PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) PRINCIPLES IN MONITORING BETA-LACTAM ANTIBIOTICS IN CRITICALLY ILL PATIENTS: EVALUATING THE CURRENT APPROACH, KNOWLEDGE, PERCEPTION, AND PRESCRIBING PRACTICE OF CLINICIANS

BY

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ABSTRACT

Infection is an independent factor associated with increased mortality in the intensive care unit (ICU). To manage such problem, antibiotics are utilized. It is argued that current antibiotic dosing approach is not sufficient for patients in the ICU due to significant pathophysiological changes. Different ICUs might employ different antibiotic dosing approach based on local guidelines and practice. Malaysia already has two published guidelines on managing infection in the ICU but data on its compliance is largely unknown. This study aimed to determine clinicians' knowledge and perception on antibiotic pharmacokinetic/pharmacodynamic (PK/PD) and its integration in antibiotic dosing, and practice of antibiotic prescribing among clinicians in the ICU. This study also investigating whether contemporary antibiotic dosing used in the ICU is adequate in achieving the recommended PK/PD target. This study consisted of two parts with both occurring simultaneously. The first part was a cross-sectional online survey among anesthesiologists, intensivists, Infectious Disease Specialists, and other specialists working primarily in the ICU. The survey consisted of 3 sections: knowledge, perception, and antibiotic prescribing practice among clinicians in ICU. The second part was a prospective, PK/PD point prevalence study involving beta-lactam antibiotics conducted in the ICU of three teaching hospitals. Two blood samples were taken from each patient during a single dosing interval. Antibiotic concentrations above the minimum inhibitory concentration (MIC) of the pathogen at mid-point (50% $fT_{>MIC}$), end of dosing interval (100% $fT_{>MIC}$), and 100% $fT_{>4xMIC}$ (four times the concentration above the MIC at end of dosing interval) were set as the PK/PD target. Data were analyzed descriptively for Study Part One, and multiple logistic regression was used to describe effect of antibiotic exposure on patient outcomes in Study Part Two. All data analyses were conducted using IBM SPSS Statistics 22 (IBM Corporation, Armonk, New York). A total of 104 respondents completed the survey in part one and they concurred the importance of PK/PD in antibiotic optimization. Majority (97.2%) perceived that current dosing of antibiotics is inadequate to achieve optimal PK/PD target in ICU patients. Most (85.6%) believed that antibiotic dose should be streamlined to the organisms' MIC. Adherence rates in terms of antibiotic choices with established guideline were at 79.8%, 77.8%, and 27.9% for HAI, INP, and CRBSI, respectively. In part two, 101 patients were recruited. The median Sequential Organ Failure Assessment score was 7 (interquartile range [IQR], 4-9). Majority of patients was able to achieved the minimum PK/PD target of 50% $fT_{>MIC}$ and 100% $fT_{>MIC}$ (88.1% and 73.3% respectively) but when the target was set higher at 100% $fT_{>4xMIC}$, only one-third (34.7%) of patients met the outcome. Continuous infusion was associated with higher attainment of PK/PD ratio of plasma concentration and pathogen's MIC (P = 0.07). Achieving a high serum concentration of beta-lactam antibiotics at mid dosing interval was 4% more likely to have better mortality outcomes (P = 0.045). Clinicians in the ICU are receptive to employ PK/PD approach in optimizing antibiotic dosing for critically ill patients but are limited by gaps in the knowledge of antibiotic PK/PD. Survivability of sepsis patients is significantly improved when serum concentration of beta-lactam antibiotics at mid-point dosing interval is high.

خلاصة البحث

تعد الانتانات عاملاً مستقلاً لارتفاع معدل الوفيات في وحدات العناية المركزة، ويتم استخدام المضادات الحيوية لمعالجتها. هناك جدل حول عدم كفاءة الطرق الحالية لإعطاء جرعات المضادات الحيوية للمرضى في وحدات العناية المركزة بسبب التغيرات الفسيولوجية المرضية الكبيرة، ولدى كل من وحدات العناية المركزة طرق مختلفة لإعطاء جرعات المضادات الحيوية وذلك بناء على الإرشادات والممارسات الداخلية. هناك في ماليزيا اثنان من المبادئ التوجيهية المنشورة حول إدارة الالتهابات في وحدات العناية المركزة ولكن البيانات المتعلقة بتطبيقها غير معروفة إلى حد كبير. هدفت هذه الدراسة إلى تحديد مستوى المعرفة بـ PK/PD للمضادات الحيوية ، و تطبيقها في تحديد الجرعات العلاجية في وحدة العناية المركزة وكذلك تحديد ما إذا كانت الطرق الحديثة لإعطاء جرعات المضادات الحيوية المستخدمة في وحدات العناية المركزة كافية لتحقيق الهدف الموصى به من PK/PD. تكونت هذه الدراسة من جزأين تم القيام بهما في وقت واحد. كان الجزء الأول عبارة عن استبيان مقطعي عبر الإنترنت بين أطباء التخدير، وأخصائيي العناية المركزة، وأخصائيي الأمراض المعدية، وغيرهم من المتخصصين العاملين بشكل أساسي في وحدات العناية المركزة. تكون الاستبيان من 3 أقسام: المعرفة، والإدراك، وممارسات وصف المضادات الحيوية في وحدات العناية المركزة. الجزء الثاني كان عبارة عن دراسة استطلاعية لانتشار نقط الـ PK/PD باستخدام مضادات بيتا لاكتام، حيث أجريت في وحدات العناية المركزة في ثلاثة مستشفيات تعليمية. تم أخذ عينتين دم من كل مريض خلال فترة واحدة لإعطاء الجرعات. تم تحديد أهداف الـ PK/PD كالتالي: تراكيز المضادات الحيوية أعلى من التركيز الأدنى للتثبيط (MIC) للعامل الممرض عند النقطة الوسطى (50٪ fT>MIC) وفي نهاية فترة إعطاء الجرعات (100٪ fT>MIC)، و 100٪ fT>MIC4x (أربعة أضعاف التركيز فوق تم التركيز الأدنى للتثبيط في نهاية فترة إعطاء الجرعات). تم تحليل البيانات وصفيًا للجزء الأول من الدراسة، واستخدم الانحدار اللوجستي المتعدد لوصف تأثير التعرض للمضادات الحيوية على نتائج المرضى في الجزء الثاني من الدراسة. تم إجراء جميع تحاليل البيانات باستخدام برنامج SPSS النسخة 22. أكمل الاستبيان 104 من المشاركين في الجزء الأول واتفقوا على أهمية الـ PK/PD في تحسين المضادات الحيوية. لاحظ الغالبية (97.2٪) أن الجرعات الحالية غير كافية لتحقيق أهداف الـ PK/PD المثلى في مرضى وحدات العناية المركزة. اعتقد معظمهم (85.6٪) أنه يجب ضبط جرعات المضادات الحيوية إلى التركيز الأدنى لتثبيط العامل الممرض. كانت معدلات التطبيق من حيث خيارات المضادات الحيوية مع المبادئ التوجيهية المحددة عند 79.8٪ لـ HAI، و 77.8٪ لـ INP و 27.9٪ لـ .CRBSI تم في الجزء الثاني من الدراسة إشراك 101 مريضا. النتيجة المتوسطة لتقييم فشل الأعضاء المتسلسل كانت 7 (المدى الربيعي [9-4 ،IQR]). . استطاع معظم المرضى تحقيق أهداف الـ PK/PD الدنيا 50% fT>MIC، و 100% fT>MIC ومن قبل 88.1% و 73.3% من المرضى على التوالي. لكن عندما تم تحديد الهدف عند 100٪ fT>MIC4x، حقق 34.7٪ فقط من إجمالي المرضى الأهداف. ارتبط التسريب الوريدي المستمر للمضادات بتحقيق أعلى لأهداف الـ PK/PD لتركيز البلازما والتركيز الأدنى لتثبيط الممرض (P=0.07). تحقيق تركيز مرتفع لمضادات بيتا لاكتام في مصل الدم عند فاصل جرعات بنسبة 50٪ كان أكثر احتمالاً وبنسبة 4.0٪ للحصول على نتائج وفيات مرغوبة (P=0.045). أظهر الاستبيان تقبل الأطباء في وحدات العناية المركزة استخدام طرق الـ PK/PD لتحسين إعطاء جرعات المضادات الحيوية للمرضى المصابين بأمراض خطيرة، ولكنهم مقيدون بفجوات في المعرفة المتعلقة بالـ PK/PD للمضادات الحيوية. كانت جرعات المضادات الحيوية الحالية المستخدمة في وحدات العناية المركزة كافية لتحقيق أهداف الـ PK/PD بنسبة 50٪ و 100٪ لـ fT>MIC4x. ومع ذلك، بالنسبة لهدف 100% fT>MIC4x للـ PK/PD، لم تحقق الطرق الحديثة هذا الهدف المستعصي.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master in Pharmaceutical Sciences (Pharmacy Practice).

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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Firstly, it is my utmost pleasure to dedicate this work to my dear parents and my family, who granted me the gift of their unwavering belief in my ability to accomplish this goal: thank you for your support and patience.

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LIST OF ABBREVIATION

ICU	Intensive care unit
PK/PD	Pharmacokinetic/pharmacodynamic
MIC	Minimum inhibitory concentration
DALI	Defining Antibiotics Level in the Intensive Care Unit Patients
$fT_{>MIC}$	Percentage of time the free unbound drug is above the minimum inhibitory concentration
$fT_{>4xMIC}$	Percentage of time the free unbound drug is four times above the minimum inhibitory concentration
EPIC II	International Study of the Prevalence and Outcomes of Infection in Intensive Care Units
V_d	Volume of distribution
AKI	Acute kidney injury
ARC	Augmented renal clearance
GFR	Glomerular filtration rate
ADME	Absorption, distribution, metabolism, and excretion
C_{max}	Peak plasma drug concentration
C_{min}	Minimum plasma drug concentration
IB	Intermittent bolus
EI	Extended infusion
CI	Continuous infusion
RRT	Renal replacement therapy
MRIC	Malaysian Registry of Intensive Care
MOH	Ministry of Health
HAP	Hospital acquired pneumonia
IAP	Infective acute pancreatitis
CRBSI	Catheter related bloodstream infection
I-CVI	Item content validity index
S-CVI	Scale content validity index
S-CVI/Ave	Scale content validity index average
SOFA	Sequential organ failure assessment
HPLV	High performance liquid chromatography
APACHE II	Acute physiology and chronic health evaluation
MREC	Medical Research and Ethics Committee
NMRR	National Medical Research Register

CHAPTER ONE

INTRODUCTION

1.1 STUDY BACKGROUND

Evidence and guidelines related to appropriate utilisation of antibiotics in the intensive care unit (ICU) are limited. Available knowledge highlights the need to integrate pharmacokinetic/pharmacodynamic (PK/PD) in dosing antibiotics when it comes to managing infection of critically ill patients in the ICU (Abdul-Aziz et al., 2015; Sinnollareddy et al., 2012; Teo et al., 2014; Yang et al., 2015). At present, practice of administering beta-lactam antibiotics is inconsistent as one ICU might opt for a different approach as compared to another ICU . Such discrepancy might be due to limited knowledge on such approaches. Furthermore, clinician's perception and understanding of using available antibiotics are also limited. Clinicians are not well-versed to fully exploit the PK/PD of available antibiotics to maximise therapeutic activity. As such, antibiotic dosing in special patient populations, including ICU patients, often relies solely on product information leaflet, which oftentimes the data were derived from healthy volunteers. Consequently, it does not take into consideration the extreme pathophysiological changes seen in ICU patients (Roberts et al., 2011; Roberts & Lipman, 2006; Teo et al., 2014; Yang et al., 2015). It is argued that current dosing approach of antibiotics, notably the beta-lactam group, is not optimised as it is not able to hit the PK/PD target consistently (Abdul-Aziz et al., 2015; Roberts & Lipman, 2009; Yang et al., 2015). As a result of that, it can lead to prolonged hospital stay, increase mortality, and increase healthcare costs. Since infection is the leading cause of mortality in the ICU (Magnason et al., 2008; Vincent, 2003; Ylipalosaari et al., 2006), evaluating

whether adequate contemporary dosing approach of antibiotics used in the ICU is crucial for further improvements to be made.

1.2 PROBLEM STATEMENT

Mortality is a prime concern whenever patients are admitted to the ICU. The risk of mortality is further increased when patients developed sepsis in the ICU or are admitted to the ICU due to sepsis (Lenz et al., 2017; Melville et al., 2015; Vincent et al., 2009; Vught et al., 2016; Ylipalosaari et al., 2006). With this in mind, clinicians in the ICU will often ponder regarding the best management approach they should take in order to achieve definite clinical resolution. Most of the times, clinicians will streamline dosing of medications for patients in the ICU the same way as those in the general wards despite relevant pathophysiologal differences. This problem can be clearly seen in antibiotics, the most frequently used drugs in the ICU. Product information leaflet that came together with the antibiotics tend to recommend using conventional dosing approach such as using short intermittent bolus infusion for beta-lactam antibiotics. Such an approach may not be optimal as it does not take into consideration the PK/PD nature of the antibiotics.

Due to the nature of beta-lactam antibiotics being a time-dependent antibiotic, the percentage of time the free (or unbound) drug is above the minimum inhibitory concentration (MIC) also known as $fT_{>MIC}$ is of utmost important. Shah and colleagues (1976) were the first investigators to report that beta-lactam antibiotics activity is enhanced when plasma concentration is persistently above the MIC concentration (Shah et al., 1976). Achieving $fT_{>MIC}$ between 40-70% is generally the accepted range as it has been shown to demonstrate better eradication of bacteria (Craig, 1984, 1998). However in sepsis and septic shock, achieving an $fT_{>MIC}$ of 100% has been suggested to be more

clinically beneficial for this population of patients (McKinnon et al., 2008). Nonetheless, present dosing approached of beta-lactam antibiotics used in the ICU today failed to achieve the recommended $fT_{>MIC}$ target as the Defining Antibiotics Level in the Intensive Care Unit Patients (DALI) study has shown (Roberts et al., 2014). DALI study only incorporates European countries only and therefore data for local population in Asian is lacking. This study was the first in Asian region to evaluate whether contemporary dosing approach used in the ICU was sufficient to achieve optimal PK/PD target which is correlated with better therapeutic outcomes.

1.3 PURPOSE OF THE STUDY

This study was conducted to explore whether current beta-lactam antibiotic dosing approach in the ICU for critically ill patients is able to achieve the PK/PD target for maximum therapeutic activity. Apart from that, ICU clinician's knowledge and perception pertaining to the use of antibiotics in managing infection together with its prescribing practice were also investigated and compared with established guideline.

1.4 RESEARCH QUESTIONS

1. Do clinicians in the ICU possess sufficient knowledge related to antibiotics and its PK/PD?
2. How the ICU clinician perceive towards the concept of integrating PK/PD profiles in antibiotic dosing for critically ill patients?
3. Does current antibiotic prescribing practice in the ICU correspond with existing guidelines?

4. Does current dosing approach of beta-lactam antibiotics in the ICU able to achieve the PK/PD target concentration in critically ill patients that is associated with maximal patient benefits?
5. Does achieving the target PK/PD exposure of beta-lactam antibiotics to the critically ill patients correlate with patients' clinical outcomes (ie. clinical cure at day 14 and mortality at day 30)?

1.5 RESEARCH OBJECTIVES

The study aimed to achieve the following objectives:

1. To assess knowledge pertaining to antibiotics and its PK/PD among clinicians in the ICU.
2. To investigate the perception of ICU clinicians towards the concept of integrating PK/PD profiles in antibiotic dosing for criticall ill patients.
3. To investigate whether the antibiotic prescribing practice of clinicians in the ICUs correspond with the existing guideline.
4. To evaluate whether contemporary dosing approach of beta-lactam antibiotics in the ICU able to achieve the PK/PD target concentration in critically ill patients that is associated with maximal patient benefits.
5. To investigate whether achieving the target PK/PD exposure of beta-lactam antibiotics to the critically ill patients correlate with patients' clinical outcomes (ie. clinical cure at day 14 and mortality at day 30).

1.6 OUTCOME MEASURE

The first outcome measure of this study was the ICU clinicians' apprehension towards the use of antibiotics for managing critically ill patients. In this outcome, several

questions will be presented to ICU clinicians with each question asking specific topic related to infection in the critically ill patients. How each respondent answered to each question will be recorded and analysed. The second outcome measure was the percentage of respondents that either “agree”, “disagree”, or “not sure” towards the concept of integrating PK/PD in antibiotic dosing for patient in the ICU. The next outcome measure was the percentage of respondents that adhered to the established ICU antibiotic guideline. In this context, one will be considered adhere if such respondent provided the correct antibiotic together with the correct dose. Moving on, the next outcome measure was the number of patients that were able to achieve the PK/PD target concentration concentration. Three PK/PD target concentration were chosen:

1. 50% $fT_{>MIC}$
2. 100% $fT_{>MIC}$
3. 100% $fT_{>4xMIC}$

The PK/PD target of 50% $fT_{>MIC}$ refers to free drug concentration maintained above minimum inhibitory concentration (MIC) of the known or suspected pathogen for at least 50% of dosing interval. Meanwhile, 100% $fT_{>MIC}$ in this context refers to free drug concentration maintained above MIC of the known or suspected pathogen throughout the entire dosing interval. On the other hand, 100% $fT_{>4xMIC}$ refers to free drug concentration maintained above a concentration four-fold higher than the MIC of the known or suspected pathogen throughout the enitre dosing interval. The final outcome measure of this study was the statistical relatinship between PK/PD concept and clinical outcomes. Variables in the PK/PD concept that showed a statistically significant value. $P < 0.05$ will be reported.

1.7 SIGNIFICANCE OF STUDY

This study provided an insight whether clinicians in the ICU was conversant with available antibiotics and their PK/PD in managing infection. Furthermore, since assimilating PK/PD concept in antibiotic dosing had garnered much attention as part of the stratagem to reduce antibiotic resistance and improve clinical outcomes, such awareness in Malaysian setting is still scant. Thus this study contributed data on the perception of Malaysian ICU clinicians when it comes to assimilating PK/PD concept in antibiotic dosing. Moreover, although an established guideline for managing infection in the ICU had been published, different ICUs might employ different approach when it comes to managing infection in the ICU. Therefore this study answered such inquiry as it provided information on the prescribing practice of antibiotics based on a given clinical scenario. As infection is an independent factor associated with increased mortality for patients admitted to the ICU, this study investigated whether contemporary dosing of beta-lactam antibiotics in the ICU is adequate to achieve the PK/PD target for maximal antibiotic activity since managing the infection is of utmost important and is part of the bundle sepsis regimen.

CHAPTER TWO

LITERATURE REVIEW

2.1 CRITICALLY ILL PATIENTS IN THE INTENSIVE CARE UNIT

A critically ill patient requires immediate and close clinical monitoring. These patients are treated in the intensive care unit (ICU) by clinicians and other health professionals who are specialized to manage such patients. This field of medicine is also known as critical care medicine. Despite relatively small number of patients in the ICU as compared to the general ward, ICU carries the highest percentage of mortality in any given hospital (Dombrovskiy et al., 2007). The mortality rate in the ICU can reach up to 30% depending on severity of illness and age (Dombrovskiy et al., 2007). Even among those who do survive until being discharged from the hospital, their mortality rate at 1, 2, and 3 years are 12.5%, 19.3%, and 27.5%, respectively (Brinkman et al., 2013).

Several factors affect the clinical outcomes and mortality of patients being admitted to the ICU, such as organ dysfunction, the presence of comorbid disease, age, infection, length of ICU stay, and the use of mechanical support such as mechanical ventilation (Chen et al., 2001; Unal et al., 2015). Thus far, infection carries the worst prognosis as those in the ICU who have infections are highly associated with increased mortality compared to those who does not have an infection (Melville et al., 2015; Vincent, 2008; Ylipalosaari et al., 2006). A prospective cohort study done by Ylipalosaari and colleagues (2006) documented that infection acquired in the ICU is an independent risk factor for hospital mortality (Ylipalosaari et al., 2006). These findings highlight the issue that infection in ICU is linked with poor outcomes.

2.2 INFECTION IN THE INTENSIVE CARE UNIT

The incidence of infection in ICU is high as between 40-60% of patients in the ICU will have an infection (Alberti et al., 2002; Vincent et al., 2009). This means that for every two patients presented to the ICU one will have an infection. For those who do not present with an infection, Vincent et al. reported that 37% of them will likely to have one as a result of acquired infection when staying in the ICU and this is especially true for those who stay more than 48 hours (Vincent et al., 2009). The outcome of patients with infection in the ICU is worse than those without infection as they generally carry a poor prognosis. Several studies have reported that patients who have an infection in the ICU tend to have prolonged length of stay and increased likelihood for mechanical ventilator use to support life (Chen et al., 2001; Dombrovskiy et al., 2007; Lambert et al., 2011). In addition, patients who are on mechanical ventilator, the duration of use is prolonged in those that have an infection as opposed to those that do not have an infection (Magnason et al., 2008).

Besides that, mortality is also a primary concern for patients who have been afflicted with infection in the ICU. This is because various studies conducted have shown that risk of death is significantly higher when patients in the ICU have an infection (Lenz et al., 2017; Unal et al., 2015; Vught et al., 2016). The International Study of the Prevalence and Outcomes of Infection in Intensive Care Units (EPIC II) reported that the rate of mortality was more than double for infected patients as compared to those non-infected (25% vs 11% respectively) (Vincent et al., 2009). However, the EPIC II study only disclosed data for one day and it was performed than five years ago. A more recent study conducted by Melville and colleagues showed that the mortality is much higher (Melville et al., 2015). The authors found that septic patients in the ICU had a 70% relative higher mortality rate as opposed to those non-

septic patients (Melville et al., 2015). The authors found that septic patients in the ICU had a 70% relative higher mortality rate as opposed to those non-septic patients (Melville et al., 2015). The study is a prospective study which covers nine years starting from 2005 until 2014. Data generated from Melville and colleagues showed that the mortality of infected patients in the ICU can be much higher than previously reported.

In terms of pharmacoeconomics, infections in the ICU consume a substantial amount of hospital's resources. Koster-Brouwer and colleagues reported that the mean cost of sepsis care in the Netherlands' ICU accounted for approximately €30,000 per admission (Koster-Brouwer et al., 2016). Moreover, the cost of critical care medicine has increased by 45% in the past few years and is expected to increase further (Halpern & Pastores, 2010). Utilisation of various medications, advanced radiographic imaging techniques, multitude biochemical blood tests, and use of assistive mechanical support all contribute to the increase cost of care which in turn lead to prolong days of hospitalization (Halpern & Pastores, 2010).

2.3 APPROACH IN MANAGING INFECTION IN THE ICU

Antibiotics are the agent of choice when it comes to combating infection in the ICU. Among the group of antibiotics available, beta-lactams are frequently used relative to other classes (Prowle et al., 2011; Ulldemolins et al., 2010). Their broad-spectrum of antibiotic activity particularly ensure that it covers both Gram-positive and Gram-negative bacteria. Besides that, the side effect profiles are much more tolerable as compared to other class of antibiotics such as the aminoglycosides which is known for its renal adverse effects (Wargo & Edwards, 2014).

Several studies have reported that early and proper administration of antibiotics to infected patients in the ICU significantly improve clinical outcomes (Nee, 2006;

Sinnollareddy et al., 2012). However, conventional dosing approach of these antibiotics cannot be directly applied to the patients in ICU as opposed to patients in the general ward (Roberts & Lipman, 2006). This is due to the fact that during drug development, these antibiotics are tested only on healthy individuals to generate pharmacokinetic data which are then later used as reference for dosing administration (Gonçalves-Pereira & Póvoa, 2011). When it comes to critically ill patients in the ICU, these data cannot be directly extrapolated and be used on these group of patients since it does not take into consideration the profound physiological changes that are commonly seen in patients being admitted to the ICU (Abdul-Aziz et al., 2015; Gonçalves-Pereira & Póvoa, 2011; Sinnollareddy et al., 2012). It cannot be simply insinuated that antibiotics given to the severely ill patients in the ICU will behave the same way as it does in patients in the general wards.

Critically ill patients in the ICU typically have marked pathophysiological changes in the body which makes dosing strategy of antibiotics not only difficult, but other drugs too (Hosein et al., 2011). Some of these changes include alterations in volume of distribution (V_d) for hydrophilic drugs particularly beta-lactam antibiotics. Due to routine use of fluids in the ICU as a means to maintain the haemodynamic pressure of patients, V_d of beta-lactam antibiotics is increased substantially as a result of the process (Hosein et al., 2011).

Besides that, various cytokines that are released during the state of infection also contribute to the increased in V_d of beta-lactam antibiotics for patients in the ICU (Angus & Poll, 2013; Roberts & Lipman, 2006). These cytokines which are released due to the interaction between endotoxins and exotoxins released from bacteria and the patient's body cause increase permeability of blood vessels. This in turn cause extravasation of fluid into extracellular spaces (Hosein et al., 2011). The increase in V_d