ANTIBIOTIC DE-ESCALATION IN CRITICAL CARE: EFFECT ON OUTCOME, MORBIDITY AND MORTALITY OF CRITICALLY ILL PATIENTS

(ABCD STUDY)

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DEPARTMENT OF ANAESTHESIOLOGY
UNIVERSITY OF MALAYA
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THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ANAESTHESIOLOGY

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ANTIBIOTIC DE-ESCALATION IN CRITICAL CARE: EFFECT ON OUTCOME, MORBIDITY AND MORTALITY IN CRITICALLY ILL PATIENTS (ABCD STUDY)

ABSTRACT

Background: Expanding antimicrobial resistance patterns in the face of stagnant growth in novel antibiotic production underscores the importance of antibiotic stewardship, in which de-escalation remains an integral component. Audit of de-escalation therapy in Malaysia is lacking and few centres have an established antimicrobial stewardship program. The frequency of antibiotic de-escalation in the ICU setting of University Malaya Medical Centre (UMMC), a 1643-bedded, tertiary university hospital, was explored. Through this study, a plausible benchmark for de-escalation therapy in the local ICU setting can hopefully be established, to provide the basis for future audits and research on the subject.

Methods: A prospective, observational study was performed by review of all patients who were admitted to the ICU of UMMC, for clinical or suspected sepsis, between April 2018 and October 2018, by the sole lead investigator. Antibiotic de-escalation was defined as the use of narrower spectrum antibiotics, reducing the number of antibiotics, reducing the number of days or the discontinuation of antibiotics after initiation of empirical broad spectrum antibiotics, or a combination of one or more of the above. Subjects dying within 72 hours of antibiotic initiation were considered not de-escalated for subsequent analysis and were subtracted from the study population in determining a modified mortality rate. An electronic collection reporting form (e-CRF) was created using REDcap to key in relevant clinical data. The data was then translated to SPSS for further analysis.

Results: A total of 57 subjects were included in this study.

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Primary Outcome: Of the 57 patients studied, 12(21.0%) had their antibiotic regimens de-escalated during their duration of ICU stay, with negative culture being the most likely reason for antibiotic de-escalation (7 of the 12 de-escalated cases). De-escalation was not adversely associated with any of the forms of composite patient outcomes studied - length of ICU and hospital stay, duration on mechanical ventilation, duration on vasoactive drugs and renal replacement therapy, emergence of multi-drug resistant (MDR) micro-organisms, re-infection rates, as well as, mortality.

Secondary Outcome: The most commonly suspected source of infection at admission to ICU was Respiratory Tract Infections (52.5%), followed by Gastrointestinal Tract Infections (21.3%). The most commonly prescribed initial empirical antibiotic therapy was penicillin with beta-lactamase inhibitor (31.6%). De-escalation did not significantly affect the total duration of antibiotic therapy.

Conclusions: De-escalation of antibiotic therapy was not adversely associated with composite patient outcome measures. It appears safe and prudent for antibiotic de-escalation to be carried out in patients with severe sepsis. However, more local studies, including larger sample sizes are required, before reliable benchmarks and conclusions can be drawn regarding antibiotic de-escalation in critical care patients and associated patient outcome in our Malaysian setting.

Keywords: Antibiotic de-escalation, Antibiotic stewardship, Benchmark, Prospective observational study, Audit

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ABSTRAK

Latar Belakang: Corak rintangan antimikrob yang semakin menular dan kekurangan penciptaan antibiotik novel menekankan kepentingan pengawasan antibiotik, di mana de-eskalasi kekal sebagai salah satu komponen yang penting. Audit terapi de-eskalasi di Malaysia kurang dan kebanyakan pusat tidak mempunyai program pengawasan antibiotik yang mantap. Amalan antibiotik de-eskalasi dalam unit rawatan rapi (ICU) Pusat Perubatan Universiti Malaya (UMMC), sebuah hospital universiti yang mempunyai 1643 katil, telah diterokai. Melalui kajian ini, diharapkan satu prosedur de-eskalasi antibiotik yang efektif dapat diwujudkan, dan juga menyediakan asas untuk menjalankan lebih banyak audit atau kajian mengenai subjek ini pada masa depan.

Kaedah: Kajian prospektif dan pemerhatian dilakukan dengan mengkaji semua pesakit yang dimasukkan ke ICU UMMC antara April 2018 dan Oktober 2018, kerana menghidapi atau disyaki menghidapi sepsis. Antibiotik de-eskalasi ditakrifkan sebagai penggunaan antibiotik spektrum sempit, mengurangkan jumlah bilangan antibiotik, mengurangkan bilangan hari rawatan atau pemberhentian antibiotik selepas permulaan antibiotik spektrum empirikal, atau gabungan satu atau lebih daripada senarai di atas. Subjek yang mati dalam lingkungan 72 jam permulaan antibiotik empirikal dianggap tidak de-eskalasi untuk analisa seterusnya dan dikurangkan daripada populasi kajian dalam menentukan kadar kematian. Borang pelaporan elektronik (e-CRF) telah dibuat menggunakan RedCAP untuk mengumpulkan data klinikal yang relevan. Data tersebut kemudian diterjemahkan ke SPSS untuk analisa lanjut.

Keputusan: Sebanyak 57 subjek telah dimasukkan ke dalam kajian ini

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Hasil utama: Daripada 57 pesakit yang dikaji, de-eskalasi dijalankan dalam 12 (21.0%) subjek semasa tempoh penginapan di ICU, dengan keputusan kultur negatif sebab utama untuk antibiotik de-eskalasi (7 dari 12 subjek). De-eskalasi tidak meningkatkan morbiditi yang dikaji - tempoh kemasukan ke ICU dan hospital, tempoh bantuan pernafasan mekanikal, tempoh penggunaan ubat vasoaktif, dialisis, kemunculan organisma rintangan pelbagai antibiotik (MDR), kadar jangkitan semula dan mortaliti.

Hasil sekunder: Sumber jangkitan yang paling disyaki semasa kemasukan ke ICU ialah jangkitan saluran pernafasan (52.5%), diikuti dengan jangkitan saluran pemakanan (21.3%). Terapi antibiotik empirikal yang paling biasa digunakan ialah penisilin dengan inhibitor beta-laktamase (31.6%). De-eskalasi tidak menjejaskan jumlah tempoh terapi antibiotik.

Kesimpulan: De-eskalasi terapi antibiotik tidak dikaitkan dengan peningkatan morbiditi dalam subjek kajian. Prosedur tersebut selamat dijalankan dalam rawatan pesakit yang menghidapi sepsis. Walau bagaimanapun, lebih banyak kajian tempatan, termasuk saiz sampel yang lebih besar diperlukan, sebelum kesimpulan dapat dibuat mengenai praktis antibiotik de-eskalasi dalam rawatan pesakit kritikal yang menghidapi sepsis.

Kata kunci: Antibiotik de-eskalasi, Pengawasan antibiotik, Tanda aras, kajian pemerhatian Calon, Audit

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LIST OF SYMBOLS AND ABBREVIATIONS

Abx	:	Antibiotics
E. coli	:	Escherichia coli
e-CRF	:	Electronic Collection Response Form
ESBL	:	Extended Spectrum Beta Lactamase
ICU	:	Intensive Care Unit
IMV	:	Invasive Mechanical Ventilation
MDR	:	Multi Drug Resistant
MRCN S	:	Methicillin Resistant Coagulase Negative Staphylococcus
OR	:	Odds Ratio
RR	:	Relative Risk
RRT	:	Renal Replacement Therapy
Spp.	:	Species
UMMC	:	University Malaya Medical Centre

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CHAPTER 1: INTRODUCTION

The present landscape of clinical sepsis is typified by increasing and rapidly developing antimicrobial resistance (Tabah et al., 2016). Yet, few new antibiotics, particularly innovative classes, are becoming available to combat this challenge (Roberts et al., 2014). As the stark imbalance between rising antimicrobial resistance and novel antibiotic therapy becomes more pronounced, a 2-step approach to the management of sepsis has emerged, with the maxim – 'hit it hard and hit early', embedded within the overall encompassing concept of antimicrobial stewardship(Masterton, 2011). Within this proposed treatment paradigm, antibiotic de-escalation, forms one of its key, yet most challenging elements and has garnered much support in the clinical realm of infectious disease management (Silva, Andriolo, Atallah, Salomao, 2013).

Antibiotic de-escalation involves commencement of appropriate broad spectrum antibiotic therapy, before reducing the number and/or duration of antibiotics, narrowing the spectrum of antibiotics or ceasing antibiotic therapy, in the shortest timeframe deemed plausible (Dellit et al., 2007). However, the impact of the aforementioned components of antibiotic de-escalation on patient outcome and antimicrobial resistance has been insufficiently evaluated thus far (Masterton, 2011). Local data on antibiotic stewardship and de-escalation polices is especially scarce (Leone et al., 2014). De-escalation can be approached in diverse ways, with a possible array of different clinical outcomes. A study into the practice of antibiotic de-escalation in the critical care unit UMMC and its subsequent effect on patient outcome has yet to be done.

The aim of this dissertation is to explore the effects of antibiotic de-escalation policy, in the ICU setting of UMMC, on patient outcome, morbidity and mortality.

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Consequently, the data obtained will be useful to serve as a benchmark for further research and studies on local antibiotic de-escalation policies and practices.

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CHAPTER 2: LITERATURE REVIEW

As the market for novel and innovative classes of antibiotics continues to dwindle, the management of patients with sepsis has to be centered on making the best use of the antibiotics available, to maximize their clinical impact and longevity (Masterton, 2011). Appropriate and early commencement of antibiotic therapy is crucial in the treatment of infections in the critically ill, with delays in antibiotic administration associated with increased mortality (Mitchel, Evans & Rhodes, 2018). Timely administration, adequate spectrum and appropriate dosing regimens are crucial to achieving good patient outcome (Vincent et al., 2009). Yet, despite the consensus regarding spectrum and timing of antibiotic therapy, pattern of antimicrobial use varies across ICUs, with variations in choice, dosing, method of administration, duration and de-escalation of empirical therapy (Tabah et al., 2016).

Moreover, whilst clinicians attempt to cover severely ill and septic patients with the most appropriate empirical antibiotic regimen, few units have established protocols regarding subsequent antibiotic de-escalation (Masterton, 2011). The widespread and prolonged use of broad-spectrum antibiotic therapy for the empirical treatment of infections has inadvertently contributed to the exponential increase in a variety of multi-drug resistant micro-organisms.

De-escalation therapy refers to the initial commencement of broad-spectrum antibiotics, followed by narrowing the spectrum of antimicrobial therapy depending on clinical response and when culture results of antimicrobial susceptibility testing are available (Garnacho, Gutierrez, Escoresca, Fernandez & Lopez, 2015). It is an approach to allow provision of effective initial therapy, while avoiding unnecessary antibiotic use which would lead to antibiotic resistance (De Waele, Ravyts, Depuydt, Blot, Decruyenaere & Vogelaers, 2010). The opportunity to de-escalate empirical therapy is

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inherently related to the choice of initial antibiotic therapy, with a higher likelihood of de-escalation when effective broad-spectrum therapy is started empirically (Dellit et al., 2007).

De-escalation typically consists of the following components (Table 1.1) – Reduction of the number of antibiotics, narrowing the spectrum of the antibiotic, reduction of the duration of antibiotic therapy, stopping unnecessary therapy, or a combination of one or more of the above elements (Dellit et al., 2007).

Table 2.1: Components of de-escalation as described in the literature

1. Reduction of the number of antibiotics
2. Narrowing the spectrum of the antibiotic
3. Reduction of the duration of antibiotic therapy
4. Stopping unnecessary therapy (therapy without in-vitro activity against the pathogen)
5. A combination of one or more of the above elements

De-escalation is considered an integral component of antimicrobial stewardship and is part of the Surviving Sepsis Campaign guidelines (Mitchel, Evans & Rhodes, 2018). De-escalation can be approached in diverse ways, oftentimes influenced by local practices or preferences of the treating clinician. The various manners in which de-escalation is approached may have considerable impacts on patient outcome (Masterton, 2011).

The impact of antibiotic de-escalation has not been sufficiently evaluated and few high quality studies on the topic are available. A recent meta-analysis on de-escalation therapy for adults with sepsis, severe sepsis, or septic shock by the Cochrane Collaboration sought to include randomized controlled trials (RCTs), but not a single such study could be found to include in the analysis (Silva, Andriolo, Atallah &

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Salomao, 2013). Furthermore, the majority of studies of antibiotic de-escalation are limited to the intensive care setting and often to one disease entity such as ventilator associated pneumonia and may not accurately depict the anticipated associated outcomes in severe infections from other clinical sources (Knaak et al., 2013).

Several retrospective, observational studies, on antibiotic de-escalation therapy have been performed. The appropriate implementation of antimicrobial de-escalation therapy has been described to be safe and not associated with poorer patient outcomes, compared with the conventional approach of maintaining the initial empirical antibiotic therapy started, when this was eliciting a favorable clinical response (Heenen, Jacobs & Vincent, 2012). Some studies have even demonstrated a beneficial effect of antibiotic de-escalation on patient mortality (Giantsou et al., 2007). Yet, it remains unclear, if the favorable clinical outcomes of de-escalation therapy are due to selection bias and thus rather apparent effect from a favorable patient population pool, or a true effect of de-escalation practices (Masterton, 2011).

Other anticipated benefits of antibiotic de-escalation include an improvement in antibiotic resistance profiles, a reduction of antibiotic-related adverse events, decreased antimicrobial exposure and reductions in both the lengths of ICU and hospital stay (Masterton, 2011). Naturally, these will all translate into substantial short and long term cost savings for the healthcare industry.

While most published data on antibiotic de-escalation therapy appear to suggest that de-escalation is a well-tolerated management strategy in critically ill and septic patients, many clinicians worldwide remain reluctant to adopt such a treatment approach, in view of a paucity of robust clinical data (Morel et al. 2014). The practice of routine de-escalation has further been challenged by the recent findings of a multicentre, randomized controlled trial, which illustrated that de-escalation was associated with

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increased antibiotic days, mainly due to an increased number of superinfections (Leone et al. 2014).

According to international literature, adherence to a de-escalation policy in ICUs is generally poor, ranging from 10 to about 70% in recent studies (Goh, Asako,Yamamoto & Kentaro, 2016). In the treatment of severe sepsis, there is a natural propensity for managing physicians to stick with the prescribed empirical antibiotic regime that a patient appears to be responding well to, than to change to an alternative of narrow spectrum antibiotics or even abruptly stopping antimicrobial therapy (Masterton, 2011). Evidently then, a significant barrier to antibiotic stewardship in most ICU settings, is largely the lack of established evidence-based guidelines and clinical trials of markers to assist in formulating de-escalation policies (Montravers et al., 2011).

As the challenge of the increasing numbers and frequency of multi-drug resistant micro-organisms continues to inflict considerable strains on healthcare facilities worldwide, it appears only prudent for clinicians and researchers to develop more robust studies on antimicrobial de-escalation practices and their associated clinical outcomes. Only with the acquisition of robust clinical and scientific data, can antibiotic de-escalation policies be better streamlined both globally and in the local clinical context, as clinicians develop more confidence and enthusiasm in the implementation of antimicrobial de-escalation practices.

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CHAPTER 3: METHODOLOGY

3.1 STUDY POPULATION

Given the explorative nature of this study, the required number of patients was not calculated. The management of antibiotic therapy for all patients admitted into the critical care unit of UMMC, over a 6-month period (April 2018 – October 2018), who fulfilled the inclusion criteria, were included in the study.

3.2 INCLUSION CRITERIA

For inclusion in the study, subjects must have fulfilled all of the following criteria:

- Age 18 years or older.
- Patient is admitted to ICU and has an anticipated need of ICU support of at least 48 hours.
- Patient has a suspected or confirmed bacterial infection (community-, healthcare-, hospital- or ICU-acquired).
- Empirical antibiotic therapy is started for this infection at any time in the ICU or no more than 24 hours prior to ICU admission. If the initial antibiotic therapy is considered inadequate and another empirical antibiotic is chosen during ICU admission, this will be considered the empirical antibiotic of the study.
- Causative pathogen and susceptibility are unidentified at time of initiation of the antibiotic therapy (Gram staining results may be known).

3.3 EXCLUSION CRITERIA

- Previous inclusion in this study for another infection – each patient can only be included once.

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3.4 STUDY DESIGN

This is a prospective observational study. Patients were selected over a 6-month period between April 2018 and October 2018. All patients admitted to the ICU of UMMC, during the study period, were screened by the PI. All patients found eligible, according to inclusion and exclusion criteria, were included into the study.

All selected patients were observed until 28 days after inclusion into the study.

3.5 DATA COLLECTION

For each patient included in the study, data was collected and stored in an e-CRF, created using REDcap. Start date of empirical antibiotic therapy was considered to be the date of inclusion in the study. For each included patient, data was collected based on the following 4 elements (Appendix A):

1. **Patient data**
   - Demographics
   - Underlying and co-morbid conditions
   - Patient characteristics on ICU admission
   - Patient characteristics on start of empirical antibiotic therapy
   - Patient characteristics on day 3 after start of empirical antibiotics
2. **Infection data**
   - Clinical aspects
   - Microbiological data
3. **Treatment data**
   - Antimicrobial therapy
   - Source control

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4. **Outcome data (28 day follow up)**
    - Supportive therapy (E.g. Mechanical Ventilation, use of vasoactive drugs, Renal Replacement Therapy)
    - ICU length of stay
    - Mortality
    - Antibiotic-free days
    - Emergence of antimicrobial resistance on day 2 or later of study inclusion
    - Infection related outcome data

3.6 STUDY DEFINITIONS, MEASUREMENTS AND ENDPOINTS

3.6.1 DEFINITIONS

De-escalation was considered to have occurred, when the empirical antibiotic therapy initiated was converted to one of narrower spectrum or stopped, when the number of antibiotics was reduced, or a combination of these occurred, within 5 days of study inclusion. A period of 5 days was chosen, as culture and susceptibility results would be available within 5 days, in our local setting.

3.6.2 MEASUREMENTS DURING STUDY

There were no additional interventions or measurements other than those that were considered to be standard of care.

3.6.3 PRIMARY ENDPOINTS

- Emergence of resistance in de-escalated patients at DAY 28
    - Multidrug resistant, extensively drug resistant and pan-drug resistant
    - Resistance to the administered empirical antibiotic therapy
- ICU length of stay and mortality in de-escalated patients at DAY 28

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- Need for supportive therapy
  - Renal Dialysis/Renal Replacement Therapy (RRT)
  - Invasive Mechanical Ventilation (IMV)
  - Vasoactive drugs
- Rate of infection relapse, superinfections, and subsequent infections in de-escalated patients at DAY 28

3.6.4 SECONDARY ENDPOINTS

- Antibiotics used in empirical therapy
- Factors associated with de-escalation
  - Clinical
  - Treatment related
  - Microbiological
- Duration of antibiotic therapy in de-escalation patients for the infection under study
- Antibiotic free days for de-escalated patients at DAY 28

3.7 DATA MANAGEMENT AND STATISTICS

3.7.1 DATA MANAGEMENT

A web-based electronic e-CRF was created using REDcap and used for the recording of the relevant patient data.

3.7.2 STATISTICAL ANALYSIS

Data compiled from the e-CRFs were translated into SPSS for further analysis and interpretation. Odds ratios and Relative risks with 95% confidence intervals were calculated to describe the effect of different variables/interventions on categorical

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outcome measures. Pearson's Chi-Square Test was used to determine statistical significance of results in 2x2 data tables. Where cell values were <5, Fisher's Exact Test was utilized instead, in determining significance. When comparing the mean difference in outcome measures with de-escalation therapy, the use of ANOVA tables was employed.

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CHAPTER 4: RESULTS

4.1: PRIMARY OUTCOMES

During the 6-month study period, 57 subjects were deemed to be eligible for inclusion under the ABCD Study. Of these, de-escalation of empirical antibiotic therapy was seen in 12 subjects (21%) (Figure 4.1).

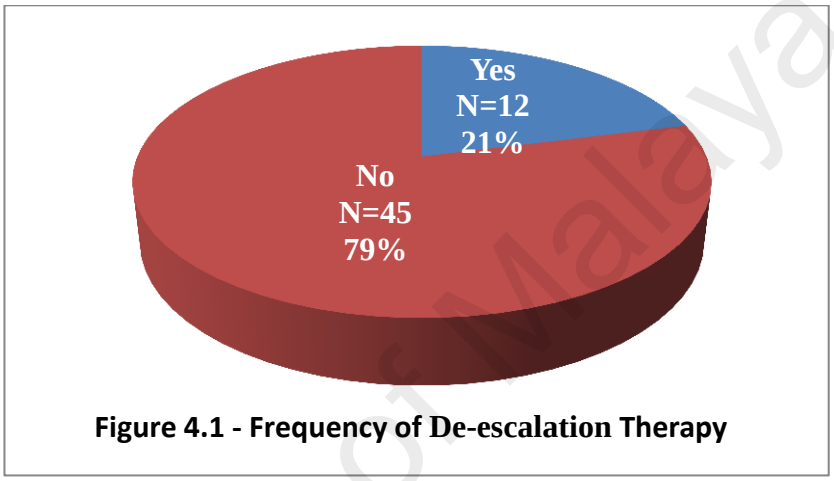

Figure 4.1 - Frequency of De-escalation Therapy

The practice of de-escalation, while not apparently conferring any tangible health benefits, was also not adversely associated with any of the composite patient outcomes measured.

Of the 12 patients whose antibiotic therapies were de-escalated, there was only 1 mortality (8.3%) in ICU during the study period, compared to 14 deaths (31.1%) in the groups of patients in whom no de-escalation of empirical antibiotic therapy was initiated (RR=0.268, CI=0.039-1.839, p=0.152), (Table 4.1). There was no mortality amongst patients who received antibiotic de-escalation, after discharge from ICU, while 1 patient remained in ICU beyond the study period of 28 days. In the group of patients where antibiotic de-escalation was not carried out, 2 patients (6.5%) died after discharge from ICU, during the study period (Table 4.2). Most deaths that occurred in our study

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population were deemed to be related to infection – 12 of 15 deaths (80%) (Table 4.3). However, the effects of de-escalation on these measured outcomes were all deemed not to be statistically significant.

Table 4.1 - Effect of De-escalation on patient mortality in ICU

		Did Patient die in ICU		Total (%)	RR (95% CI)	P-Value
		Yes (%)	No (%)			
De-Escalation Therapy Initiated	Yes	1 (8.3)	11 (91.7)	12 (100)	0.268 (0.039-1.839)	0.152
	No	14 (31.1)	31 (68.9)	45 (100)		

Table 4.2 - Effect of De-escalation on patient mortality after ICU Discharge

		Did Patient die after discharge from ICU during study period		Total (%)	RR (95% CI)	P-Value
		Yes (%)	No (%)			
De-Escalation Therapy Initiated	Yes	0 (0)	10 (100)	10 (100)	0 (-)[a]	1.000
	No	2(6.5)	29 (93.5)	31 (100)		

a - Confidence Interval cannot be determined in view of null value in numerator

Table 4.3 - Effect of De-escalation on Mortality related to Infection

		Was Death Related to Infection		Total (%)	RR (95% CI)	P-Value
		Yes (%)	No (%)			
De-Escalation Therapy Initiated	Yes	1 (100)	0 (0)	1 (100)	1.273 (0.968-1.673)	1.000
	No	11 (78.6)	3 (21.4)	14 (100)		

There was no significant bearing of de-escalation therapy on patient discharge from ICU during the study period (RR=0.909, p=0.262) (Table 4.4).

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Table 4.4 - Effect of De-escalation Therapy on Patient Discharge from ICU

		Was Patient Discharged from ICU during Study Period		Total (%)	RR (95% CI)	P-Value
		Yes (%)	No (%)			
De-Escalation Therapy Initiated	Yes	10 (90.9)	1 (9.1)	11 (100)	0.909 (0.754-1.096)	0.262
	No	31 (100)	0 (0)	31 (100)		

De-escalation of empirical antibiotic therapy did not appear to result in increased emergence of MDR micro-organisms. Positive MDR micro-organism on Day 2 of study period, or later, were cultured in 23 of 45 (51.1%) patients (Table 4.5) who did not receive de-escalation of their antibiotic therapy, while that in the group of patients who received de-escalation therapy was only 3 of 12 (25%), (p=0.107). No patients in the study experienced infection relapse, further infection or super infection during the study period.

Table 4.5 - Effect of De-escalation on MDR Micro-organisms

		MDR emergence (Day 2 or after)		Total (%)	RR (95% CI)	P-Value
		Yes (%)	No (%)			
De-Escalation Therapy Initiated	Yes	3 (25)	9 (75)	12 (100)	0.489 (0.076-1.334)	0.107
	No	23 (51.1)	22 (48.9)	45 (100)		

De-escalation did not appear to have any significant adverse effect on various composite patient outcome measures analysed in this study. The duration of patients on invasive mechanical ventilation (mean 6.4 vs 5.8days, p=0.739), duration on renal replacement therapy (mean 2.2 vs 1.8 days, p=0.725), duration on vasoactive drug

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support (mean 4.7 vs 4.8 days, p=0.992), antibiotic-free duration (mean 1.9 vs 1.3 days, p=0.519) and duration of ICU stay (mean 6.4 vs 5.0 days, p=0.342) were not significantly different in patients who experienced antibiotic de-escalation or those who did not.

Table 4.6 – Impact of De-escalation Therapy on Composite Patient Morbidity

		Duration on IMV[1] (Days)	Duration on RRT (Days)	Duration on Vasoactive drugs[1] (Days)	Anti-biotic Free Duration (Days)	Duration in ICU (Days)
De-escalation	**Mean**	6.4	2.2	4.7	1.9	6.4
	N	45	45	45	45	31
	SD	5.3	3.7	4.6	2.9	4.4
	Median	5.0	0	4.0	0	6.0
	Variance	28.3	13.8	21.5	8.4	19.0
	Range	22.0	17.0	20.0	12.0	18.0
	Max	22.0	17.0	20.0	12.0	19.0
	Min	0	0	0	0	0
No De-escalation	**Mean**	5.8	1.8	4.8	1.3	5.0
	N	12	12	12	12	10
	SD	7.3	3.7	6.3	3.5	2.8
	Median	4.0	0	2.5	0	4.0
	Variance	53.7	14.0	39.7	12.2	8.0
	Range	28.0	13.00	23.00	12.00	9.0
	Max	28.0	13.00	23.00	12.00	11.0
	Min	0	0	0	0	2.0
ANOVA (p-value)		0.739	0.725	0.992	0.519	0.342

[1]

[1] Patients were deemed to be dependent on invasive mechanical ventilation or vasoactive drug therapy, only if either was necessary for more than 1hour, in a particular day, unrelated to any form of surgical procedures.

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4.2: SECONDARY OUTCOMES

As mentioned earlier, 12 patients (21%) in our study experienced de-escalation of empirical antibiotic therapy (Figure 4.1) and the prime reason for de-escalation to be commenced was due to negative culture results – 7 out of 12 patients (Figure 4.2).

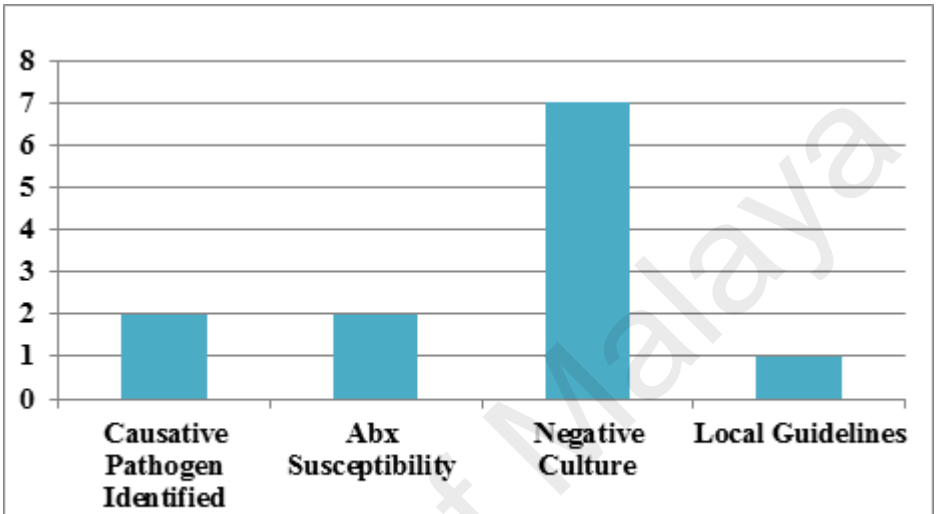

Figure 4.2 – Reason for De-escalation

Infection of the upper/lower respiratory tract was revealed as the most probable initial diagnosis (56.1%), as well as the most common final diagnosis (50.5%). This was followed by Gastrointestinal tract infections (Initial diagnosis = 22.8%, Final diagnosis = 21.1%), while other sources of infections were seemingly less common in our study population. (Tables 4.7 & 4.8)

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Table 4.7 Initial Probable Focus of Infection, by Frequency

Probable Focus of Infection (At initiation of empirical antibiotic therapy)	**Responses (N)**	**% of total responses**
Bone and Joint Infections	1	1.8%
Central Nervous System Infections	2	3.5%
Gastrointestinal Tract and Intraabdominal Infections	13	22.8%
Genitourinary Tract Infections	2	3.5%
Lower & upper respiratory tract infections	32	56.1%
Skin & soft tissue infections	6	10.5%
Other focus of infection	1	1.8%
Unknown focus of infection	4	7.0%

Table 4.8 Final Source of Infection, by Frequency

Final Diagnosis (Source of Infection)	**Responses (N)**	**% of total responses**
Bone and Joint Infections	1	1.8%
Central Nervous System Infections	2	3.5%
Gastrointestinal Tract and Intraabdominal Infections	12	21.1%
Genitourinary Tract Infections	1	1.8%
Lower & upper respiratory tract infections	29	50.9%
Skin & soft tissue infections	6	10.5%
Other focus of infection	1	1.8%
Unknown focus of infection	6	10.5%

The most common cause of respiratory tract infection was CAP - 58% of patients with confirmed respiratory traction infection (Figure 4.3).

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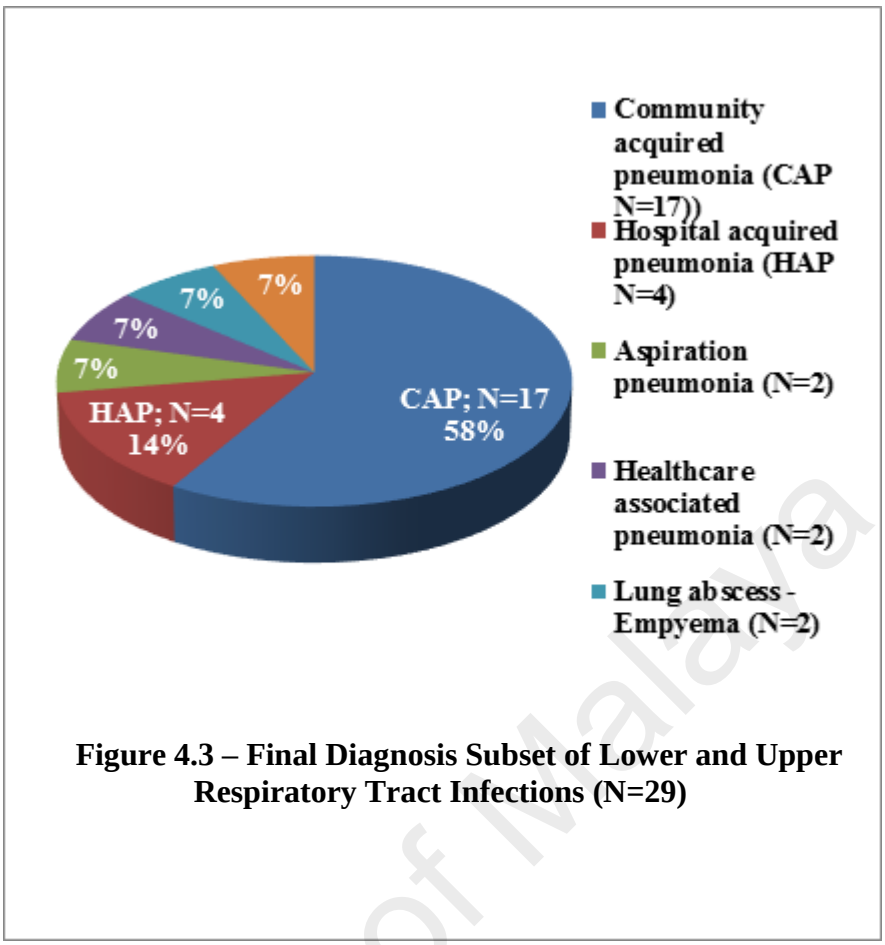

Figure 4.3 – Final Diagnosis Subset of Lower and Upper Respiratory Tract Infections (N=29)

39 of the 57 patients (68.4%) in our study received antibiotics prior to ICU admission, with Penicillin + B-lactamase inhibitor combination therapy the most common antibiotic of choice (48.7% of patients on empirical antibiotics) (Figure 4.4).

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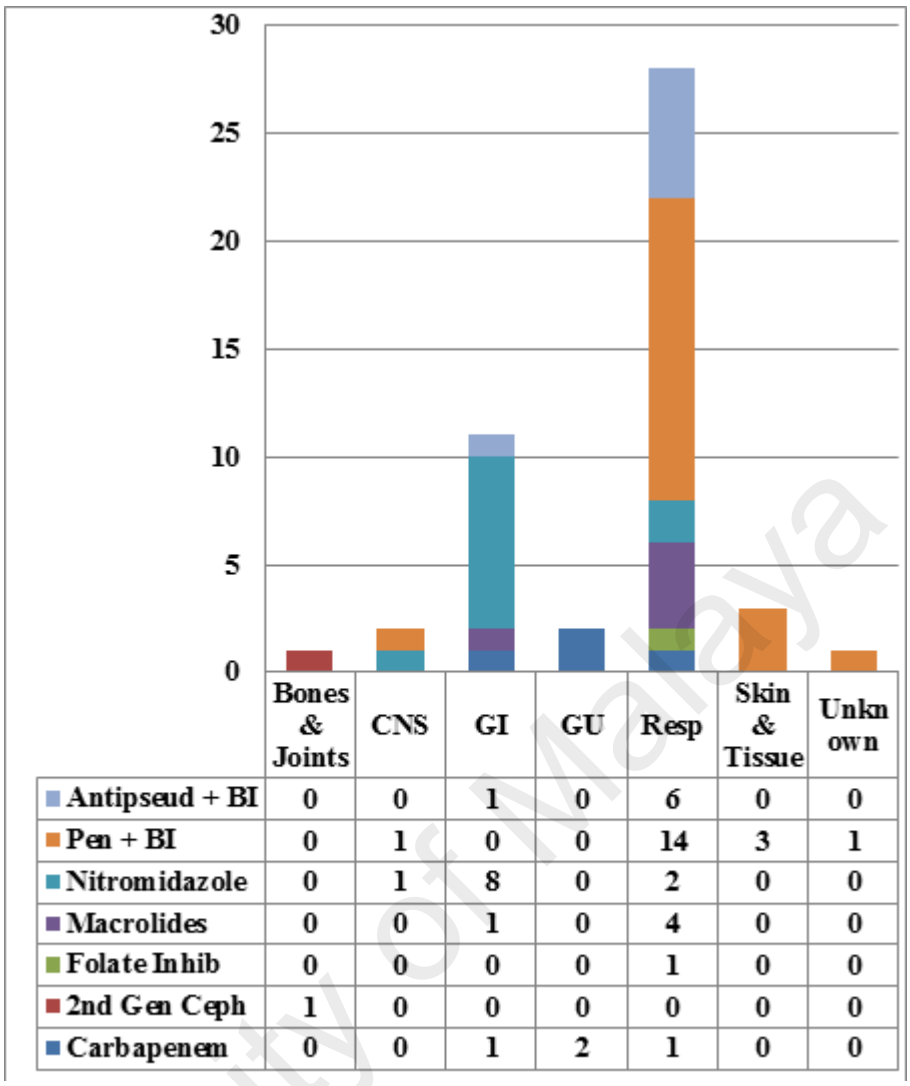

	Bones & Joints	CNS	GI	GU	Resp	Skin & Tissue	Unknown
Antipseud + BI	0	0	1	0	6	0	0
Pen + BI	0	1	0	0	14	3	1
Nitromidazole	0	1	8	0	2	0	0
Macrolides	0	0	1	0	4	0	0
Folate Inhib	0	0	0	0	1	0	0
2nd Gen Ceph	1	0	0	0	0	0	0
Carbapenem	0	0	1	2	1	0	0

Figure 4.4 – Empirical Antibiotic Based on Suspected Infection

A wide variation of antibiotics has been administered for the most common infections – respiratory tract and gastrointestinal tract infections. However, choice of antibiotics has been relatively tailored to accepted local common distribution patterns of causative pathogens and antimicrobial susceptibility. In our study population, this corresponds to a predilection for Nitromidazoles and Penicilllins+B-lactamase inhibitors to be favoured for gastrointestinal and respiratory tract infections, respectively. Carbapenems and Penicillin+B-lactamase inhibitors appear to be the drug of choice for genitorurinary and skin+soft tissue infections, respectively. However, the sample size in the latter 2 is small.

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There did not appear to be any statistically significant difference in the total duration of antibiotic therapy for patients who had their antimicrobial therapy de-escalated, compared to those who did not, based on antibiotic-free days, as described earlier (Table 4.6).

29 patients (51%) in the study had positive cultures for MDR micro-organisms on Day 2 of our study, or later (Figure 4.5). The most common MDR micro-organism cultured in our study was Klebsiella (ESBL) - Positive yield in 12 of 57 patients (21.1%) (Figure 4.6).

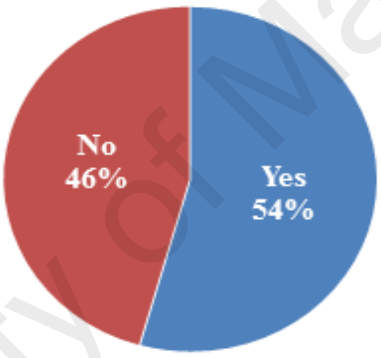

Figure 4.5 – MDR Micro-organisms cultured on D2, or later

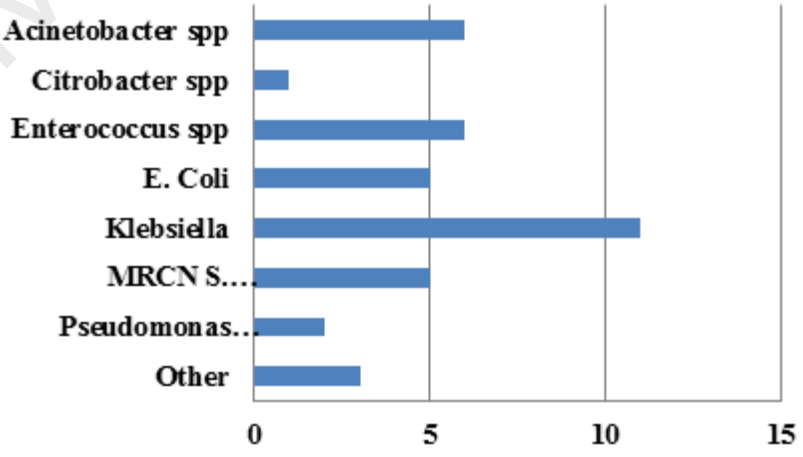

Figure 4.6 – Frequency of MDR Micro-organisms

The appropriateness of initial empirical antibiotic therapy was not studied.

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4.3 - FACTORS AFFECTING DE-ESCALATION

Factors possibility affecting the implementation of antibiotic de-escalation were also analysed in this study. Age 60years and above (Odds Ratio 0.522, p=0.324) at study inclusion, Obesity (BMI≥30) (Odds ratio 0.500, p=0.292), gender and total APACHE score on admission to ICU (Odds ratio 1.120, p=0.863) all did not appear to have any bearing on decision for de-escalation (Table 4.9).

Table 4.9 - Patient factors affecting decision for Abx De-escalation

Patient Factors		Was De-escalation Therapy Initiated		Total (%)	Odds Ratio (95% CI)	P-Value
		Yes (%)	No (%)			
1. **Age**	**<60**	5 (16.1)	26 (83.9)	31 (100)	0.522 (0.144-1.898)	0.324
	≥60	7 (26.9)	19 (73.1)	26 (100)		
2. **BMI**	**<30**	6 (16.7)	30 (83.3)	36 (100)	0.500 (0.138-1.817)	0.292
	≥30	6 (28.6)	15 (71.4)	21 (100)		
3. **Gender**	**M**	7 (18.9)	30 (81.1)	37 (100)	1.081 (0.803-1.455)	0.591
	F	5 (25)	15 (75)	20 (100)		
4. **Total APACHE Score on Admission**	**<25**	7 (21.9)	25 (78.1)	32 (100)	1.120 (0.309-4.067)	0.863
	≥25	5 (20%)	20 (80%)	25 (100%)		

Analysing the initiation of antibiotic de-escalation against the established source of infection revealed that none of the patients with central nervous system or skin and soft tissue infections received de-escalation therapy. Only 1 patient each were diagnosed with bone and joint and genitourinary tract infection. Using respiratory tract infection as reference, the patients with gastrointestinal tract and unknown sources of infection receiving antibiotic de-escalation were more likely to experience de-escalation of initial empirical antibiotic therapy, though this difference was not statistically significant. (Both RR=2.417, p-values 0.154 and 0.234 respectively) (Table 4.10).

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Patients with respiratory tract infections were used as the reference, as the practice of antibiotic de-escalation was the least prevalent in this group.

Table 4.10 – Final Infection and Initiation of De-escalation

Final Infection	Was De-escalation Therapy Initiated		Total (%)	Relative Risk (95% CI)	P-Value
	Yes (%)	No (%)			
1. Bone & Joints	1 (100)	0 (0)	1 (100)	-	-
2. CNS	0 (0)	2 (100)		0	-
3. GI	4 (33.3)	8 (66.7)		2.417 (0.719-8.118)	0.154
4. GU	1 (100)	0 (0)		-	-
5. Respiratory (Reference)	4 (13.8)	25 (86.2)		1	-
6. Skin	0 (0)	6 (100)		0	-
7. Unknown	2 (33.3)	4 (66.7)		2.417 (0.566-10.324)	0.234
	12	45	57		

An analysis of how positive results from different culture sites affected the decision for antibiotic de-escalation was also done. 40 patients had positive culture results (7 patients had 2 positive culture sites). Taking positive cultures from respiratory tract samples as the reference, decision to de-escalate initial empirical antibiotic therapy was deemed to be more likely when the positive culture came from blood (RR=4.846, p=0.027) and operative sample cultures (RR=3.000, p=0.179) respectively. This difference was statistically significant for positive blood culture results (Table 4.11).

No patients were de-escalated based on positive wound culture results.

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Table 4.11 - Culture Site and Practice of Abx De-escalation

Culture site	Was De-escalation Therapy Initiated		Total (%)	Relative Risk (95% CI)	P-Value
	Yes (%)	No (%)			
1. Blood	7 (53.8)	6 (46.2)	13 (100)	4.846 (1.195-19.657)	0.027
2. Respiratory Tract (Reference)	2 (11.1)	16 (88.9)	18 (100)	1	-
3. Operative Sample	3 (33.3)	6 (66.7)	9 (100)	3.000 (0.606-14.864)	0.179
4. Wound	0 (0)	4 (100)	4 (100)	0	-
5. Others	0 (0)	4 (100)	4 (100)	0	-

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4.4 - OTHERS

Total APACHE Score has been illustrated to be useful in predicting mortality rates. An APACHE Score of ≥25 represents a predicted mortality of ≥50%, reaching ≥80% if the APACHE Score is ≥35 (Bouch and Thompson, 2008). Comparing patients with Total APACHE Scores <25 and ≥25 upon admission to ICU, revealed that the Total APACHE Score did not have a significant impact on the mortality rates (RR=0.723, p=0.590), or the number of empirical antibiotic agents commenced in our study population (p=0.160) (Table 4.12, Figure 4.6).

Table 4.12 - Effect of Total APACHE Score on Patient Mortality

		Did Patient die in ICU		Total (%)	RR (95% CI)	P-Value
		Yes (%)	No (%)			
Total APACHE Score	**<25**	7 (23.3)	23 (76.7)	30 (100)	0.723 (0.222-2.358)	0.590
	≥25	8 (29.6)	19 (70.4)	27 (100)		

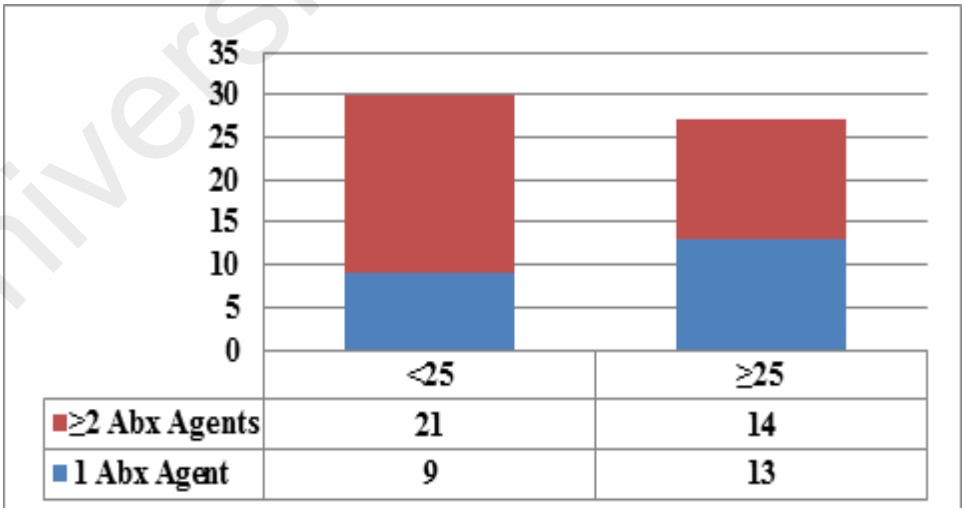

Figure 4.6 – Number of Empirical Abx, based on Total APACHE Score upon ICU Admission

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CHAPTER 5: DISCUSSION

De-escalation is defined as the reduction of the number of antibiotics, reduction of the number of days on antibiotics, narrowing of spectrum of antibiotics, stopping initial empirical antibiotic therapy, or a combination of the above (Dellit et al., 2007). In most published literature, de-escalation of empirical antibiotic therapy has been considered to have taken place, if 'step down' was initiated within a 72-hour time frame from the start of empirical antibiotic treatment (Tabal et al., 2016). For the purposes of our study, de-escalation was considered to have occurred, if initiated within 5 days of starting empirical antibiotic therapy, as this was considered the accepted time frame in which culture and susceptibility results will be made available.

In our study on antibiotic de-escalation practices, in patients with severe sepsis, in the critical care setting of a local tertiary hospital, UMMC, the rate of antibiotic de-escalation was 21% (12 of 57 patients). This rate of antibiotic de-escalation, while within the commonly quoted de-escalation range (10%-70%) of most other published studies (Masterton 2010), appears to fall within the more conservative range of the spectrum.

Our study aimed to describe the effect of empirical antibiotic de-escalation on patient clinical outcomes. Factors possibility affecting decision for de-escalation were also looked into.

Although our study was not sufficiently powered to describe clinical outcomes, de-escalation of initial empirical antibiotic therapy was not associated with adverse patient outcomes including patient mortality, emergence of MDR micro-organisms, duration of ICU stay, duration on IMV, duration on RRT, duration on vasoactive drug therapy and overall duration on antibiotics (Liu et al., 2016). This suggests that antibiotic de-

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escalation is relatively safe and not associated with poorer composite patient outcomes (Morel et al., 2010). In fact, some studies have even described lower mortality and MDR emergence rates with de-escalation therapy (Garnecho et al., 2014) and our study does show a trend towards lower, albeit non-statistically significant, relative risks in these aspects as well.

The main reason for antibiotic de-escalation in our study population was due to negative culture results (7 of the 12 patients (58.3%) de-escalated). However, there were a total of 17 culture negative results from our study population, which translates to only 41% of patients with culture negative results receiving de-escalation of empirical antibiotics. Absence of positive microbial cultures did not appear to affect decision to de-escalate. It is worthwhile to look into the reasons why the majority of patients with negative culture results did not have their empirical antibiotic therapy de-escalated. Oftentimes, clinicians are understandably hesitant to change a management option that appears to be effective for a very sick patient (Heenen, Jacobs & Vincent, 2012).

In our study, 6 patients who had their initial empirical antibiotic therapy regime de-escalated subsequently required re-escalation of antibiotics. However, this did not appear to significantly affect any of their composite morbidity and mortality measures studied. Yet, continued vigilance has to be advised in patients who have their initial antibiotic regimes de-escalated, as this study has shown that the need for re-escalation of antibiotics may be necessary.

An integral aspect of the practice of antibiotic de-escalation, is the use of an effective empirical antibiotic regime, followed by appropriate de-escalation in the shortest time-frame deemed clinically safe to do so (Masterton, 2011). The surviving sepsis campaign guidelines advocate starting empirical antibiotic therapy within 1 hour, for patients with severe sepsis (Mitchel, Evans & Rhodes, 2018). In our study population, only 39 of 57

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patients (68.4%) were administered with empirical antibiotic therapy, prior to admission to ICU. The reason for delaying the commencement of empirical antibiotic therapy in our local setting should be further explored.

The most common source of infection in our study population was infection of the respiratory tract, making up >50% of patient admissions to ICU for severe sepsis, the majority (58%) of which were diagnosed to have community acquired pneumonia. A combination empirical antibiotic therapy of penicillin + B-lactamase inhibitor was the empirical therapy of choice in patients suspected to have infections of the respiratory tract.

Our study further analysed possible factors that may affect de-escalation of empirical antibiotics by attending clinicians. Age, BMI, Gender and source of infection were all not significantly associated with de-escalation rates. Only the site of positive culture appeared to significantly affect decision to initiate de-escalation in our study population. With samples cultured from the respiratory tract as reference, the relative risk of de-escalation was 4.846, with p=0.027, when blood cultures yielded positive results. This might suggest that a blood culture results weigh more significantly in the minds of clinicians, in subsequently affecting their management of patients with severe sepsis, and their decision whether to initiate antibiotic de-escalation.

While the Total APACHE score has been deemed to be a good predictor of patient mortality (Bouch & Thompson, 2008), it was not significantly related to number of antibiotics administered as empirical therapy, death, or decision to de-escalate empirical antibiotic therapy in our study population. It appears to suggest that rather than the numbers of different antibiotics to fight infections, the choice of effective initial antibiotic is more crucial in affecting patient outcome. Also, severity of infection evidently did not play a significant impact on the decision of clinicians to initiate

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antibiotic de-escalation (Liu et al., 2016). Furthermore, with appropriate management, it appears that even patients with severe sepsis and higher initial Total APACHE scores recovered well from their infection.

It is evident then that effective antibiotic stewardship, in which de-escalation of empirical antibiotics forms an important cornerstone, requires a multidisciplinary approach. The onus is on the primary team or attending clinician to administer effective empirical antibiotic therapy upon the diagnosis of sepsis and relevant culture(s) sent. Microbiologists should strive to ensure efficient release of culture and susceptibility results. It is imperative that infectious disease clinicians, intensive care physicians and pharmacists work to establish a system of keeping track of data on local microbial activity patterns, including MDR emergence, to appropriately advise and institute safe and effective antibiotic treatment regimes to patients with severe sepsis.

The main drawback of our study is the modest sample size we obtained.

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CHAPTER 6: CONCLUSION

In the face of the global rise in MDR micro-organisms and the scarcity of new, novel antibiotic therapy, antibiotic stewardship is fundamental in our fight against microbes, in which the effective de-escalation of initial empirical antibiotic therapy forms an integral component. De-escalation appears to be safe and feasible in most clinical settings and patient subsets, even in patients with severe sepsis. However, few local hospitals have an established antibiotic de-escalation policy and the de-escalation rates in most local healthcare settings are likely less than to be desired, such as is described in our study population.

The paucity of local data often hinders antibiotic de-escalation in the Malaysian setting, as many clinicians inadvertently are reluctant to de-escalate broad spectrum antibiotic therapy, when critically ill patients appear to be responding well and improving with the prescribed empirical therapy, without established local guidelines and protocols on de-escalation to support their cause. More published studies pertaining to de-escalation practices and patient outcomes are necessary in the local context, before local guidelines and protocols can be established and the practice of effective and appropriate de-escalation of empirical antibiotic therapy becomes more commonplace.

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