IMPACT OF EXTENDED AND RESTRICTED ANTIBIOTIC DE-ESCALATION ON MORTALITY

TEH HWEI LIN

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IMPACT OF EXTENDED AND RESTRICTED ANTIBIOTIC DE-ESCALATION ON MORTALITY

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TEH HWEI LIN

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LIST OF ABBREVIATION

AHR	Adjusted Hazard Ratio
AMS	Antimicrobial Stewardship
AOR	Adjusted Odds Ratio
APACHE	Acute Physiologic Assessment and Chronic Health Evaluation
CCS	Charlson's Comorbidity Score
CDC	Centre for Disease Control
CI	Confidence interval
CRE	Carbapenem resistant Enterobacteriaceae
CRP	C-reactive protein
CVC	Central venous catheter
EAA	European Union and European Economic Area
ESBL	Extended Spectrum β Lactamase
ESICM	European Society of Intensive Care Medicine
ESRF	End Stage Renal Failure
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HREC	Human Research Ethics Committee
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IQR	Interquartile range
IDSA	Infectious Disease society of America
IMR	Institute of Medical Research
JEPeM	Research Ethics Committee of University Sains Malaysia
LTFU	Lost to follow-up
MEWS	Modified early warning score
MOH	Ministry of Health
MREC	Medical Research and Ethics Committee
MRO	Multidrug Resistant Organism
OR	Odds Ratio
RCT	Randomized Controlled Trial
RR	Relative Risk
RRR	Relative Risk Reduction
SAPS II	Simplified Acute Physiology II
SCCM	Society of Critical Care Medicine
SD	Standard Deviation
SE	Standard error
SOFA	Sequential Organ Failure Assessment
STATA®	Data analysis and statistical software
VIF	Variance inflation factor
WBC	White blood cell
WHO	World Health Organization

LIST OF SYMBOLS

<	Less than
>	More than
≤	Less than or equal to
≥	More than or equal to
α	Level of significance (alpha)
b	Regression coefficient
=	Equal
%	Percentage
1-β	Power
n	Number of samples

KESAN DE-ESKALASI ANTIBIOTIK TERHAD DAN TERKAWAL TERHADAP KEMATIAN

ABSTRAK

Pengenalan: Lebih banyak data diperlukan untuk memahami keselamatan antibiotik de-eskalasi di kalangan pesakit dalam situasi klinikal tertentu sebagai strategi untuk mengurangkan pendedahan kepada antibiotik spektrum luas.**Objektiv:** Membanding lengkung *survival* di kalangan pesakit yang de-eskalasi antibiotik (awal atau lewat) dengan pesakit dimana antibiotik dilanjutkan, mengenalpasti pengaruh ciri-ciri pesakit, klinikal dan kudis tekanan atau alat perubatan atas kematian pesakit dan menyiasat kesan antibiotik de-esckalasi terhadap *30-day all-cause mortality*. **Kaedah**: Kajian kohort retrospektif ini dijalankan dengan meninjau rekod perubatan pesakit Wad Perubatan Hospital Kuala Lumpur dengan jangkitan bakteria yang telah dimulakan antibiotik terhad atau terkawal dan layak untuk menjalankan de-eskalasi antara Jan 2016 hingga Jun 2019. Pembolehubah bersandar kajian ini adalah *30-day all-cause mortality*. Keluk *survival Kaplan Meier* dan ujian *Fleming-Harrington test* diguna untuk membanding kadar kelangsungan hidup secara keseluruhan antara antibiotik de-eskalasi awal,lewat dan mereka yang tidak menjalani antibiotik de-eskalasi. Regressi *Multivariable Cox* digunakan untuk menentukan faktor-faktor yang mempengaruhi kematian, dan menganalisis kesan de-eskalasi awal dan lewat pada *30-day all cause mortality*. Semua analisis dibuat dengan STATA versi 14. **Keputusan**: Sejumlah 180 pesakit dimasuk kajian ini. Daripada bilangan ini terdapat 62 kes kematian (34.4%) dan 118 kes *censored* (65.6%) di akhir susulan. Lapanbelas

kematian(29%) berlaku antara golongan pesakit tidak de-eskalasi antibiotik, 28 kematian (45.2%) dan 16 kematian (25.8%) di golongan di-eskalasi lewat dan awal masing-masing *Fleming-Harrington test* berdasarkan kumpulan de-eskalasi menunjukkan kadar kematian keseluruhan tidak berbeza secara ketara apabila pesakit tidak menjalankan de-eskalasi antibiotik dibanding dengan pesakit yang mejalankan de-eskalasi antibiotik awal atau lewat (P = 0.760).Faktor yang mempengaruhi *30-day all cause mortality* adalah Skor Sequential Organ Fungsi Penilaian (SOFA) pada hari intervensi *Antimicrobial Stewardship* (AMS) (HR 6.74, 95% CI 3.98,11.42; P <0.001), skor comorbiditi Charlson (HR 2.00, 95% CI 1.56,3.35; P = 0.009), serta ketiadaan tren protein C-reaktif (HR 3.10, 95% CI 1.56,6.10; P = 0.001). Selepas mengawal ketiga-tiga *confounders* ini, de-eskalasi antibiotic (awal atau lewat) tidak menyebabkan kesan peningkatan risiko kematian; dimana HR adalah masing masing 0.58 (95% CI 0.32,1.07; P = 0.085) dan 0.77 (95% CI 0.38,1.54; P = 0.456) .**Kesimpulan:** Hasil kajian ini mengukuhkan bahawa de-eskalasi antibiotik terhad atau terkawal di kalangan pesakit tidak mempunyai kesan mudarat ke atas *30-day all cause mortality* berbanding dengan pesakit yang kesinambungan antibiotik terhad atau terkawal. Skor SOFA pada hari intervensi *Antimicrobial Stewardship* (AMS), skor comorbiditi Charlson ,serta serta ketiadaan tren protein C-reaktif antara 3 faktor penting prognostik dijumpai mengaitkan *30-day all cause mortality*.

IMPACT OF DE-ESCALATION OF EXTENDED AND RESTRICTED ANTIBIOTIC ON MORTALITY

ABSTRACT

Background: More data is needed about the safety of antibiotic de-escalation in specific clinical situations as a strategy to reduce exposure to broad-spectrum antibiotics. **Objective:** To compare the survival probabilities of patient de-escalated (early or late) against those not de-escalated on extended or restricted antibiotic, to determine the association of patient related , clinical related , and pressure sore/device related characteristics on all-cause 30-day mortality and determine the impact of early and late de-escalation antibiotic de-escalation on 30-day all-cause mortality. **Methods**: This retrospective cohort study was conducted by reviewing medical records of patients eligible for antibiotic (extended or restricted) de-escalation in medical ward Hospital Kuala Lumpur, between Jan 2016 to June 2019. The primary outcome of interest is 30-day all-cause mortality. Kaplan Meier survival curve and Fleming-Harrington test were used to compare the overall survival rates between early, late and those not de-escalated on antibiotic. Multivariable Cox regression was used to determine prognostic factors associated with mortality, and impact of de-escalation (early and late) on 30-day all-cause mortality. All statistical tests were carried out using STATA version 14. **Results**: A total of 180 patients were included, with 62 deaths (34.4%) and 118 censored events (65.6%). Out of the 62 deaths, 18 deaths (29%) occurred in non-de-escalated group, 28 deaths (45.2%) and 16 deaths (25.8%) in early and late de-escalation group respectively. Fleming-Harrington test showed the overall mortality rates were not significantly different when patient was not de-escalated on extended or restricted antibiotics, compared to those de-escalated early or later

(P=0.760). Variables associated with 30-day all-cause mortality were Sequential Organ Function Assessment (SOFA) score on the day of antimicrobial stewardship (AMS) intervention (AHR 6.74, 95% CI 3.98,11.42; P<0.001) , Charlson's comorbidity score (AHR 2.00, 95% CI 1.56,3.35 ;P=0.009), and the unavailability of C-reactive protein(CRP) trend values were found to be significant factors associated with mortality of patients with infection who were on extended and restricted antibiotic (AHR 3.10, 95% CI 1.56,6.10; P=0.001). After controlling for abovementioned confounders, early and late antibiotic de-escalation were not associated with increased risk of mortality; AHR were 0.58 (95%CI 0.32,1.07; P=0.085) and 0.77 (95%CI 0.38,1.54;P=0.456) respectively. **Conclusion**: The results of this study reinforces that restricted or extended antibiotic de-escalation in patients does not significantly affect 30-day all-cause mortality compared to continuation with extended and restricted antibiotics. Patient Charlson's Scoring index, SOFA score and unavailability of CRP trend are significant factors found to be associated with 30-day all-cause mortality.

CHAPTER 1 : INTRODUCTION

1.1 Background of antimicrobial resistance

Antibiotic therapy is one of the most important medical developments of the 20th Century. It was known as the "golden era" where antibiotics prevented millions of premature deaths due to bacterial infection (Nathan and Cars, 2014). Such an era has ended because researchers were unable to cope with the pace of emergence of resistance pathogen with new novel antibiotics. The aetiology behind antibiotic resistance is multifaceted which includes inadequate regulations and inappropriate usage, awareness deficiency in best practices, use of antibiotics as a poultry and livestock growth promoter rather than to control infection, and unrestricted production of low-grade antibiotics (Bartlett *et al*., 2013; Spellberg *et al*., 2011). However, antibiotic overconsumption remains the key driver of bacterial resistance, which is the ability of a bacteria to stop an antibiotic from working against it. 30-50% of prescribed antibiotic in hospital settings have been inappropriate when indications, agent choice, and therapy duration were investigated (Read and Woods, 2014; Ventola, 2015), and all antibiotics prescribed in acute-care hospitals, 20–50% are either unnecessary or inappropriate (Davey *et al*., 2017; Hulscher *et al*., 2010; Spoorenberg *et al*., 2014).

The pattern of inappropriate antibiotic use was also studied in a tertiary care centre in Thailand and found that 25% antibiotic were inappropriately used (Apisarnthanarak *et al*., 2006). In another study from secondary care

public hospitals in Western Switzerland reviewing 600 antibiotic prescription, 37% of antibiotic were considered unnecessary (von Gunten *et al*., 2009). The most frequent characteristics of inappropriate treatments included: No indication (17.5%); incorrect choice of antimicrobials (7.6%); incorrect application of drugs (9.3%); and divergence from institutional guidelines (8%) (Cusini *et al*., 2010). A cross-sectional study in Malaysia concluded that antibiotic prescribing rates are high in both public and private primary care settings which provides evidence of excessive and inappropriate antibiotic prescribing for self-limiting conditions (Ab Rahman *et al*., 2016).

The World Health Organization (WHO) in 2014 report on global surveillance of antimicrobial resistance revealed that antibiotic resistance is no longer a prediction for the future and is now serious global health treat, it threatens the effective prevention and treatment of ever-increasing range of infection. This report showed that five out of the six WHO regions had more than 50% resistance to third generation cephalosporins and fluoroquinolones in *Escherichia coli*, resistance to third generation cephalosporins and carbapenems in *Klebsiella pneumoniae*, and methicillin resistance in *Staphylococcus aureus* in hospital settings (WHO,2014). Reports from Institute of Medical Research (IMR) showed increasing resistance of gram-negative bacilli to third/fourth generation cephalosporins, and an alarming increase in emergence of carbapenem resistant *enterobacteriaceae* (CRE). In a separate report of Malaysia National Antibiotic Resistance Surveillance report 2017 on resistance to carbapenems (imipenem and meropenem) is fast approaching 10% (Institute for Medical Research, 2017). Antibiotic use has

been shown to drive resistance and hence unnecessary antibiotic use, irrespective of class adds to selection pressure for resistant bacteria (Dellit *et al*., 2007a; Lepper *et al*., 2002).

Antimicrobial resistance can cause clinical and economic adverse outcomes and the magnitude of such outcomes is affected by disease severity, virulence and host vulnerability. Such negative impacts of antibacterial resistance can be seen at patient level as it causes increased morbidity and mortality, at the healthcare level by increased resource utilization, higher healthcare costs (Friedman *et al*., 2016). Hospitals spend an average of additional USD 10,000 to 40,000 to treat a patient infected by Multidrug Resistant Organism (MRO) and increased mortality, prolonged sickness and reduced labour efficiency are estimated to double this figure (Friedman *et al*., 2016). In the European Union and European Economic Area (EAA), the health care burden from antimicrobial resistance is similar to the combined burden of Human immunodeficiency virus(HIV), influenza, and tuberculosis in 2015 and has doubled of what was recorded in 2017 (Tacconelli and Pezzani,2019). A systematic review by Naylor *et al* in 2018, the global excess healthcare system costs from antimicrobial resistance ranged from non-significance to $1 billion per year, whilst economic burden ranged from $21,832 per case to over $3 trillion in gross domestic product loss (Naylor *et al*., 2018). Aside from economic burden, bacterial resistance was associated with nearly three times higher odds of mortality (Founou *et al*., 2017) while The WHO surveillance report attributed 45% of deaths in both Africa and South-East Asia to MRO (WHO, 2014).

The development of new antibiotics by the pharmaceutical industry had essentially been hindered due to reduced economic incentives and challenging regulatory obstacles (Bartlett *et al*., 2013). Of the 18 largest pharmaceutical companies, 15 abandoned the antibiotic field and one of the main reasons were the lack of investment return as they are not as profitable as drugs used for chronic diseases. On top of that, profits are prematurely curtailed when resistance soon after its use (Gould *et al*., 2010). With the lack of new and effective antibiotics down the pipeline coupled with increasing development of antimicrobial resistance, available broad-spectrum antibiotics need to be used judiciously. To address the increasing burden of multi-drug resistant bacterial infections, antimicrobial stewardship (AMS) programmes are promoted worldwide to rationalize antibiotic prescribing and conserve remaining antibiotics, while improving patient outcomes. The current effort to improve antibiotic stewardship in Malaysia is still in the early stages since the national protocol on AMS is launched nationwide in 2014 (Ministry of Health, 2012).

De-escalation is strongly recommended in the practice of AMS program in order to promote judicious antimicrobial use and to limit costs, adverse events, and the risk of developing antibiotic resistance (Dellit *et al*., 2007b). Hence, one of the main aims of de-escalation is by reducing exposure at the individual and group levels to drugs with a undesired ecological effect. There is however still conflicting evidence of its impact on patient outcomes. A meta-analysis on 23 studies showed that there was no difference in mortality

for most infections, and some studies favoured de-escalation over non-de-escalation for better survival. The quality of most studies included however are not high (Ohji *et al*., 2016). Another recent meta-analysis in 2016 by Paul *et al*.(2016) concluded observational studies show lower mortality following antibiotic de-escalation with culture sensitivity results among patients with bacteraemia, pneumonia or severe sepsis, whereas three small Randomized Controlled Trials (RCT) favoured no de-escalation without reaching statistical significance (Paul *et al*., 2016). Despite the strong evidence supporting no detrimental effects of de-escalation, there is less frequency of de-escalation than is desirable. One of the main barriers is the uncertainty that revolves among safety of de-escalation despite it being a standard of care among practising physician , especially in negative cultures (Kollef and Kollef, 2005; Rello and Diaz, 2003).Other barriers identified in previous studies include a clinician's perception that the patient had improved on escalation to broad-spectrum antimicrobials causing physician reluctance to de-escalate even when new microbiological data were available (Heenen *et al*., 2012). Some studies documented that failure to de-escalate are due to lack of trust on microbiological data, under-estimating potential opportunities, not equipped on how to do de-escalate, and, above all, a lack of high-quality evidence(Donaldson and Barkham, 2010; Duchene *et al*., 2013; Eachempati *et al*., 2009; Shime *et al*., 2011).Thus, by offering more evidence about safety of de-escalation , it will not only increase implementation, but also to improve knowledge of the variables influencing the overall outcome of de-escalation.

1.2 Problem Statement

Even though it is well established that de-escalation is safe in various studies overseas, in Malaysia there are currently only one study on antibiotic de-escalation, which focuses on a single infection which is ventilator-associated pneumonia in the intensive care unit (ICU) (Khan and Aziz, 2017). Although it is a well conducted study and have attempted to adjust for confounding using multivariable analysis, it has restricted its generalizability to ICU patients and a single infection. In addition, there are no studies to date, examining the factors of clinical outcome in patients de-escalated on antibiotic.

Hence, local studies on impact and safety of antibiotic de-escalation is still lacking and there is no study on prognostic factors of antibiotic failure or poor clinical outcome in patients de-escalated on antibiotics. Study results from other country cannot be directly applied to a local setting for various reasons, which include difference in microbiology resistance pattern, lack of advanced rapid diagnostics for infection, difference in infection control support, and infectious disease support team. For instance, rapid diagnostics tools for bacterial profiling has been shown to improve clinical outcome in antibiotic de-escalation via improvement in the timeliness of appropriate therapy (Buehler *et al*.,2016). However, such diagnostics tools are not readily available in Malaysia Ministry of health leading to lack of confidence in safety of antibiotic de-escalation. Other strategies which helps clinicians to cope with de-escalation

strategies, for example antibiograms which reflecting local antimicrobial resistance may not be available in all countries, hence clinicians lack of guide correct use of empirical antibiotic which can significantly impact clinical outcome such as mortality (Kuo *et al.*,2018; Lueangarun and Leelarasamee,2012,Qadeer *et al*.,2016). Difference in infection control practices or lacking of such practices can also significantly impact infection clinical outcome (Darmstadt *et al*,.2005;Haley *et al*,.1985; Shojania *et al*,.2001,Wenzel 2005). Moreover, the difference in resistance pattern has resulted in different treatment success rates. Countries with higher antimicrobial resistance will have difficulty in treating common infections like urinary tract infections and pneumonia. It is postulated that Asian countries will have the highest mortality due to antimicrobial resistance in the world, followed by Africa, Europe, and America (Review on antimicrobial resistance,2014). Therefore, it is important that different countries have evidence on safety of de-escalation to tailor for such variation in practice, guidelines and resistance pattern.

1.3 Justification of The Study

The safety of de-escalation and prognostic information has value not only to the healthcare system, but to the healthcare provider and the patient as well. Stakeholders can utilise such information to guide and support local policy changes. For example, if safety of antibiotic de-escalation is proven in local settings, it will encourage healthcare providers to embed routine practice of antibiotic de-escalation. Patients de-escalated on antibiotic will be spared from misuse, which will help conserve its effectiveness when it is truly needed,

and prevent adverse drug reactions as a result of antibiotic misuse. Stakeholders can use such evidence-based research to form policies of antibiotic de-escalation and spearhead AMS programmes nationwide. Similarly, by knowing the factors that predict clinical failure of antibiotic use in patients de-escalated on antibiotic, healthcare providers can be reminded to be more conscientious in their decision when de-escalated an antibiotic. With the awareness of the impact of such predictors, healthcare providers can further maximize the benefits and safety of antibiotic de-escalation.

Considering the limited applicability of de-escalation studies conducted in developing countries, and the absence of study on prognostic factors that affect mortality in patients initiated on extended and restricted antibiotic, such a study will improve understanding on safety of antibiotic de-escalation while causing minimal to no harm on study participants.

1.4 Research Question

a) Is there a difference in 30-day all-cause mortality between those de-escalated (early and late) vs non de-escalated on extended or restricted antibiotic?
b) What are the factors associated with 30-day all-cause mortality for patients with suspected bacterial infection initiated with extended or restricted antibiotics?