs. without)	0.764	0.503	1.292	2.044 (0.692-5.738)	>0.05
Enteral nutrition (with vs. without)	1.185	0.517	4.324	3.155 (1.093-8.349)	<0.05
Carbapenems (with vs. without)	1.361	0.374	5.125	4.326 (1.254-14.316)	<0.05
Use of more than 3 antibiotics before infection (yes vs. no)	0.793	0.684	1.602	0.571 (0.168-1.372)	>0.05

is also shown in this study that carbapenems is an independent risk factor for PDRAB-induced VAP, and the resistance mechanism of *A. baumannii* against carbapenems is mainly the production of KPC-2 and blaOXA-23 type enzyme as well as absent expression of 25ku outer membrane protein with efflux system overexpression probably involved in drug resistance of meropenem. It is realized that following targeted prevention and control measures should be taken according to the clinical characteristics of VAP caused by PDRAB, (1) pay attention to the monitoring of PDR bacteria and implement PDRAB screening system. High-risk patients are given close monitoring with high focus on ICU patients undergoing invasive treatments such as tracheotomy, ventilator and long-term medication of antibiotics, and patients should be immediately treated in isolation as soon as they are found the signs of PDRAB infection; (2) strengthen training of knowledge about PDR bacteria infections and enhance management consciousness of the infection in medical personnel; (3) strictly carry out disinfection and isolation system as well as hand hygiene management. The sign of contact isolation is pasted on medical records and bedside the patients infected with PDRAB; the staff contacting such patients are strictly given the implement of standard precautions and hand hygiene system; when taking invasive procedures, the operating rules and systems must be strictly abided by; (4) conduct regular evaluation on the patients undergoing invasive operation to reduce invasive time and (5) make sure the correctness and timeliness of sample collection. Antibiotics are correctly chosen according to the results of drug sensitivity to prevent the resistance caused by abuse of antibiotics. Enteral malnutrition and the use of carbapenems are two significant risk factors for PDRAB-induced VAP, which are necessary to take active preventive measures in clinical practice.

Conflict of interest:

No conflict of interest between any of the authors.

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