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RESEARCH ARTICLE

A retrospective study of antibiotic de-escalation in patients with ventilator-associated pneumonia in Malaysia

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Abstract *Background* Antibiotic de-escalation is an important strategy to conserve the effectiveness of broad-spectrum antibiotics. However, the outcome of this strategy for the treatment of ventilator-associated pneumonia (VAP) has not been widely studied in developing countries. *Objectives* To evaluate the outcome on intensive care unit (ICU) mortality, 28 days mortality, and length of ICU stay among VAP patients who receive de-escalation therapy. *Setting* This study was conducted in an ICU of a Malaysian public hospital. *Method* The electronic medical records of patients who developed VAP in the ICU were retrieved and relevant data was collected. Records of antibiotic prescriptions were also reviewed to collect the details of changes to antibiotic therapy (de-escalation). *Main outcome measure* Impact of antibiotic de-escalation on mortality. *Results* The mean age of the 108 patients was 46.2 ± 18.2 years; the majority being males (80%). The antibiotic de-escalation rate was about 30%. Out of this, 84% involved a change from broad to narrow-spectrum antibiotics and the remaining, withdrawal of one or more antibiotics. ICU mortality was 23% while 28 days mortality was 37%. There was no statistically significant difference in mortality rate, survival probability and the mean length of ICU stay between the de-escalation and the non-de-escalation group. However, patients with Simplified Acute Physiology Score II of ≥50 were significantly associated with ICU mortality and 28 days mortality. *Conclusions* In VAP patients, antibiotic de-escalation provides an opportunity to promote the judicious use of antibiotics without affecting the clinical outcomes.

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Keywords Antibiotic de-escalation · Critically-ill patients · Intensive care unit · Malaysia · Ventilator-associated pneumonia

Impacts on practice

- Antibiotic de-escalation therapy appears safe to implement in patients with ventilator-associated pneumonia in intensive care unit as it is not associated with increased mortality or length of stay.
- Diagnostic Score such as Simplified Acute Physiology Score (SAPS) can be a useful measure to predict mortality in patients with ventilator-associated pneumonia.

Introduction

Ventilator-associated pneumonia (VAP) is the most common infection in the intensive care unit (ICU) [1, 2]. The key factor for a good clinical outcome for patients with VAP is the appropriate administration of antibiotics therapy [3–11]. Since the organisms causing VAP may not always be evident, it is essential to initiate empirical broad-spectrum antibiotic therapy prior to culture results. However, with the lack of availability of new and effective antibiotics and an increase in the development of antimicrobial resistance, available broad spectrum antibiotics need to be used judiciously. Thus, one of the strategies to conserve the effectiveness of antibiotic therapy is by implementing antibiotic de-escalation [4, 5, 10, 12–22]. In practice for antibiotic de-escalation, a broad-spectrum empirical antibiotic is initiated and later switched to a

narrower-spectrum based on the microbiological data and patient's condition [5, 23–26].

Antibiotic de-escalation is one of the components of the antibiotic stewardship programme. This programme refers to a multidisciplinary approach which aims to promote the appropriate use of antibiotics by the optimisation of the drug regimen, dose, duration, and route of administration for better patients' outcome [27, 28] and to safeguard the effectiveness of antibiotic therapy for future generations [29–32]. Currently, antibiotic de-escalation in VAP is gaining interest in developed countries as it assists in promoting the prudence use of antibiotics without causing an increase in mortality rate or the length of stay [7, 10, 12, 15, 16, 21]. Compared to developed countries, data on antibiotic de-escalation in the treatment of VAP in ICU is still lacking in the developing countries. Currently, only two studies which focussed on the treatment of VAP in ICU are available [33, 34]. Other published studies involve antibiotic de-escalation in septic shock and sepsis [35–37], and in overall infections [38, 39].

It is known that the practice of antibiotic de-escalation and its outcomes may vary between ICUs due to the difference in term of types of ICU, case-mix and the local microbiological environment. In fact, several studies which involve both developed and developing countries found that geographical region and socioeconomic level affect the prevalence of infection, types of infecting microorganisms and antibiotic resistance pattern [40–43]. Consequently, it is expected that the practice of antibiotic de-escalation may differ between ICUs in developed and developing countries.

In Malaysia, a study on antibiotic de-escalation in VAP is still lacking. Hence, it is necessary to determine the local practice of antibiotic de-escalation and its impact in VAP patients. The result of the study is important to justify whether antibiotic de-escalation should be widely used in the care of patients with VAP in Malaysia as well as in countries in the same geographical regions and socioeconomic level.

Aim of the study

We aimed to compare the impact of antibiotic de-escalation in VAP patients on intensive care unit (ICU)-mortality, 28 days mortality, and length of ICU stay.

Ethics approval

Ethical approval was obtained from the local Medical Research and Ethic Committee, Ministry of Health Malaysia (NMRR-14-1269-22984).

Method

Study design

This study was a retrospective observational study conducted in an ICU of a public hospital in Malaysia. The ICU has 38 beds and is managed as a closed ICU by intensivists. This ICU also has full-time clinical pharmacists who actively participate in the management of medicine therapy for all patients, with particular emphasis on antibiotics. For the optimisation of antibiotic dosing regimen, the pharmacokinetics and pharmacodynamic properties of antibiotics were considered.

Inclusion and exclusion criteria

Patients were eligible for inclusion if they were an adult (older than 18 years old) and had been diagnosed with VAP in the ICU from January 2012 to December 2014. Patients were excluded if they died less than 48 h of VAP diagnosis, if their data were missing and if they are pediatric patients.

Data collection

Data collected from hospital's electronic medical records include patient's demographic profile, Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) Score on admission, mechanical ventilation information, types of pathogens, antibiotics prescribed, inflammatory markers, the length of ICU stay, ICU mortality and 28 days mortality. Microbiological cultures which include respiratory and blood cultures had to be obtained prior to the commencement of empirical antibiotics. Data for antibiotic prescriptions, microbiological cultures, and clinical notes were reviewed to identify if de-escalation therapy had been implemented.

Definitions

The patient is diagnosed to have VAP when persistent, new pulmonary infiltrates appear on chest radiographs more than 48 h after endotracheal intubation and in conjunction with purulent respiratory secretions. At least one of the following criteria is also required: blood leukocytes greater than 12,000 or less than 4000/μL; temperature greater than 38 °C or less than 36 °C [44]. In a patient with diagnosed VAP, SOFA score was used to determine the patient's organ function and SAPS II was used to determine the severity of the disease.

Patients with the growth of a pathogen on blood or sputum cultures (tracheal aspirate or bronchoalveolar

lavage) were considered culture-positive while patients without growth of pathogen were considered culture-negative [5]. For both culture-positive and culture-negative results, de-escalation therapy was defined as either the switch from a broad-spectrum antibiotic (colistin, carbapenem, vancomycin, piperacillin/tazobactam, cefepime) to an agent that was a narrow-spectrum or the use of fewer drugs within 24 h following the availability of final culture and sensitivity results [5, 14–16, 18, 21, 45]. On the contrary, non-de-escalated therapy was defined as the continuation of empirical antibiotic in the culture-negative result, the continuation of broad-spectrum empirical antibiotic in the culture-positive result when a narrow-spectrum would have been sufficient, and the continuation of combination empirical antibiotics in the culture-positive result when a fewer agent would have been sufficient [18].

ICU mortality was defined as a patient who died in ICU due to either the VAP infection itself or complications related to patients' concomitant diseases (overall ICU mortality) and 28 days mortality refers to overall hospital mortality. The length of ICU stay was calculated from the day of initiation of empirical antibiotic therapy for VAP till the day of transfer out of ICU. Patients who died in the ICU were excluded from the comparisons of length of stay in ICU.

Data analysis

Data analysis was conducted using IBM®SPSS® Statistics Version 21. For continuous variables, the differences in mean and median between two groups were compared using t test and Mann–Whitney U test respectively. For categorical variables, Chi-square test or Fisher exact test was used. Multiple regressions were used to estimate the influence of de-escalation therapy on length of ICU stay. The risk factors for mortality were determined by using logistic regression analysis. Survival analysis was performed using Cox regression analysis. All reported p values were two-tailed. The threshold for statistical significance was at $p < 0.05$.

Results

Characteristic of VAP patients

Insert Fig. 1 here describes the flowchart for the selection of participants according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guideline [46]. Patients with missing data were excluded because they had no microbiological culture prior to empirical antibiotic for VAP (4 patients), not given an empirical antibiotic for VAP (1 patient) and missing

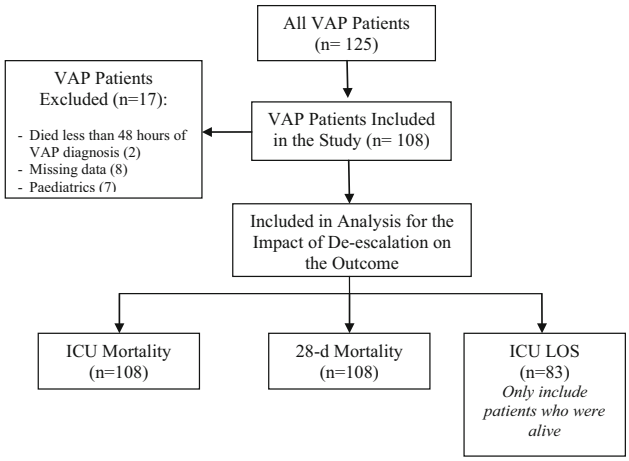

Fig. 1 Flowchart of study selection process

outcome data for 28 days mortality (3 patients). The mean age of the patients was 46.2 ± 16.8 years; 84 (80%) were male. The mean SAPS II on admission was 45.6 ± 18.2 while SOFA Score on admission was 9.9 ± 2.9. VAP was late onset in 65 (60%) of cases. The case mix was neurosurgical (49%), medical (32%), surgical (14%) and others (5%). Antibiotic de-escalation was initiated in 32 patients. Antibiotic treatment was streamlined to narrow-spectrum in 27 patients whereas, in the remaining 5 patients, one or more antibiotics were withdrawn. No statistically significant differences were noted between de-escalated and non-de-escalated groups in term of patient characteristics (insert Table 1) except for gender whereby male patients were significantly higher in the non-de-escalated group. In term of empirical antibiotics prescribed (insert Table 2), no statistically significant difference was found between the two groups. Of the 108 patients with VAP, causative pathogens (culture-positive) were identified in 82 patients (Insert Table 2). The culture-negative result (unidentified organism) was significantly higher in the non-de-escalation group (insert Table 2).

Endpoints

In this study population, the rate of ICU mortality was 23%, 21.9% in the de-escalation group and 23.7% in the non-de-escalation group. For 28-day mortality, 40 patients died (37%); 13 (40.6%) in the de-escalation group and 27 (35.5%) in the non-de-escalation group. The difference in mortality rate between the de-escalation and the non-de-escalation groups was not statistically significant (insert Table 3). Similarly, the mean length of ICU stay for the two groups was not statistically significant [10.1 ± 4.6 days in the de-escalation group versus 10.3 ± 9.1 days in the non-de-escalation group; [t (81) = 0.863, $p > 0.05$] (insert Table 3). Insert Fig. 2 here reveals there was no statistical

Table 1 Characteristic of patients with ventilator-associated pneumonia

Patient characteristic	De-escalation (n = 32)	Non-de-escalation (n = 76)
Age, mean ± SD, years	47.5 ± 16.2	45.8 ± 17.1
Male, no (%)*	20 (62.5)	64 (84.2)
VAP onset, mean ± SD, day	9.3 ± 8.0	6.1 ± 3.3
Length of mechanical ventilation, mean ± SD, day	13.4 ± 7.1	11.9 ± 5.6
Diagnostic Score, mean ± SD		
SAPS II Score	45.0 ± 18.9	45.5 ± 18.1
SOFA Score	10.0 ± 3.3	9.8 ± 2.8

* Statistically significant at $p < 0.05$

Table 2 Empirical antibiotics prescribed and pathogens identified

Antibiotics and pathogens	De-escalation (n = 32)	Non-de-escalation (n = 76)
Antibiotics		
Colistin	4 (12.5)	4 (5.3)
Carbapenems	9 (28.1)	13 (17.1)
Cefepime	6 (18.8)	27 (35.5)
Piperacillin/tazobactam	3 (9.4)	7 (9.2)
Ampicillin/Sulbactam**	5 (15.6)	15 (19.7)
Cefazolin	0 (0.0)	2 (2.6)
Comb. of broad spectrum antibiotics	5 (15.6)	8 (10.6)
Pathogens[a]		
Culture-positive		
Acinetobacter multi resistant organism (MDRO)	8 (24.2)	14 (17.7)
P. aeruginosa	7 (21.2)	15 (19.0)
Extended spectrum ß-lactamase (ESBL)	1 (3.0)	5 (6.3)
Polymicrobials	5 (15.2)	9 (11.4)
Other organisms	9 (27.3)	13 (16.5)
Culture-negative*	3 (9.1)	23 (29.1)

[a] Since > 1 microorganisms possible for VAP, total count will exceed 108

* Statistically significant at $p < 0.05$

** Ampicillin/sulbactam (high dose) is used for empirical therapy when Acinetobacter infections is suspected [54]

difference between the de-escalation and the non-de-escalation groups in terms of survival. When the outcome was stratified based on the diagnostic score of organ dysfunction and severity of disease, SAPS II $\geq$ 50 was significantly associated with a higher ICU mortality and 28 days mortality compared to SAPS II < 50 (insert Table 3).

Discussion

This retrospective single-centre study compared the impact of antibiotic de-escalation in VAP patients on ICU-mortality, 28 days mortality, and length of ICU stay. The antibiotic de-escalation rate observed was 29.6%. This rate was almost similar to another retrospective study (32.1%) conducted in Korea [4] involving 137 ICU patients with nosocomial pneumonia. A Brazilian retrospective study [33] involving 120 ICU patients with VAP reported 10% de-escalation rate compared to about 30% in our study. The different de-escalation rate maybe due to the dissimilar resistant pattern between the two countries despite them having comparable common pathogen isolated. A prospective study involving 115 VAP patients conducted in Spain [10] found a similar rate of de-escalation (31.4%). However, the de-escalation rate of this study was lower than a study involving only surgical patients with VAP (57%) [15]. The difference in the rate of de-escalation could be due to the types of the patient included since our study involved all types of ICU patients. Another study conducted in India also reported a higher rate of de-escalation of 68% [34]. This could be probably due to the small sample size (49 patients) and the lower incidence of multidrug-resistant organisms.

Several studies identified factors limiting the practice of antibiotic de-escalation. These include the presence of

Table 3 Outcomes on mortality and length of ICU stay

Predictors	Mortality			Length of ICU stay			
	N	ICU mortality OR (95% CI)	28-day mortality OR (95% CI)	F	*p* value	t	*p* value
De-escalation[a]	108	0.894 (0.315–2.541)	1.214 (0.488–3.020)	0.446	0.721	0.896	0.373
SAPS II $\geq$ 50[b]		2.859 (1. 066–7.668)*	2.588 (1.095–6.114)*			0.492	0.624
SOFA Score $\geq$ 10[c]		0.928 (0.350–2.459)	1.435 (0.607–3.392)			0.743	0.460

OR, odds ratio; 95% CI, 95% confidence interval

* Statistically significant at $p < 0.05$

[a] Non-de-escalation is the reference category

[b] SAPS II < 50 is the reference category

[c] SOFA Score < 10 is the reference category

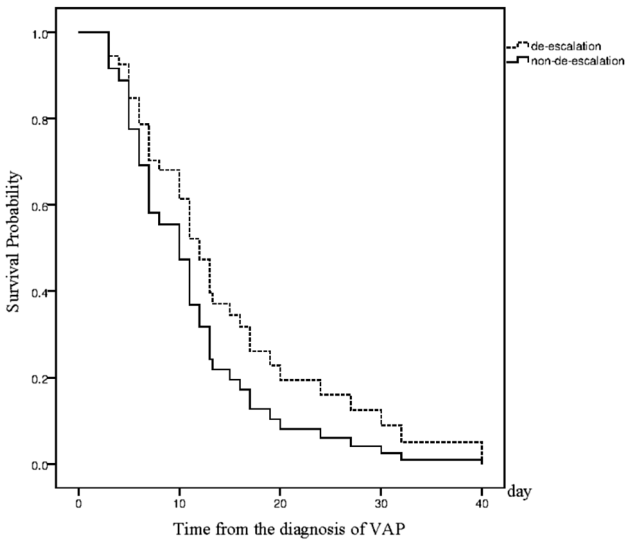

Fig. 2 All-cause mortality between de-escalation and non-de-escalation groups

multi-drug resistant organisms (MDRO) and non-fermenting gram-negative bacilli (NFGNB) [4, 10, 14, 24, 25, 47], culture-negative results [4, 10, 14, 34, 48] and the use of narrow-spectrum antibiotics as empirical therapy [24]. In our study, a factor that might hamper the de-escalation practice is the culture-negative results (23%) as it was significantly higher in the non-de-escalation group (88.5%). In a culture-negative situation, clinicians are often faced with competing concerns regarding their treatment decision especially when a clinical condition does not correlate with the culture result. Strengthening the antibiotic stewardship programme [12] may be necessary to improve the de-escalation rate in this centre. Rapid microbiologic methods such as Polymerase Chain Reaction (PCR), Multiplex PCR, Nanoparticle Probe Technology and Peptide Nucleic Acid Fluorescent In Situ Hybridisation are also needed to incorporate with antibiotic stewardship programme [49, 50] so that the clinicians will be guided accordingly and infection can be treated effectively without escalation therapy or prolonging the duration of empirical antibiotic treatment. In our study, the three patients with culture-negative who underwent de-escalation had lower SAPS II (less than 40) and SOFA Score (less than 8). Perhaps the decision to de-escalate antibiotic in these patients was made based on the severity of disease and patient's organ function. Another study also reported less multi-organ dysfunction in de-escalated patients with culture-negative findings [18].

In term of ICU-mortality, 28-day mortality and length of ICU stay, there was no significant difference between the de-escalation and the non-de-escalation groups. Our findings are in agreement with the results of the randomized controlled trial for clinically suspected VAP patients [12] and observational studies of critically ill surgical and neurosurgical patients with VAP [15, 45]. Similarly, a study conducted in Brazil also found no different in mortality between de-escalation and non-de-escalation groups [33]. A recent systematic review evaluating the clinical outcome of antibiotic de-escalation in the intensive care unit also found that the de-escalation therapy neither reduced the length of stay nor compromising survival [47]. Indeed, other studies involving VAP patients reported de-escalation therapy to be associated with significantly lower ICU mortality [10, 21]. Similarly, Giantsou (2007) in his observational study of VAP patients also reported significantly decreased 28 days mortality and reduced length of ICU stay in the de-escalation group [16]. In the light of our findings, the implementation of antibiotic de-escalation has the potential to contribute to the management of antibiotic resistance without compromising patients' outcomes.

The risk of mortality increases with increasing SAPS II points [51] and SOFA points [52]. In our study, the only factor which predicts mortality was SAPS II which is also similar to the finding from the Brazilian study [33]. Another similar tool commonly used to predict mortality is

Acute Physiology and Chronic Health Evaluation (APACHE) score [53]. However, our hospital did not collect data for this tool. Other factors such as age [14, 15], APACHE Score [14, 15, 33], unadjusted renal dose [33] and recurrent pneumonia [15] were reported to be associated with mortality.

Our findings have contributed to the data on de-escalation practice in developing countries. However, several aspects of our methodology may limit its applicability. First, this is an observational retrospective study which vulnerable to influence by confounding factors. Though, due to the complexity of ICU patients, the observational study may be the next best method after randomized control trials to address de-escalation practice and its impact. The influence of confounding factors has been minimised in this study by the multivariate analysis. Second, this study only involved a single ICU centre which means that a type II error is possible in a cohort of a small number of patients. However, since there is no standard protocol for antibiotic de-escalation and the differences between ICUs in terms of types of patients, a single centre study is less heterogeneous, thereby diminishing the confounding factors.

Conclusions

This study found that the de-escalation of antibiotic therapy in ICU patients with VAP did not lead to increased mortality or prolonged length of stay. Hence, due to its acknowledged benefits in conserving the efficacy of broad-spectrum antibiotics and combating antimicrobial resistance, antibiotic de-escalation may be implemented in all suitable medical-surgical and neurosurgical ICU patients.

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Conflicts of interest The authors declare no conflict of interest.

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