

Antibiotics De-Escalation in the Treatment of Ventilator-Associated Pneumonia in Trauma Patients: A Retrospective Study on Propensity Score Matching Method

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Abstract

Background: Antimicrobial de-escalation refers to starting the antimicrobial treatment with broad-spectrum antibiotics, followed by narrowing the drug spectrum according to culture results. The present study evaluated the effect of de-escalation on ventilator-associated pneumonia (VAP) in trauma patients.

Methods: This retrospective study was conducted on trauma patients with VAP, who received de-escalation therapy (de-escalation group) or non-de-escalation therapy (non-de-escalation group). Propensity score matching method was used to balance the baseline characteristics between both groups. The 28-day mortality, length of hospitalization and Intensive Care Unit stay, and expense of antibiotics and hospitalization between both groups were compared. Multivariable analysis explored the factors that influenced the 28-day mortality and implementation of de-escalation.

Results: Among the 156 patients, 62 patients received de-escalation therapy and 94 patients received non-de-escalation therapy. No significant difference was observed in 28-day mortality between both groups (28.6% vs. 23.8%, $P = 0.620$). The duration of antibiotics treatment in the de-escalation group was shorter than that in the non-de-escalation group (11 [8–13] vs. 14 [8–19] days, $P = 0.045$). The expenses of antibiotics and hospitalization in de-escalation group were significantly lower than that in the non-de-escalation group (6430 ± 2730 vs. 7618 ± 2568 RMB Yuan, $P = 0.043$ and $19,173 \pm 16,861$ vs. $24,184 \pm 12,039$ RMB Yuan, $P = 0.024$, respectively). Multivariate analysis showed that high Acute Physiology and Chronic Health Evaluation II (APACHE II) score, high injury severity score, multi-drug resistant (MDR) infection, and inappropriate initial antibiotics were associated with patients' 28-day mortality, while high APACHE II score, MDR infection and inappropriate initial antibiotics were independent factors that prevented the implementation of de-escalation.

Conclusions: De-escalation strategy in the treatment of trauma patients with VAP could reduce the duration of antibiotics treatments and expense of hospitalization, without increasing the 28-day mortality and MDR infection.

Key words: De-Escalation; Propensity Score Matching; Trauma; Ventilator-Associated Pneumonia

INTRODUCTION

Trauma, a common emergency and critical disease, is the major cause of death in individuals of <46-year-old.^[1] About 80% of the patients died within the first 24 h post trauma, establishing a direct correlation, while 20% of the deaths occurred later due to infection.^[2] Due to immunoparalysis, endotracheal intubation, impaired cough reflex, and some other factors, trauma patients are prone to suffer from ventilator-associated pneumonia (VAP),^[3] also known as trauma-associated pneumonia (TAP). This manifestation not only prolongs hospital stay but also increases the mortality. Antimicrobial therapy plays a key role in the treatment of VAP, and appropriate initial antimicrobial treatment is associated

with decreased mortality.^[4] Therefore, broad-spectrum or combination antibiotics are usually administered within the 1st h to combat against the likely causative pathogens. However, long-term use of broad-spectrum antimicrobial therapy may lead to the emergence of bacterial resistance,

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Received: 23-01-2018 **Edited by:** Qiang Shi

How to cite this article: Li H, Yang CH, Huang LO, Cui YH, Xu D, Wu CR, Tang JG. Antibiotics De-Escalation in the Treatment of Ventilator-Associated Pneumonia in Trauma Patients: A Retrospective Study on Propensity Score Matching Method. Chin Med J 2018;131:1151-7.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.231529

increasing the medical costs and some antibiotic-related adverse events. To limit the emergence of resistance, international guidelines recommend that antimicrobial therapy should be discontinued or narrowed according to the identity of the specific pathogens and their susceptibility to specific antibiotics, which is termed as de-escalation. Currently, literatures regarding the de-escalation therapy are mainly focused on VAP and sepsis,^[5,6] and the results have shown that de-escalation therapy is a safe strategy without increasing the mortality. However, the effects of de-escalation strategy on VAP in trauma patients are rarely reported. In this study, we assessed the impact of antibiotics de-escalation strategy on trauma patients with VAP.

METHODS

Ethical approval

This retrospective study complied with the *Declaration of Helsinki* and was approved by the Institutional Ethics Committee of Shanghai Fifth People's Hospital. All patients included in the study or their supervisors provided the informed consents.

Patient selection

All mechanically ventilated trauma patients admitted to the Department of Emergency and Intensive Care Unit (ICU) from January 2013 to December 2017 were assessed for enrolment in the study. A total of 156 trauma patients on mechanical ventilation (MV) had a documented VAP by laboratory tests and radiological examination, of which 62 constituted the de-escalation group and the remaining 94 were in the non-de-escalation group. TAP was defined as pneumonia that occurs ≥ 48 h after endotracheal intubation in trauma patients and diagnosed according to the criterion of VAP.^[7] The VAP is defined by the following criteria: the presence of chest infiltrates plus at least two of the following criteria: fever, leukocytosis, purulent sputum, and isolation of pathogenic bacteria. The following patients were excluded from the study: those who died within 48 h after intubation, those with acquired immune deficiency syndrome, and those without bacteriological examination.

Study methods

Each patient's clinical characteristics, demographics, laboratory and radiological test results, and bacterial culture results were collected from the electronic medical record by trained medical students and reviewed by two registered physicians. The patients' injury severity was measured using injury severity score (ISS). In the present study, strategies of antibiotic de-escalation therapy included shifting from combined antibiotics to a single antibiotic, narrowing the antibiotic spectrum, or discontinuation of the antibiotics. The decision about de-escalating the initial antibiotics was made by the attending physician based on the results of the microbiological examination. If these results were not available, the decision of de-escalation was based on the patients' clinical condition, laboratory tests, and radiological examination. The change in anti-fungal treatment was not

considered as de-escalation. Early-onset TAP was defined as pneumonia occurring within 5 days post-tracheal intubation in trauma patients; otherwise, it was late-onset TAP. Inappropriate initial antimicrobial treatment was defined as insufficient coverage of all isolated pathogens by antimicrobial treatment at the onset of VAP. Sepsis was diagnosed according to the third international consensus definitions for sepsis and sepsis shock in the study.^[8]

Statistical analysis

Categorical variables were expressed as frequency and percentages, and were compared using Pearson's Chi-squared tests. Continuous variables were expressed as a mean \pm standard deviation (SD) or median and interquartile range (IQR) as appropriate. Student's *t*-test or Mann-Whitney test was used to evaluate the difference between the two groups. All statistical analyses were performed using the Stata/MP 14.2 software (College Station, Texas, USA), and a value of $P < 0.05$ were considered as statistically significant. To control the influence of potential confounders on the outcome, a propensity score matching (PSM) analysis was used to match the de-escalated with the non-de-escalated patients in a 1:1 ratio by the nearest neighbor matching based on the width of caliper = 0.05. The command "psmatch2" was used for PSM. The covariates for propensity matching included age, gender, principal problem when admitted to the ICU, comorbidity, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, clinical pulmonary infection score, ISS scores, late-onset VAP, sepsis, infections with multi-drug resistant (MDR) bacteria, and appropriate initial antimicrobial treatment. Univariable logistic regression analysis was performed to detect risk factors associated with patients' 28-day mortality and de-escalation before PSM. Independent risk factors were screened by stepwise backward multivariable logistic regression, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable.

RESULTS

Baseline characteristics before and after propensity matching

During the study period, a total of 177 mechanically ventilated trauma patients were screened for eligibility, of these, 21 were excluded as a result of death within 48 h after admission or no results of bacterial detection or other reasons. The remaining 156 patients were included in the study. The de-escalated antibiotic treatment was administered in 62 patients, and non-de-escalation in 94 patients. Before propensity matching, a large number of patients in the de-escalation group suffered from diabetes mellitus (37.1% vs. 18.1%, $P = 0.008$), sepsis (35.5% vs. 19.2%, $P = 0.022$), late-onset VAP (48.4% vs. 68.1%, $P = 0.014$), and infection with MDR bacteria (19.4% vs. 36.2%, $P = 0.024$). In addition, APACHE II scores among the non-de-escalated patients were higher than the de-escalation patients (17 [14–21] vs. 14 [12–19], $P = 0.012$). After propensity matching, the difference in the listed variables between the two groups

did not show any significance. The baseline characteristics in both groups before and after propensity matching are presented in Table 1. Initial empirical antibiotics and isolated pathogens are listed in Table 2.

Treatment efficacy and economic benefits in both groups before and after propensity matching

Before propensity matching, the expenses of antibiotics and hospitalization in the de-escalation group were significantly lower than that in the non-de-escalation group (6504 ± 2578 vs. 7445 ± 2277 RMB Yuan, $P = 0.018$ and 18,755 ± 6564 vs. 21,995 ± 9572 RMB Yuan, $P = 0.021$, respectively). Furthermore, no difference was observed regarding the length of hospital and ICU stays, duration of MV, 28-day mortality, and period of antibiotics treatment. After adjusting for the confounding factors using PSM method, the difference in antibiotics and hospitalization expenses in both groups still existed (6430 ± 2730 vs. 7618 ± 2568 RMB Yuan, $P = 0.043$ and 19,173 ± 16,861 vs. 24,184 ± 12,039 RMB Yuan, $P = 0.024$, respectively). The days of antibiotics treatment in the de-escalation group were shorter than that in the non-de-escalation group (11 [8–13] vs. 14 [8–19] days, $P = 0.045$); however, no difference was noted in the mortality between both groups [Table 3].

Risk factors associated with 28-day mortality using univariable and multivariable logistic regression analysis before propensity matching

In univariable analysis, factors associated with patients' 28-day mortality were high APACHE II score ($OR\ 1.13$, 95% $CI: 1.05–1.22$, $P = 0.001$), high ISS score ($OR\ 1.09$, 95% $CI: 1.03–1.14$, $P = 0.001$), and inappropriate initial antimicrobial treatment ($OR\ 2.91$, 95% $CI: 1.42–5.94$, $P = 0.003$). Multivariable logistic regression analysis showed that high APACHE II score ($OR\ 1.14$, 95% $CI: 1.05–1.24$, $P = 0.002$), high ISS score ($OR\ 1.09$, 95% $CI: 1.04–1.16$, $P = 0.001$), MDR infection ($OR\ 2.34$, 95% $CI: 1.04–5.26$, $P = 0.041$), and inappropriate initial antimicrobial treatment ($OR\ 2.34$, 95% $CI: 1.07–5.14$, $P = 0.034$) were independent factors associated with patients' 28-day mortality [Table 4].

Risk factors associated with de-escalation using univariable and multivariable logistic regression analysis before propensity matching

In univariable analysis, factors preventing the antibiotics de-escalation included high APACHE II score ($OR\ 0.91$, 95% $CI: 0.84–0.98$, $P = 0.013$), sepsis ($OR\ 2.32$, 95% $CI: 1.11–4.82$, $P = 0.024$), MDR infection ($OR\ 0.42$, 95% $CI: 0.19–0.90$, $P = 0.026$), and late-onset VAP ($OR\ 0.44$, 95% $CI: 0.23–0.85$, $P = 0.015$), while appropriate initial

Table 1: Baseline characteristics of patients in both groups before and after propensity score matching

Characteristics	Before propensity score matching				After propensity score matching			
	De-escalation group (n = 62)	Non-de-escalation group (n = 94)	Statistics	P	De-escalation group (n = 42)	Non-de-escalation group (n = 42)	Statistics	P
Causes of admission, n (%)								
Head or neck injury	22 (35.5)	35 (37.2)	0.049*	0.824	16 (38.1)	18 (42.9)	0.198*	0.657
Thoracic or abdominal injury	18 (29.0)	27 (28.7)	0.002*	0.967	12 (28.6)	10 (23.8)	0.246*	0.620
Spinal or pelvic injury	15 (24.2)	20 (21.2)	0.183*	0.669	11 (26.2)	9 (21.4)	0.263*	0.608
Others	7 (11.3)	12 (12.8)	0.076*	0.783	3 (7.1)	5 (11.9)	–	0.713
Comorbidities, n (%)								
Hypertension	8 (12.9)	20 (21.3)	1.779*	0.182	5 (11.9)	10 (23.8)	2.029*	0.154
Diabetes mellitus	23 (37.1)	17 (18.1)	7.082*	0.008	16 (38.1)	9 (21.4)	2.791*	0.095
COPD	12 (19.4)	31 (33.0)	3.473*	0.062	9 (21.4)	12 (28.6)	0.571*	0.450
Heart failure	12 (19.4)	9 (9.6)	3.068*	0.080	7 (16.7)	5 (11.9)	0.389*	0.533
Others	7 (11.3)	17 (18.1)	1.325*	0.250	5 (11.9)	6 (14.3)	0.105*	0.746
Gender (male), n (%)	43 (69.4)	61 (64.9)	0.335*	0.563	29 (69.1)	27 (64.3)	0.214*	0.643
Ages (years), mean ± SD	43 ± 12	46 ± 17	1.544†	0.125	45 ± 17	46 ± 12	0.435†	0.665
APACHE II scores, median (IQR)	14 (12–19)	17 (14–21)	2.528‡	0.012	16 (14–20)	15.5 (14–19)	0.942‡	0.346
CPIS scores, median (IQR)	7 (6–10)	8 (6–9)	0.468‡	0.640	9 (8–9)	9 (8–9)	0.407‡	0.684
ISS scores, median (IQR)	25 (18–28)	19 (16–26)	1.993‡	0.046	24 (17–27)	22 (18–26)	0.040‡	0.968
Sepsis, n (%)	22 (35.5)	18 (19.2)	5.228*	0.022	10 (23.8)	9 (21.4)	0.068*	0.794
MDR infection, n (%)	12 (19.4)	34 (36.2)	5.081*	0.024	10 (23.8)	10 (23.8)	0.000*	1.000
Positive culture results, n (%)	50 (80.7)	73 (77.7)	0.200*	0.655	36 (85.7)	33 (78.6)	0.730*	0.393
Onset of VAP, n (%)								
Early-onset	32 (51.6)	30 (31.9)	6.053*	0.014	18 (42.9)	22 (52.4)	0.764*	0.382
Late-onset	30 (48.4)	64 (68.1)			24 (57.1)	20 (47.6)		
Initial appropriate antibiotics, n (%)	49 (79.0)	51 (54.3)	9.967*	0.002	31 (73.8)	26 (61.9)	1.365*	0.243

* χ^2 value for Pearson's Chi-squared test; † t value for group t -test; ‡ Z value for Mann–Whitney test. –: Not applicable; SD: Standard deviation; IQR: Interquartile range; COPD: Chronic obstructive pulmonary disease; APACHE II: Acute Physiology and Chronic Health Evaluation II; CPIS: Clinical pulmonary infection score; ISS: Injury severity score; MDR: Multi-drug resistant; VAP: Ventilator-associated pneumonia.

Table 2: Initial empirical antibiotics and isolated pathogens before and after propensity score matching

Items	Before propensity score matching				After propensity score matching			
	De-escalation group (n = 62)	Non-de-escalation group (n = 94)	χ^2	P	De-escalation group (n = 42)	Non-de-escalation group (n = 42)	χ^2	P
Initial empirical antibiotics, n (%)								
Carbapenems	15 (24.2)	32 (34.0)	1.722	0.190	8 (19.1)	13 (31.0)	1.587	0.208
Piperacillin and tazobactam	21 (33.9)	19 (20.2)	3.655	0.056	14 (33.3)	11 (26.2)	0.513	0.474
Cefoperazone and sulbactam	19 (30.7)	15 (16.0)	4.728	0.030	11 (26.2)	6 (14.3)	1.844	0.175
Cefepime	11 (17.7)	26 (27.7)	2.031	0.154	5 (11.9)	7 (16.7)	0.389	0.533
The 3 rd -generation cephalosporin	9 (14.5)	21 (22.3)	1.473	0.225	5 (11.9)	10 (23.8)	2.029	0.154
Tigecycline	5 (8.1)	11 (11.7)	0.537	0.464	0 (0)	3 (7.14)	–	0.241
Fluoroquinolone	11 (17.7)	30 (31.9)	3.873	0.049	9 (21.4)	14 (33.3)	1.497	0.221
Aminoglycosides	15 (24.2)	19 (20.2)	0.347	0.556	11 (26.2)	16 (38.1)	1.365	0.243
Glycopeptides	11 (17.7)	20 (21.3)	0.293	0.588	5 (11.9)	14 (33.3)	5.509	0.019
Linezolid	4 (6.5)	11 (11.7)	1.185	0.276	1 (2.38)	4 (9.52)	–	0.360
Antifungal agents	8 (12.9)	15 (16.0)	0.277	0.599	5 (11.9)	7 (16.7)	0.389	0.533
Combination therapy	35 (56.5)	72 (76.6)	7.037	0.008	23 (54.8)	27 (64.3)	0.791	0.374
Isolated pathogens, n (%)								
<i>Acinetobacter baumannii</i>	14 (22.6)	24 (25.5)	0.177	0.674	9 (21.4)	11 (26.2)	0.263	0.608
<i>Pseudomonas aeruginosa</i>	18 (29.0)	29 (30.9)	0.059	0.809	15 (35.7)	23 (54.8)	3.076	0.079
<i>Klebsiella pneumoniae</i>	11 (17.7)	11 (11.7)	1.125	0.289	6 (14.3)	4 (9.52)	0.454	0.500
<i>Escherichia coli</i>	9 (14.5)	20 (21.3)	1.128	0.288	7 (16.6)	15 (35.7)	3.941	0.047
ESBL (+)	22 (35.5)	48 (51.1)	3.666	0.056	18 (42.9)	23 (54.8)	1.191	0.275
MRSA	8 (12.9)	21 (22.3)	2.199	0.138	6 (14.3)	12 (28.6)	2.546	0.111
MDR	12 (19.4)	34 (36.2)	5.081	0.024	10 (23.8)	10 (23.8)	0.000	1.000
Others	13 (21.0)	19 (20.2)	0.013	0.909	10 (23.8)	15 (35.7)	1.424	0.233

–: Not applicable; ESBL: Extended-spectrum beta-lactamase; MRSA: Methicillin-resistant *Staphylococcus aureus*; MDR: Multi-drug resistant.

antimicrobial treatment (*OR* 0.36, 95% *CI*: 0.17–0.79, *P* = 0.010) contributed to antibiotics de-escalation. Multivariable logistic regression analysis showed that APACHE II score (*OR* 0.89, 95% *CI*: 0.83–0.98, *P* = 0.012), MDR infection (*OR* 0.34, 95% *CI*: 0.15–0.80, *P* = 0.014), and inappropriate initial antimicrobial treatment (*OR* 0.42, 95% *CI*: 0.18–0.96, *P* = 0.039) were independent factors associated with antibiotics de-escalation [Table 5].

DISCUSSION

Antibiotic de-escalation prevented the emergence of MDR bacteria with a narrow spectrum of antibiotics according to the culture sensitivity,^[9] which plays a major role in the treatment of infectious diseases in clinical practice. In this retrospective study, we evaluated the influence of de-escalation on VAP in trauma patients using PSM for the first time. Although unbalanced baseline characteristics were present in both groups before PSM such as disease constitution and baseline APACHE II scores, the difference in these characteristics disappeared after PSM. The current results showed that de-escalation strategy in the treatment of TAP did not increase patients' mortality, as well as, significantly decreased the medical expenses. Multivariable analysis revealed that high APACHE II score, MDR infection, and inappropriate initial antibiotic treatment prevented the implementation of de-escalation.

Currently, there are several studies regarding the antibiotic de-escalation in medical or surgical patients;^[10,11] however,

only a few reports are available in trauma patients. VAP in trauma patients is not completely equivalent to VAP in medical or surgical patients and exhibits specific features. Furthermore, in trauma patients, VAP is more common as compared to other critically ill patients with MV,^[12] and ventilator care bundle could not prevent the occurrence of VAP in trauma patients efficiently.^[13] In clinical practice, the diagnosis of VAP in the trauma patients is yet an enigma due to the similarity in features with a pulmonary contusion or acute respiratory distress syndrome.^[14] Diagnosing TAP according to the clinical criterion may include patients without VAP. Therefore, the definition of the American Center for Disease Control criterion was used for diagnosing VAP accurately as in the study because of its best fit for trauma population,^[15] and the patients without bacterial cultures were excluded from the study.

Clinicians are concerned about the efficacy and safety of de-escalation as compared to the non-de-escalation. Recently, a meta-analysis including patients with VAP, community-acquired pneumonia, hospital-acquired pneumonia, and sepsis showed that mortality was similar in most of the infections, and some studies favored the de-escalation for enhanced survival.^[16] However, the meta-analysis included randomized clinical trial (RCT) and observational studies simultaneously, and the quality of evidence was low. In the current study, we focused on the impact of de-escalation in trauma patients, which is rarely discussed in previous literature. Although a low rate of mortality was observed in the de-escalation group before

Table 3: Antibiotic treatment efficacy in the two groups of patients before and after propensity score matching

Parameters	Before propensity score matching				After propensity score matching			
	De-escalation group (n = 62)	Non-de-escalation group (n = 94)	Statistics	P	De-escalation group (n = 42)	Non-de-escalation group (n = 42)	Statistics	P
Length of hospital stay (days), median (IQR)	28 (21–34)	25 (22–32)	0.513 [‡]	0.608	24 (22–31)	25 (19–33)	0.170 [‡]	0.865
Length of ICU stay (days), median (IQR)	20 (16–29)	19 (15–23)	1.252 [‡]	0.211	19 (15–23)	19 (15–26)	0.300 [‡]	0.764
Duration of MV (days), median (IQR)	14 (10–18)	13 (11–15)	0.783 [‡]	0.434	13 (11–15)	14 (10–17)	0.252 [‡]	0.801
Days of antibiotics treatment (days), median (IQR)	15 (11–18)	16 (12–19)	2.131 [‡]	0.079	11 (8–13)	14 (8–19)	2.868 [‡]	0.045
Tracheotomy, n (%)	9 (14.5)	16 (17.0)	0.174 [*]	0.676	6 (14.3)	7 (16.7)	0.091 [*]	0.763
Antibiotics expense (RMB Yuan), mean ± SD	6504 ± 2578	7445 ± 2277	2.396 [†]	0.018	6430 ± 2730	7618 ± 2568	2.055 [†]	0.043
Hospitalization expense (RMB Yuan), mean ± SD	18,755 ± 6564	21,995 ± 9572	2.327 [†]	0.021	19,173 ± 16,861	24,184 ± 12,039	2.296 [†]	0.024
MDR infection after antimicrobial treatment, n (%)	23 (37.1)	49 (52.1)	3.396 [*]	0.065	13 (31.0)	17 (40.5)	0.830 [*]	0.362
28-day mortality, n (%)	16 (25.8)	38 (40.4)	3.528 [*]	0.060	12 (28.6)	10 (23.8)	0.246 [*]	0.620

* χ^2 value for Pearson's Chi-squared test; [†]t value for group t-test; [‡]Z value for Mann-Whitney test. IQR: Interquartile range; ICU: Intensive Care Unit; MV: Mechanical ventilation; SD: Standard deviation; MDR: Multi-drug resistant.

Table 4: Factors associated with 28-day mortality using univariable and multivariable logistic regression analysis before propensity score matching

Variables	Univariable logistic regression analysis		Multivariable logistic regression analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.021 (0.99–1.03)	0.202		
Male	0.78 (0.39–1.55)	0.476		
APACHE II scores	1.13 (1.05–1.22)	0.001	1.14 (1.05–1.24)	0.002
CPIS scores	0.83 (0.64–1.07)	0.145		
ISS scores	1.09 (1.03–1.14)	0.001	1.09 (1.04–1.16)	0.001
De-escalation	0.51 (0.25–1.03)	0.062		
Sepsis	1.37 (0.65–2.87)	0.407		
MDR infection	1.96 (0.96–3.98)	0.063	2.34 (1.04–5.26)	0.041
Inappropriate initial antimicrobial treatment	2.91 (1.42–5.94)	0.003	2.34 (1.07–5.14)	0.034
Late-onset VAP	1.52 (0.76–3.02)	0.235		

SD: Standard deviation; OR: Odds ratio; CI: Confidence interval; APACHE II: Acute Physiology and Chronic Health Evaluation II; CPIS: Clinical pulmonary infection score; ISS: Injury severity score; MDR: Multi-drug resistant; VAP: Ventilator-associated pneumonia.

Table 5: Factors associated with de-escalation using univariable and multivariable logistic regression analysis before propensity matching

Variables	Univariable logistic regression analysis		Multivariable logistic regression analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.02 (0.99–1.04)	0.126		
Male	1.22 (0.62–2.43)	0.563		
APACHE II scores	0.91 (0.84–0.98)	0.013	0.89 (0.83–0.98)	0.012
CPIS scores	0.92 (0.72–1.17)	0.492		
ISS scores	1.04 (0.66–1.07)	0.070		
Sepsis	2.32 (1.11–4.82)	0.024		
MDR infection	0.42 (0.19–0.90)	0.026	0.34 (0.15–0.80)	0.014
Inappropriate initial antimicrobial treatment	0.36 (0.17–0.79)	0.010	0.42 (0.18–0.96)	0.039
Late-onset VAP	0.44 (0.23–0.85)	0.015		

OR: Odds ratio; CI: Confidence interval; APACHE II: Acute Physiology and Chronic Health Evaluation II; CPIS: Clinical pulmonary infection score; ISS: Injury severity score; MDR: Multi-drug resistant; VAP: Ventilator-associated pneumonia.

PSM, and this finding might be partially attributed to the low APACHE II scores. After we balanced the difference

in APACHE II scores between both groups using the PSM method, the difference in mortality between both groups

was disappeared. These findings were similar to studies focused on medical and surgical VAP patients.^[11,17] Although a systemic review^[18] showed that de-escalation exerted a protective effect on mortality, the authors revealed that this effect might be attributed to clinical improvement or low risk of treatment failure, and thus, could not be retained as evidence. Moreover, our results showed that the patients' length of hospital and ICU stays, and duration of MV did not differ between the two groups before and after PSM, indicating that de-escalation therapy was a safe strategy.

De-escalation therapy usually aims to reduce the emergence of bacterial resistance,^[19] however, currently, none of the studies were designed to evaluate this effect. In the current study, we evaluated the emergence of MDR bacteria about 14 days after initial antimicrobial treatment. As a result of high rate of MDR infection in the non-de-escalation group at the time of inclusion, MDR bacteria were frequently detected in the non-de-escalation group. Nonetheless, after adjusting some confounding factors using PSM, the difference in MDR pathogens isolated from both groups after antimicrobial treatment was not significant (31% vs. 40.5%, $P = 0.362$). This finding was consistent with a previous retrospective study that evaluated the antibiotic de-escalation in patients with VAP.^[20,21] Broad-spectrum antibiotics or combined therapy poses a burden on bacteria, thereby inevitably leading to the emergence of MDR. Thus, the de-escalation strategy would reduce this burden, and decrease the emergence of MDR.

Although guidelines recommend that de-escalation therapy should be performed when the results of bacterial culture were available,^[7] this was not common in clinical practice. In the current study, the rate of de-escalation was <40%, which is higher than that exhibited in other studies.^[17,22] Furthermore, in medical institutions, several barriers may hinder the implementation of de-escalation. A large number of studies have identified the factors limiting the practice of antibiotic de-escalation: the presence of MDR bacteria,^[23] culture-negative results,^[20] and initial narrow-spectrum antibiotics.^[21] Herein, the de-escalation strategy was less common in trauma patients with high APACHE II scores, high ISS score, sepsis, MDR bacterial infection, inappropriate empirical antibiotic treatment, and late-onset VAP. Multivariable analysis demonstrated that high APACHE-II scores and inappropriate empirical antibiotic treatment were independent factors influencing the de-escalation strategy. In clinical practice, the clinicians would rather de-escalate the antibiotic treatment according to patients' clinical conditions than the microbiological data and are often reluctant to de-escalate the antibiotic treatment out of fear of poor outcome even if the microbiological data are available when patients' clinical conditions do not improve. Different from a previous study,^[17] the duration of antibiotic treatment in the de-escalation group was shorter than the non-de-escalation group. This phenomenon might be explained by the improvement in patients' clinical conditions in de-escalation group.

Nevertheless, the present study has some limitations. The inherent flaw of retrospective study would interfere with this study's strength, although PSM was applied to adjust some confounding factors in the study. The method of PSM could only adjust the known confounding factors; however, it was difficult to balance the unknown factors by PSM that might influence current results. In addition, we did not calculate the sample size using the conventional statistical methods. Thus, our sample size might be relatively small, and insufficient for detection of the difference in mortality between both groups. Moreover, a 3-year period of population recruitment is considered as long, and local microbiology and empirical antibiotic treatment might be altered considerably that might influence our results. Finally, these findings could not be applied to other departments as the results were obtained from a single-center study conducted in the ICU. Furthermore, due to the lack of data integrity, the emergence of MDR and occurrence of adverse events were not assessed in the present study.

In conclusion, in the current study we compared the effect of de-escalation strategy on the treatment of TAP to non-de-escalation using PSM. De-escalation was associated with low hospitalization expense and a short period of antibiotic treatment, and it did not affect the trauma patients' mortality. Although PSM was performed to adjust the bias, RCT is essential for further substantiation of the results.

Acknowledgements

We thank Prof. Wang-Hong Xu in the Department of Epidemiology, Public Health College of Fudan University, for the check of statistics.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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创伤患者呼吸机相关性肺炎的抗生素降阶梯治疗：一项基于倾向得分匹配法的回顾性研究

摘要

背景： 抗生素降阶梯治疗是采用广谱抗生素进行起始抗感染治疗，随后根据细菌学培养结果针对特定病原菌改用窄谱抗生素抗感染治疗。本研究旨在评估抗生素降阶梯治疗对创伤合并呼吸机相关性肺炎患者的影响。

方法： 该回顾性研究纳入创伤合并呼吸机相关性肺炎的患者，在诊治过程中采用抗生素降阶梯治疗（降阶梯治疗组）或未采用抗生素降阶梯治疗（非降阶梯治疗组）。采用倾向得分匹配法平衡两组患者基线特征，比较两组患者的28天死亡率、住院和住重症监护病房时间，以及抗生素使用费用和住院总费用，并采用多元分析探索影响患者28天死亡率和抗生素降阶梯治疗的危险因素。

结果： 共有156例患者纳入研究，其中62例接受抗生素降阶梯治疗，94例未接受抗生素降阶梯治疗。两组患者的28天死亡率未见明显差异（28.6% vs. 23.8%, $P=0.620$ ）。降阶梯治疗组患者的抗生素使用时间短于非降阶梯治疗组（11 [8-13] vs. 14 [8-19] 天, $P=0.045$ ），并且降阶梯治疗组患者的抗生素使用费用和住院总费用低于非降阶梯治疗组（ 6430 ± 2730 vs. 7618 ± 2568 元人民币, $P=0.043$ and $19,173 \pm 16,861$ vs. $24,184 \pm 12,039$ 元人民币, $P=0.024$ ）。多元分析提示患者的高APACHE II评分、高ISS评分、多重耐药菌感染和不恰当的起始抗感染治疗与患者的28天死亡率相关，而高APACHE II评分、多重耐药菌感染和不恰当的起始抗感染治疗是影响抗生素降阶梯的独立危险因素。

结论： 采用抗生素降阶梯策略治疗创伤合并呼吸机相关性肺炎患者，可以减少抗生素的使用时间和患者住院总费用，并且不增加患者的28天死亡率和多重耐药菌感染。