A Prospective Study on Antibiotic De-escalation Practice in the Medical Wards of Penang General Hospital

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Abstract

Introduction: The increase of antimicrobial resistance (AMR) rate is a burden to the country due to the high treatment cost and increased mortality rate. One of the strategies to reduce AMR under antimicrobial stewardship (AMS) was antibiotic de-escalation.
Objective: The objective of the study was to assess the practice of antibiotic de-escalation and the reasons of not de-escalating antibiotics therapy in the medical wards of Penang General Hospital.
Methods: This prospective study was carried out in three medical wards of Penang General Hospital for three months. The frequency of de-escalation and the reasons for no de-escalation were determined.
Results: Among 99 patients included in this study, antibiotics were de-escalated in 86 patients (86.9%). The most stated reasons for no de-escalation were clinical deterioration (28%), fear of de-escalation in complicated patients (20%), and immuno-compromised patients (12%). There was no significant difference in the length of hospitalisation between the de-escalation and no de-escalation group.
Conclusion: The percentage of antibiotic de-escalation in medical wards of Penang General Hospital was high. Thus, this study may serve as a precedent to introduce AMS with antibiotic de-escalation to other disciplines or wards to help tackle the increasing AMR rate.

Keywords: quality use of medicines, Penang, antibiotic, de-escalation, antimicrobial stewardship

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Introduction

Antimicrobial resistance (AMR) have been steadily increasing worldwide, which causes increase in cost of treatment and mortality rate[1,2]. This AMR crisis have been reported to occur due to antibiotics overuse and misuse such as inappropriate antibiotics prescribing practice for colds which viruses are the most common causative agent, thus causing redundancy in antibiotic prescribed[3]. In addition, the lack of new antibiotics development, extensive agricultural use of antibiotics and regulatory barriers associated with drug use and development are also the contributing factors to the rising AMR worldwide[4]. The resistance rate in Malaysia was reported to increase among the regularly used antibiotics against common local bacteria such as *Staphylococcus aureus, Streptococcus pneumonia, Klebsiella pneumonia* and *Escherichia coli* based on data obtained from the hospitals in the country[5]. The National Antibiotic Guideline and Antimicrobial Stewardship (AMS) Programme were implemented to reduce AMR[6,7].

Antibiotics de-escalation, which is a component of AMS, has been implemented to cope with current emergence of AMR[7]. Antibiotic de-escalation involves three vital components, which are switching from broad spectrum to a narrow spectrum antibiotic, stopping the on-going antimicrobial treatment once no infection is identified, and / or use a single antibiotic instead of multiple agents based on clinical response, culture results and susceptibilities of the microorganism identified[8]. Morel *et al.* reported that recurrent infection was found to be lower (5%) in patient with de-escalation compared to patient without de-escalation (19%, p=0.01)[9]. In addition, Singh *et al.* also stated AMR were only documented in 15% of the patients in the de-escalation group compared to 35% in patients receiving standard antibiotic therapy (p=0.017)[10]. Besides that, decrease in the length of stay was also found to be associated with de-escalation practice[11,12].

Although the importance and safety of de-escalation have been well documented, the rate of antibiotic de-escalation was still reported to be inadequate. Antibiotic de-escalation was only accomplished in approximately 35–50% of the patients with severe sepsis and this was considered unsatisfactory[9,13,14]. In addition, a study showed that antibiotic de-escalation was only performed in 28.3% of 9,319 patients admitted with healthcare-associated pneumonia[15]. Salahuddin reported that de-escalation failure was commonly observed in critically ill patients, as antimicrobial de-escalation only occurred in 48% of patients. This reflected the physicians' reluctance to de-escalate antibiotic therapy in complicated and sicker patients, or in multidrug resistance or fungal sepsis[16].

Several reasons could explain these unsatisfying rates of antibiotic de-escalation by physicians in the critical care setting, such as the reluctance to change an antibiotic regimen that was proven to be effective, clinically deteriorating patients, lack of microbiological data or lack of confidence in the obtained culture and sensitivity results, fear or poor understanding on how to de-escalate, and the controversial data about its effectiveness and safety[17]. The severity of the patient's illness and presence of drug resistance also influence the decision making in antibiotic de-escalation implementation due to the potential complications involved[16,18]. In addition, physician also faced difficulties in de-escalating the broad spectrum antibiotics in the case of polymicrobial infection[18].

In this study, we prospectively assessed the frequency of antibiotic de-escalation and clinical impact of the de-escalation in terms of length of hospitalisation in medical wards of Penang General Hospital. We also identified the reasons of the physicians in the medical wards for not performing antibiotic de-escalation.

Methods

This prospective and observational study included patients of any gender, aged more than 18 years old and admitted to the three medical wards (General Medical ward, Endocrinology & Neuromedical ward and Nephrology ward) of Penang General Hospital from July to September 2017. The inclusion criteria were patient who was given empiric broad spectrum antibiotics, and had positive culture and sensitivity results from laboratory. Patients who did not receive empiric antibiotics, those whom

infection was not suspected, with negative culture and sensitivity test from the laboratory, discharged home or deceased before the result of culture and sensitivity test was released, or transferred from the medical wards to other wards were excluded.

Patients were recruited by universal sampling method. Patients with positive culture and sensitivity result were identified from the laboratory, and their case notes were reviewed in respective wards within 48 hours after the result of culture and sensitivity test was released. Patients' diagnosis, empiric antibiotics and start date, culture and sensitivity test results, de-escalation of antibiotics (yes / no), antibiotic administered and length of hospitalisation were recorded in the Empiric Antibiotic De-escalation Survey Data Collection Form. For those whose antibiotic dose was not de-escalated in 48 hours after the release of culture and sensitivity test result, Antibiotic Non-de-escalation Review Form was filled by the doctor-in-charge to state the factors that influenced his or her decision. All the physicians participated in this study gave their consent.

The data was analysed using IBM Statistical Package for the Social Sciences (SPSS) version 21.0. Descriptive results of continuous variables were expressed as mean and standard deviation (SD). Variables were tested for their association with de-escalation using Chi-square test or Fisher's exact test for categorical data and independent t-test for numerical outcome variable. To assess the impact of de-escalation on the length of hospital stay, *p*-value were determined and reported.

Results

Population description

We reviewed the cases of 488 patients and 389 were excluded because they were discharged or deceased before the review date, transferred to non-medical wards, no empiric antibiotic started or the antibiotic used were not included in our research protocol (Figure 1). Ninety-nine patients with the average age of 58 years old were included in this study. Demographic data and infection-related data were presented in Table 1. Slightly more than half of the patients were male (51.5%, n=51) and the majority of patients were admitted to the Nephrology ward (46.5%, n=46). The most frequently prescribed empirical antibiotics were third and fourth-generation Cephalosporins (60.6%, n=60), followed by Piperacillin / Tazobactam (30.3%, n=30) and Carbapenems (9.1%, n=9).

In the 99 included patients, the samples that were sent for culture and sensitivity analysis were blood samples (77%) (77 samples), tracheal aspirate (6.1%), urine (5.1%), swab at brachiocephalic (BCF) (4%), peritoneal fluid (3%), tissue (1%), pus (1%), broncho-alveolar (BAL) pathogen (1%) and sputum (1%).

De-escalation

De-escalation was performed in 86.9% of included patients (n=86). Most of the de-escalation was performed in Nephrology Ward (51.2%, n=44). The General Medical ward and Endocrinology & Neuromedical ward had 38.4% (n=31) and 12.8% (n=11) of de-escalated patients respectively. Empirical antibiotics that was most frequently de-escalated was the cephalosporin group (60.4%, n=52), piperacillin/tazobactam (29.1%, n=25) and carbapenem group (9%, n=9). The mean length of hospitalization with de-escalation of antibiotics performed was 15.4 days.

No de-escalation

Out of the 99 patients, de-escalation was not performed in 13 patients. The non-de-escalated patients from General Medical ward was 53.8% (n=7), Endocrinology & Neuromedical ward was 30.8% (n=4) and Nephrology Ward was 15.4% (n=2). It was noted that cephalosporin group (61.5%, n=8) and piperacillin/tazobactam (38.5%, n=5) was the antibiotics that was not de-escalated. The reasons for no de-escalation were patient was clinically deteriorating (28%), fear of de-escalating in complicated patient (20%), immunocompromised patient (12%), lack of confidence in sampling quality or technique

(8%), lack of confidence on laboratory culture and sensitivity result (12%), patient was clinically improving (4%), suspected polymicrobial infection (12%), and did not aware of culture result (4%).

Outcome

De-escalation was performed in 86.9% of culture-positive patients but it did not influence the length of stay of patients in medical wards, which were 15.4 days (SD 8.3) in de-escalation versus 14.0 days (SD 7.3) in no de-escalation (p=0.727).

Figure 1: Flow chart of study population inclusion and exclusion process

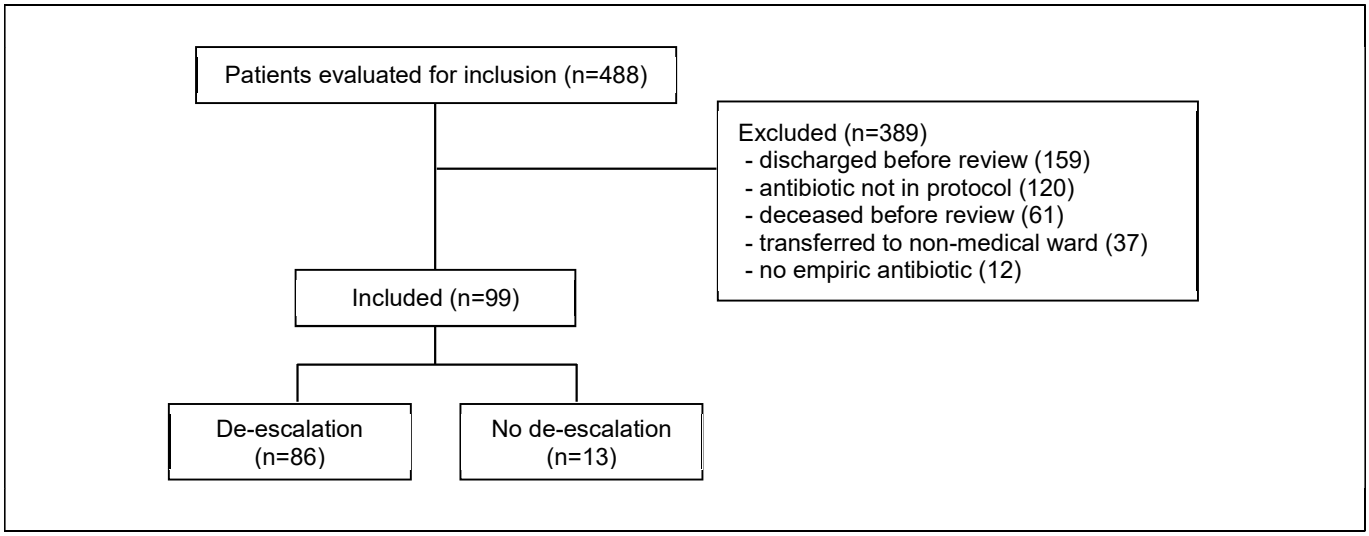

Table 1: Characteristics and patients' outcome according to the therapeutic strategy

Characteristics	All	De-escalation	No de-escalation	*p*-value
Overall, n (%)	99	86 (86.9)	13 (13.1)	
Age, mean (SD)	58.6 (14.3)	58.0 (14.6)	61.5 (12.2)	0.481[a]
Gender, n (%)				0.763[b]
Male	51 (51.5)	45 (45.4)	6 (6.1)	
Female	48 (48.5)	41 (41.4)	7 (7.1)	
Ward, n (%)				0.040[c]
General Medical	38 (38.4)	31 (31.3)	7 (7.1)	
Endocrinology & Neuromedical	15 (15.2)	11 (11.1)	4 (4.1)	
Nephrology	46 (46.5)	44 (44.4)	2 (2.0)	
Antibiotic group, n (%)				0.429[c]
Cephalosporin	60 (60.6)	52 (52.5)	8 (8.1)	
Piperacillin/tazobactam	30 (30.3)	25 (25.2)	5 (5.1)	
Carbapenem	9 (9.1)	9 (9.1)	0	
Length of stay, days, mean (SD)	15 (8.2)	15.4 (8.3)	14.0 (7.3)	0.727[a]

[a] Independent t-test; [b] Chi-square test; [c] Fisher's Exact Test

Discussion

This single-centre prospective study demonstrated that 86.9% of patients in the Medical wards had their antibiotics de-escalated. Our finding was almost similar to Liu *et al*. that reported the rate of de-escalation was 73% in their retrospective study of 240 patients[19]. Nonetheless, studies focusing on specific subgroups of patients gave various results. The de-escalation ranged from 6% to 74% in

patients with ventilator-associated pneumonia and was 34.9% in patients with severe sepsis or septic shock[14,15].

Most of the studies on antibiotic de-escalation were confined to the intensive care setting and were disease-specific. For example, a randomised, prospective trial by Singh *et al.*, in 81 patients in the intensive care unit with ventilator-associated pneumonia whose antibiotics was de-escalated were less likely to develop antibiotic resistant super-infections compared to those whose regimen was not de-escalated[20]. In addition, an observational prospective study by Giantsou *et al*. involving 143 ventilator associated pneumonia patients demonstrated decreased mortality with shorter ICU and hospital stay in patients whose antibiotic regimens were de-escalated[21]. Nevertheless, a study by Moraes *et al.* reported that among the 224 patients with severe sepsis and septic shock, de-escalation was performed in only 44 patients (19.6%)[22]. Another study by Turpkaet *et al*. stated that among 283 suspected pneumonia requiring mechanical ventilation patients, antibiotics in 140 (49%) patients were de-escalated[23]. These studies were done mostly on critically-ill patients in non-medical wards.

From 488 culture positive patients, 389 (79.7%) were excluded in our study. One of the reasons of high exclusion rate was due to the patients being discharged early before the review date. These patients may have improved clinically and conversion of intravenous to oral antibiotics was possible. A study by Liu *et al*. has also excluded those patients who were discharged early from the review date[19]. Short duration of injection use (around two days) followed by oral medications to complete the course of therapy would benefit many patients (except in certain conditions such as life-threatening infections, in critically ill patients, or in the presence of contraindications to oral administration) as it would reduce the length of hospital stay and the risk of hospital acquired infection[26].

Bacterial culture is the best method for diagnosis of infection but it does not indicate the host's response or differentiate between bacterial colonisation and systemic complications. In addition, it takes more than 24 hours to get the result. Markers like procalcitonin (PCT) or C-Reactive Protein test (CRP) respond to both infection and inflammation, and reflect both microbiological findings and the host response, which have significant influence on the prognosis and outcome. PCT is stable in blood samples, easy to perform, not too expensive, and provides a quick answer (30 minutes for automated PCT assay on Kryptor using TRACE technology and more sensitive than the luminometric assay). Meta-analysis done by Uzzan *et al*. showed that PCT had a greater accuracy than CRP in this context[27]. As a screening test, PCT could help decide which patients were likely to have infection and thus should be offered multiple cultures and empirical antibiotic therapy. Increased PCT also indicated a systemic inflammatory host response to infection, probably endangering the patient by an increased risk of organ dysfunction[27]. Thus, biomarkers can be a complementary method to improve the practice of de-escalation of antibiotics.

Study by Shafazand *et al.* documented that up to 50% of positive cultures might be sample contamination in critically ill patient[28]. Positive microbial cultures in critically ill patients often prompt reflexive antimicrobial therapy, regardless of the sampling site or the contamination potential. Specifically, positive "sterile site" cultures (such as blood cultures) better represente true infection than positive "non-sterile site" cultures (such as wound cultures). Non-sterile sites were more likely to be colonisation or contamination. Appropriate antimicrobial use should preferentially be based on positive cultures from the sterile sites rather than from non-sterile sites. Distinguishing between contamination and true positives can be difficult, and clinicians may benefit from AMS assistance with regimen choice and education surrounding contamination potential[28]. AMS education programme on proper sampling technique with multiple sets of blood culture taken may improve the confidence of doctors on the sampling technique and results. Immediate microbiology laboratory reporting to wards on positive blood cultures should be encouraged as most therapy interventions occurred after notification of results. By doing so, it may be possible to establish a framework for the improvement of test result

communications that heeds the dual requirements of patient-centred care and logistical constraint, consequently improving the frequency of antibiotic de-escalation.

This study was only conducted for three months due to the time constraint thus smaller sample size was enrolled. Therefore in future it is encouraged to conduct this study for longer period of time in order to enrol more patients. In this study, only three medical wards were included. For example, the General Medical ward is an acute ward with limited beds and shorter hospital stay. The frequently used broad spectrum antibiotics such as Unasyn® and Augmentin® were excluded from this study. Therefore, more wards, especially critical ward (Intensive Care Unit), Surgical, Orthopaedic or Obstetrics and Gynaecology (O&G) wards, where patients need longer hospitalisation and with higher utilisation of empirical antibiotics should be enrolled. In addition, the study did not evaluate the appropriateness of antibiotics in both empiric and de-escalated regimens. In this study, we focused only on the de-escalation practice of antibiotics. Nevertheless, this study may serve as a benchmark and path for future study in this area.

Antibiotic de-escalation is a key function of AMS. The implementation of AMS may facilitate the implementation of antibiotic de-escalation[24,25]. As a result, the frequency of de-escalation observed in this study was higher than no de-escalation. However, our study did not compare the frequency of antibiotic de-escalation before and after the establishment of the AMS. Rather, it assessed the antibiotic de-escalation practice with the aim of providing a benchmark for other institutions with AMS. Future studies could compare the practice of antibiotic de-escalation with and without established AMS.

Conclusion

The percentage of antibiotic de-escalation in the medical wards of Penang General Hospital was high. The length of hospital stay did not differ between patients with or without antibiotic de-escalation. Clinical worsening of patients despite antibiotic therapy was the most common reason for not performing de-escalation. This study may serve as a precedent to introduce AMS with antibiotic de-escalation to other disciplines or wards to help tackle the increasing AMR rate.

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Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

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