UNIVERSITI TEKNOLOGI MARA

EVALUATION OF EMPIRICAL ANTIBIOTIC TREATMENT ADEQUACY IN CRITICALLY ILL SEPSIS PATIENTS: IMPACT ON OUTCOMES AND THEIR PREDICTORS

KHALID AHMAD ALI AL-SUNAIDAR

Thesis submitted in fulfillment
of the requirements for the degree of
Doctor of Philosophy

Faculty of Pharmacy

December 2018

ABSTRACT

Inadequate antibiotic treatment has an impact on high mortality. The administration of adequate empirical antibiotics in the management of sepsis in intensive care units has been the cornerstone for treatment success. This study was to investigate the adequacy of empirical antibiotic in critically ill sepsis adult patients and the impact on outcomes such as mortality, severity index and ICU length of stay before being discharged. It had compared the outcomes of most common used antibiotics, supportive treatments with their predictors. It also examined the characteristics of patients admitted in ICU with sepsis. This is a retrospective observational cohort study and it was conducted in tertiary hospital Sungai Buloh -Selangor. The data have been obtained from computerized system /medical records of hospital for patients who were diagnosed as sepsis (based on the diagnosis or sepsis criteria) or have sepsis symptoms based on systemic inflammatory response criteria and being admitted from 2011-2015. Data was retrieved from computer systems, it was double screened and checked by the researcher with patient's files in department of records. The adequacy was determined based on ICU guidelines, bacterial sensitivity patterns, dose, frequency, creatinine clearance and time of empirical antibiotics. APACHE II score was determined with online clinical calculator. Out of 228 ICU adult's patients, 193 (84.6%) died with 119 (52.2%) male and 74 (32. 5%) female respectively. The mean ICU-length of stay (LOS) was 9.86 ±8.96 days, while the mean APACHE II score was 29.59±7.49 points. The inadequate empirical antibiotics (non-AEA) was significantly associated with mortality and ICU-LOS (P<0.005). In multivariable (MV) logistic regression, only the model of non-AEA was a predictor for non-survival OR=.395 (95% CI 0.184- 0.85) (P=0.004). In simple linear regression, the model of non-AEA was a predictor of ICU-LOS (R^2=.055, 95% CI -7.184- -2.114). In MV linear regression, four variables were more likely to be associated with reduction of APACHE II scores, such as mild Glasgow coma scale, CNS source of infection, cefepime 2gm dose every 8 hours. and albumin received treatment respectively. While only two variables were more likely associated for increment of APACHE II scores septic shock diagnosis and continuous renal replacement therapy (CRRT) supported patients respectively (R^2=0.779). In MV linear regression, six variables were more likely associated as predictors for the increment of ICU-LOS (Imipenem 250mg dose every 12 hours., Intermittent dialysis, *Enterococcus faecalis* bacterial infection, *Acinetobacter* infection with multiple resistance organisms (AC-MRO) infection, deep vein thrombosis (DVT) disease and surgery as source of infection) respectively. Besides, in MV cox regression, there was one variable associated with risk of mortality the dose of meropenem 1000mg/8hr/day [HR 19.254 CI95 % (3.124-118.647) (P=.001)]. Meanwhile, other four variables have a protective effect, such as dose of AB exceeds the recommended dose based on. CrCL. [HR .186 CI 95 % (.040-.868) (P=.032)], four organ dysfunctions [HR .128 CI 95%(.025-.654) (P=.014)], AC MRO bacteria [HR .102 CI 95%(.013-.780) (P=.028)] and intermittent dialysis [HR .027 CI 95% (.002-.321) (P= .004)] respectively. AEA was predictor for survival. The septic shock and CRRT were predictors to increase the APACHE II. Meanwhile, predictors for ICU-LOS were Imipenem dose 250mg/12hours, Intermittent dialysis, *Enterococcus faecalis*, *Acinetobacter* with MRO infection, DVT and surgery as source of infection. The implementation of antimicrobial stewardship programs, reduces the emergence of MDR infections and appropriate empirical antibiotics would improve the outcomes of sepsis ICU patients.

ACKNOWLEDGEMENT

(Alhamdulillah) الحمد لله الذي بنعمته تتم الصالحات (All praise and thanks are only for Allah, the One who, by His blessing and favour, perfected goodness/good works are accomplished).

Firstly, all praise to Allah Almighty for giving me the opportunity to embark on my PhD and for completing this long and challenging journey successfully. My gratitude also goes to my supervisor, Professor. Dr. Noorizan Binti Abdul Aziz for her patience, guidance as well as the time she spent. Without her continuous encouragement and support, this study may not have been completed well. I am truly indebted to her, who has been enthusiastically giving comments and has encouraged me throughout the research. Besides, I would like to express my appreciation towards Prof. Dr. Yahaya Hassan for his support and guidance. All the same time, my thanks to all the faculty members of Faculty of Pharmacy -Universiti Teknologi MARA (UiTM), specially to the respected Dean Prof. Dr. Aishah Adam, Dr. Ibtisam Abdul Wahab and last but not least, Puan. Siti Haida Hj Ab Rahman for her assistance.

My appreciation also goes to Dr. Noorizan in CRC Department at Hospital Sungi Buloh and to all staff at patient's record department especially to Puan. Hartini Abul Hadi who provided me the facilities and assistance during data collection.

Last, but definitely not the least, I am greatly indebted to my family. This thesis is dedicated to my beloved wife, daughters and son for their patience, tiredness and encouragement given to me to complete this thesis. Also, I would like to express my utmost gratitude to my parents' unconditional love, care and tolerance which made the hardship of writing the thesis worthwhile. Without their support, I do not think that I could overcome the difficulties during these years This piece of victory is dedicated to both. May Allah the Almighty bless you all, Alhamdulillah.

TABLE OF CONTENT

CHAPTER ONE
INTRODUCTION

1.1 Overview

1.1.1 Defining of Sepsis, Pathophysiology and Classification

Sepsis affects over 26 million people worldwide each year causing death in every 3 to 4 seconds (Ingles et al., 2016). Sepsis is a life-threatening problem pertaining to morbidity and mortality in the clinical setting. It is considered as the top cause of morbidity and mortality. Sepsis can be the result of several pathologies and can greatly complicate the care of patients in and out of the hospital setting (Scholar, Pirozzi, & Mcginley, 2016). Sepsis is defined as a syndrome of life-threatening organ dysfunction caused by a dysregulated host response to infection (Shankar-Hari et al., 2016). The microcellular alteration of sepsis is stimulated by the invading organism which would be bacterial, fungal, or viral or by pathogen producing substance (endotoxin). The endotoxin binds with receptors located on macrophages polymorphonuclear and endothelial cells which promote the release of proinflammatory immune mediators. These inflammatory cascades would then cause vasodilatation and change the function of endothelial cell which alters blood flow, increased vascular permeability and tissue edema. The physiologic alteration that may occur include peripheral vasodilation, myocardial depression, systemic microcapillary injury, coagulopathy and end-organ mal-perfusion. It may also lead to alter gut barrier function which would increase the bacterial translocation and release the intestine related factors that trigger the immune response (Greenwood & Orloski, 2017; Vincent, 2017) .

Nevertheless, there is development in the understanding of the mechanisms underlying the sepsis process. The achieved improvement in establishing global agreement on the terminology of sepsis is still moderate in terms of typical manifestation of disease. Although the sepsis is a result of infection, it becomes confusing as many definitions have been developed to differentiate patient's infection. The reason for the problem with the definition is that sepsis, is such a multifaceted process; although typical signs and symptoms exist, these may not occur in all patients, or in the same patient during the sepsis progression. For example, there are many signs