ADEQUACY OF EMPIRICAL ANTIBIOTIC FOR PATIENT ADMITTED TO ICU WITH SEPSIS

BY

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ABBREVIATIONS

BSI	Blood Stream infection
CCIS	Critical Care Information System
CKD	Chronic Kidney Disease
COAD	Chronic Obstructive Airway Disease
CVP	Central Venous Pressure
DM	Diabetes Mellitus
HIS	Hospital Information System
HPT	Hypertension
ICU	Intensive Care Unit
LOS	Length of Stay
MSIC	Malaysian Society of Intensive Care

ABSTRAK

KECUKUPAN RAWATAN ANTIBIOTIK SECARA "EMPIRIKAL" KEPADA PESAKIT YANG DIMASUKKAN KE UNIT RAWATAN RAPI AKIBAT "SEPSIS"

Objektif : Sepsis merupakan salah satu penyebab utama kemasukan pesakit ke Unit Rawatan Rapi, Hospital Sultanah Nur Zahirah yang menyebabkan kematian dan komplikasi. Rawatan awal antibiotic secara "empirical" bagi pesakit yang mengalami sepsis adalah sangat penting untuk memperbaiki hasil rawatan . Matlamat kajian ini adalah untuk mengkaji kecukupan rawatan antibiotic secara "empirical" kepada pesakit-pesakit 'sepsis' yang dimasukkan ke Unit Rawatan Rapi, Hospital Sultanah Nur Zahirah, Kuala Terengganu.

Metodologi : Kajian ini menggunakan kaedah retrospektif, untuk menilai kecukupan rawatan antibiotic secara "empirical" kepada pesakit yang dimasukkan ke Unit Rawatan Rapi disebabkan oleh sepsis. Seramai 130 orang pesakit yang sepsis yang dimasukkan ke Unit Rawatan Rapi pada 1 Januari 2013 hingga 31 Desember 2013 telah dipilih dan rekod perubatan mereka diambil melalui Sistem Informasi Hospital (HIS). Latarbelakang pesakit, penyakit, penggunaan antibiotic, keputusan ujian darah dan kesan terhadap pesakit dikaji. Penggunaan antibiotic empirical yang optimum ditentukan. Penggunaan antbiotik dikategorikan sebagai optimum apabila jenis antibiotic, dos, kaedah pemberian, dan tempoh rawatan adalah berdasarkan panduan oleh Persatuan Rawatan Rapi Malaysia (MSIC).

Keputusan : Seramai 119 (91.5%) orang pesakit daripada 130 pesakit sepsis yang dimasukkan ke Unit Rawatan Rapi telah menerima rawatan antibiotic secara "empirical" yang mencukupi. Dalam kumpulan ini, purata umur pesakit adalah 51.8 tahun dan 51.3 peratus adalah lelaki. 112 (86.2%) pesakit mengalami 'septic shock' dan 104 (87.4%) daripadanya menerima rawatan antibiotic empirical yang optimum. Punca utama jangkitan kuman dalam darah bagi kumpulan ini adalah daripada paru-paru (42%), abdomen (21%) atau kulit dan tisu (15.1%). Kuman yang paling banyak menjangkiti pesakit adalah *Escherichia coli* 13 (37.1%), *Burkholderia pseudomallei* 7 (20.0%), *Klebsiella pneumonia* 6 (17.1%), *Acinobacter baumanii* 4 (11.4%) dan *Leptospira interrogan* 2 (5.7%). Bagi pesakit yang dijangkiti kuman dari gram positif iaitu sebanyak 25 orang, kuman yang paling banyak adalah coagulase negative staphylococcus 11 (44.0%) dan *staphylococcus aureus* 11 (44.0%) diikuti oleh *streptococcus pneumonia* sebanyak 3 (12.0%) kes. Dalam kumpulan yang menerima rawatan optimum, kumpulan antibiotic yg paling banyak digunakan adalah cephalosporin,seramai 63 (52.9%) pesakit, carbapenem, 21 (17.6%) orang pesakit, diikuti oleh Piperacillin/tazobactam seramai 17 (14.3%) orang and Amoxycillin / clavulanic acid sebanyak 6 (5.0%) kes.

Perbandingan antara kedua-dua kumpulan ini, didapati kesannya secara statistiknya adalah kurang meyakinkan. Ini termasuklah tempoh penggunaan alat bantuan pernafasan, tempoh rawatan hospital serta kematian. Walaupun begitu, didapati jumlah kematian adalah berkurangan sebanyak 10% apabila diberikan rawatan empirical antibiotic yang optimum.

Kesimpulan : Lebih daripada 90 peratus pesakit "sepsis" menerima rawatan antibiotik empirikal yang optimum. Antibiotik dari kumpulan 'cephalosporin' paling banyak diberikan kepada pesakit iaitu sebanyak 52.9 peratus manakala bagi pesakit yang menerima dua jenis antibiotik, kumpulan 'macrolide' merupakan antibiotic yang paling banyak diberikan. Didapati tiada perbezaan terhadap kesan kepada pesakit dalam kedua-dua kumpulan.

ABSTRACT

ADEQUACY OF EMPIRICAL ANTIBIOTIC THERAPY FOR PATIENT ADMITTED TO ICU WITH SEPSIS

Objectives: Sepsis is one of the commonest causes of ICU which lead to high mortality and morbidity. Early empirical antibiotic treatment is important to improve the patient's outcome . The aim of this study was to assess the adequacy of empirical antibiotic therapy for sepsis patients in Intensive Care Unit (ICU), Hospital Sultanah Nur Zahirah (HSNZ), Kuala Terengganu.

Methods: This was a retrospective, observational study to evaluate the adequacy of empirical antibiotic given to patients who were diagnosed with sepsis in ICU. 130 cases who were admitted to ICU for sepsis from January 2013 to December 2013 were selected and their medical record were traced from HIS (Hospital Information System) and reviewed. Their demographic profiles, underlying comorbidities, antibiotic usage, culture and sensitivity results as well as patient's outcome were reviewed. The adequacy of empirical treatment in each case was determined. Adequate empirical antibiotic treatment was considered adequate if spectrum, dose, application modus, and duration of therapy were appropriate according to MSIC (Malaysian Society of Intensive Care) guidelines.

Results: Among 130 intensive care unit patients with sepsis, 119 (91.5%) received adequate antimicrobial treatment. In this group, the mean age of patients was 51.8 year old and 51.3% of them were men.112 (86.2%) patients presented with septic shock and 104 (87.4%) of them were given adequate empirical antibiotic. The main sources of bacteremia in this group were from lungs (42%), abdomen (21%) or skin and soft tissue (15.1%). The microorganisms most frequently isolated were *Escherichia coli* 13 (37.1%), *Burkholderia pseudomallei* 7 (20.0%), followed with *Klebsiella pneumonia* 6 (17.1%), *Acinobacter baumanii* 4 (11.4%) and *Leptospira interrogan* 2 (5.7%). For patients with gram positive culture, which affected 25 patients with adequate treatment, coagulase negative staphylococcus, 11 (44.0%), and *staphylococcus aureus*, 11 (44.0%), were the most common organisms. This was followed with *streptococcus pneumonia* in 3 (12.0%) patients. Among the adequate group of patients, cephalosporin was the most frequently used, 63 (52.9%), carbapenem in 21 (17.6%) patients became the second option followed with Piperacillin/tazobactam in 17 (14.3%) patients and Amoxycillin / clavulanic acid 6 (5.0%).

Comparing both group of patients who received adequate and inadequate empirical antibiotics therapy, the outcome were not statistically significant in terms of the duration of ventilation and ICU stay, duration of hospitalization as well as patient mortality and survival. However there was 10% reduction of mortality in adequate treatment group.

Conclusion: More than 90 percent of patients with sepsis were given adequate empirical antibiotic treatment. The most common empirical antibiotic used was cephalosporin group (52.9%), whereas, macrolides was the most common second types of empirical antibiotics. However, there were no significant differences in term of outcome between adequate and inadequate group of therapy.

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Prof Dr Shamsul Kamalrujan Hassan: Supervisor

Dr Rhendra Hardy: Co-Supervisor

Dr Nik Azman Nik Adib: Co-Supervisor

CHAPTER 1

1.0 INTRODUCTION

Sepsis is the most common causes for ICU admission all over the world. During the previous 2 decades, the incidence of sepsis in the United States has tripled and is now the tenth leading cause of death. In spite of the use of antimicrobial agents and advanced life-support, the mortality rate for patients with sepsis has remained between 20% to 30% during the past 2 decades. The first Surviving Sepsis Campaign (SSC) was introduced to improve the care of patients with severe sepsis and septic shock. It was launched by the Society of Critical Care Medicine, the European Society of Intensive Care Medicine and the International Sepsis Forum in 2002. The guidelines were updated once in 2008 with 85 recommendations (Marik, 2011) . The latest update was in 2012.

Early antibiotic administration is one of the recommended therapies in the SSC guidelines. The aim of therapy is the administration of effective intravenous antimicrobials within the first hour of recognition of septic shock and severe sepsis without septic shock (Dellinger *et al.*, 2013). Important consideration when prescribing empirical antibiotics is the selection of an antibiotic that aims to be effective against any pathogen suspected of causing the infection(Swanson and Wells, 2013) . Empirical antibiotics are typically a broad-spectrum which can cover both gram- negative and gram- positive bacteria.

Empirical antibiotic can be inadequate or adequate based on the in vitro susceptibilities of the identified pathogens (Swanson and Wells, 2013). Inadequate antimicrobials and delayed administration of adequate antimicrobial therapy associated with increase in mortality rate in sepsis patient (Lueangarun and Leelarasamee, 2012).

1.1 RATIONALE OF STUDY

From this study, I hope that the results will give:

- Information regarding adequacy of empirical antibiotics given to patients who were admitted to ICU with sepsis and also can give information regarding our adherence to the local antibiotics guidelines by MSIC (Malaysian Society of Intensive Care).

- Knowledge regarding common organisms affected the sepsis patient and the common antibiotics given in sepsis patient.

- Increase awareness among the clinician the importance of adequate empirical antibiotic in sepsis patients.

CHAPTER 2

2.0 LITERATURE REVIEW

2.1 INFECTION

Infection is defined as the invasion of the body by pathogenic microorganisms that reproduce and multiply, causing disease by local cellular injury, secretion of a toxin, or antigen-antibody reaction in the host (Mosby, 2009)

The American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus committee approved a set of definitions to create a worldwide understanding including the bacteremia, SIRS, sepsis, severe sepsis and septic shock (Bone *et al.*, 1992).

2.2 BACTEREMIA

Bacteremia is the presence of viable bacteria in blood. The presence of viruses, fungi, parasites, and other pathogens in the blood should be described in a similar manner (ie viremia, fungemia, parasitemia, etc)

2.3 SIRS (Systemic inflammatory distress syndrome)

Systemic inflammatory response to various insults manifested by two or more of the following:

a) temperature > 38^{o}C or < 36^{o}C,

b) heart rate > 90 beats per minute,

c) tachypnea manifested by a respiratory rate > 20 breaths per minute or hyperventilation as indicated by PaCO2 < 32mmHg

d) white blood cell count > 12000mm^{-3} , < 4000mm^{-3} or > 10% immature (band) forms.

2.4 SEPSIS

The systemic response to infection, manifested by two or more of the following as a result of infection: temperature > 38^{o}C or < 36^{o}C, heart rate > 90 beats/min, respiratory rate > 20breaths per minute, and white blood cell count > 12000mm^{-3}, < 4000mm^{-3} or > 10% immature (band) forms

2.5 SEVERE SEPSIS

Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but not limited to lactic acidosis, oliguria, or an acute alteration in mental status.

2.6 SEPTIC SHOCK

Sepsis-induced with hypotension (systolic blood pressure, 90mmHg or a reduction of > 40mmHg from baseline in the absence of other causes for hypotension), despite adequate fluid resuscitation, along with the presence of perfusion abnormalities. These may include, but are not limited to, lactic acidosis oliguria or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

2.7 COMMUNITY- ACQUIRED INFECTION

Community acquired infection can be defined as an infection occurring in the community and manifest prior to hospital and ICU admission (Vincent *et al.*, 1995; Valles *et al.*, 2003) . In addition, all community acquired infections were required to be established within 48 hour of hospitalization (Kollef *et al.*, 1999). Commonly involve strains of *Haemophilus influenza* or *Streptococcus pneumonia* and are usually more antibiotic sensitive (Harris and Nagy, 2009).

Community-acquired pneumonia (CAP) is associated with significant mortality and morbidity, especially in the elderly. For patient admitted with CAP, about 10% will require ICU admission. The mortality for severe CAP can be up to 20-50%. The causative pathogen remains unidentified in up to 60% of cases (Rello *et al.*, 1993; Almirall *et al.*, 1995).

2.8 HOSPITAL-ACQUIRED INFECTION

Hospital- acquired infection of nosocomial infections refer to any systemic or localized conditions that result from the reaction by an infectious agent or toxin (Kouchak and Askarian, 2012). The infection occurring within 48 hours of hospital admission, 3 days of discharge or 30 days of an operation (Zaragoza *et al.*, 2003; Path, 2005).

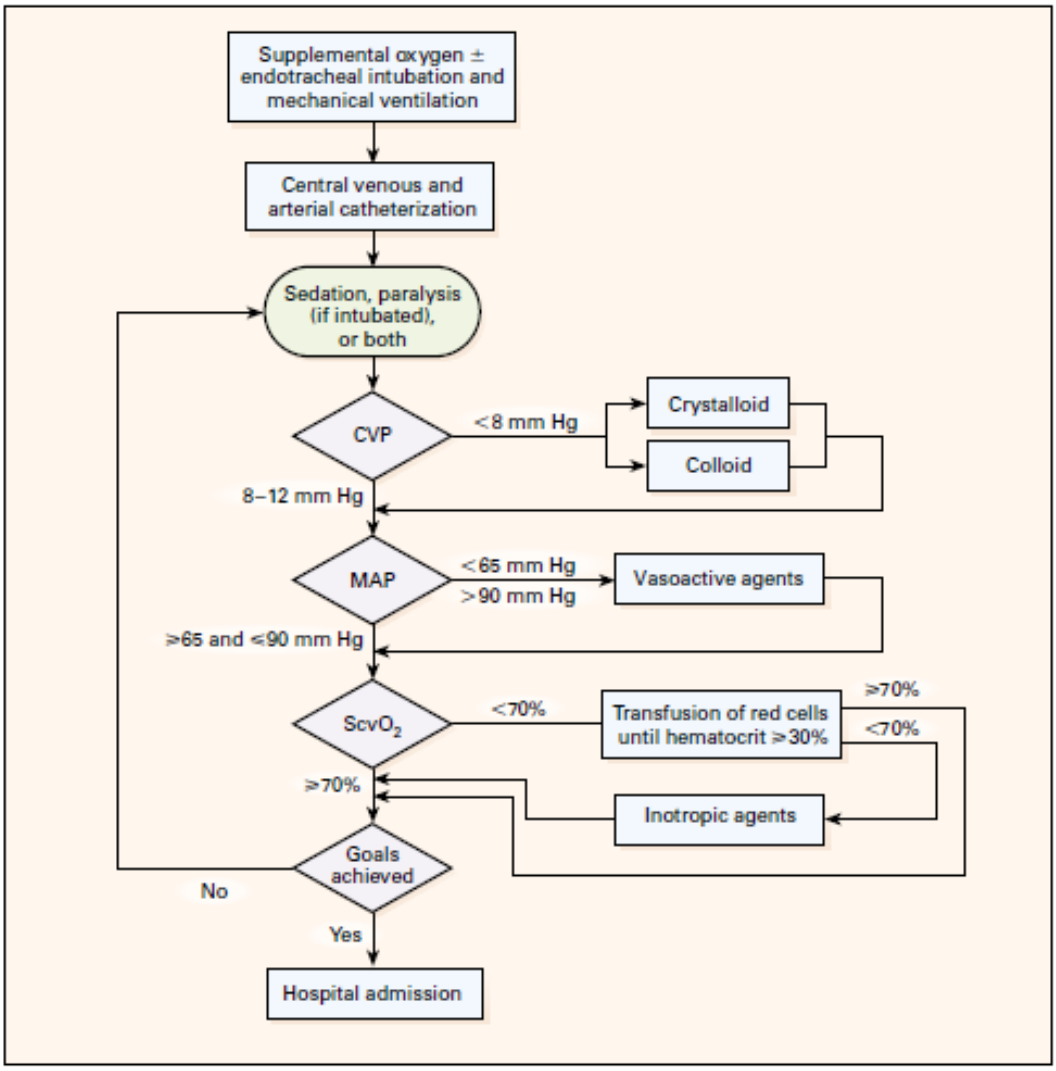
Health-care associated infection includes any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection, resided in a nursing home or long-term care facility, received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection, or attended a hospital or hemodialysis clinic (Society and America, 2005).

2.9 EARLY GOAL-DIRECTED THERAPY

Early goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach includes adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand.

Figure 2.1: Protocol for Early Goal-Directed Therapy from Rivers et al.

CVP denotes central venous pressure, MAP mean arterial pressure, and ScvO2 central venous oxygen saturation.



Two essential features of early goal-directed therapy include:

1) maintaining an adequate central venous pressure (CVP) to carry out other hemodynamic adjustments
2) maximizing mixed or central venous oxygen saturation (ScvO2)

The protocol was as follows. A 500-ml bolus of crystalloid was given every 30 minutes to achieve a central venous pressure of 8 to 12 mm Hg. If the mean arterial pressure was less than 65 mm Hg, vasopressors were given to maintain a mean arterial pressure of at least 65 mm Hg. If the mean arterial pressure was more than 90 mm Hg, vasodilators were given until it was 90 mm Hg or below. If the central venous oxygen saturation was less than 70 percent, red cells were transfused to achieve a hematocrit of at least 30 percent. When the central venous pressure, mean arterial pressure, and hematocrit were thus optimized, if the central venous oxygen saturation was less than 70 percent, dobutamine administration was started at a dose of 2.5 μg per kilogram of body weight per minute,a dose that was increased by 2.5 μg per kilogram per minute every 30 minutes until the central venous oxygen saturation was 70 percent or higher or until a maximal dose of 20 μg per kilogram per minute was given. Dobutamine was reduced in dose or stopped if the mean arterial pressure was less than 65 mm Hg or if the heart rate was more than 120 beats per minute. To reduce oxygen consumption, patients in whom hemodynamic optimization could not be achieved received mechanical ventilation and sedatives.

Following the bundle, once lactate is ≥4 mmol/L (36 mg/dL), or hypotension has been demonstrated to be refractive to an initial fluid challenge with 30 mL/kg of crystalloid, patients should then have their CVP maintained at ≥8 mm Hg. In adhering to this strategy, patients receive the initial minimum 30 mL/kg fluid challenge prior to placement of a central venous catheter and attempts to maximize CVP (Rivers *et al.*, 2001).

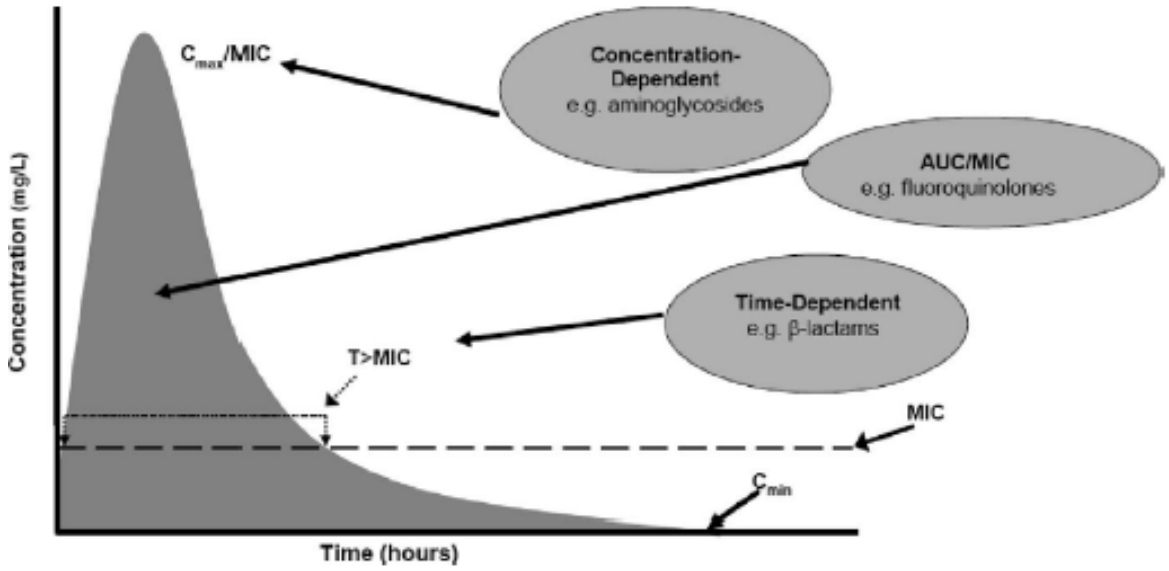
The end points used to confirm the achievement of such a balance include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit, and pH.8. Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy .In cases in which the pulmonary-artery catheter is not available, venous oxygen saturation can be measured in the central circulation (Tisherman *et al.*, 2004).

2.10 PHARMACOLOGY AND TYPES OF ANTIBIOTICS

Early administration of antimicrobial therapy is essential in sepsis patient especially before development of severe sepsis and septic shock (Brun-Buisson *et al.*, 1995). Antibiotics can be defined as pharmacological agents that selectively kill or inhibit the growth of bacterial cells, while having little or no effect on human. Bacteriostatic antibiotics prevent further replication of bacteria, and therefore rely on an intact immune system to clear the infection, whereas bactericidal antibiotics kill the bacteria. . Cidal activity can sometimes be achieved by a combination of antibiotics (Varley *et al.*, 2009). The pharmacokinetic and pharmacodynamics parameters will determine the ability of the

antibiotic to kill or inhibit the infective organism. Different antibiotic classes have different kill characteristics on bacteria as shown in figure 2 and table 1. There can be classified as concentration-dependent killing, time-dependent killing and both time-dependent with concentration- dependent killing.

Figure 2.2: Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration vs. time curve from Roberts and Lipman, 2009.



Key words: T MIC—The time for which a drug's plasma concentration remains above the minimum inhibitory concentration (MIC) for a dosing period; Cmax/MIC, the ratio of the maximum plasma antibiotic concentration (Cmax) to MIC; AUC/MIC, the ratio of the area under the concentration time curve during a 24-hour time period (AUC0 –24) to MIC.

The aminoglycosides and fluoroquinolones exhibit 'concentration-dependent killing' with peak concentration/MIC and AUC/MIC being the parameters that correlate with efficacy. For particular organism, these antibiotics also had prolonged antibiotic effects after the serum level decreases below the MIC. Larger doses result in greater efficacy and one-daily dosing for aminoglycosides maximizes the peak concentration/MIC. Different ratios have been found to be efficacious for different drug-bug combinations. For instance, for fluoroquinolones, the optimal AUC/MIC ratio for successful treatment of *Streptococcus pneumonia* is 25-35, whereas ratios 100 may be required for successful treatment of Gram-negative bacilli. Greater AUC/MIC ratios are also less likely to be associated with development of resistance.

B-Lactam, erythromycin, clindamycin, and linezolid demonstrate 'time-dependent killing' with time/MIC become the most important index for efficacy. Thus, for these agents, the proportion of time above MIC is the most important parameter. AUC/MIC correlates best with efficacy for azithromycin, tetracyclines, and glycopeptides (Varley *et al.*, 2009).

Table 2.1: Pharmacodynamic properties that correlate with efficacy of selected antibiotics from Roberts and Lipman, 2009.

Antibiotics	*B*-lactams Carbapenems Linezolid Erythromycin Clarithromycin Lincosamides	Aminoglycosides Metronidazole Fluoroquinolones Telithromycin Daptomycin Quinupristin/ dalfopristin	Fluoroquinolones Aminoglycosides Azithromycin Tetracyclines Glycopeptides Tigecycline Quinupristin/ dalfopristin Linezolid
PD kill characteristics	Time-dependent	Concentration-dependent	Concentration-dependent with time-dependence
Optimal PD Parameter	T >MIC	*C*max:MIC	$AUC_{0–24}$:MIC

MIC, minimum inhibitory concentration; AUC, area under curve; PD, pharmacodynamics; Cmax, maximum concentration.

2.11 PRINCIPLES OF EMPIRICAL ANTIMICROBIAL THERAPY

Empirical antibiotic should be guided by the most likely site of infection and likely organisms. All appropriate microbiological specimens including blood cultures should be taken before starting the antibiotics whenever possible. Besides associated with poor outcomes, inappropriate antimicrobial therapy can lead to the emergence of resistant organisms, antimicrobial-related adverse events as well as increase in healthcare costs.

When initiating appropriate empirical antibiotics in patients with severe sepsis, few factors must be consider including the likely causative organisms, patient factors and properties of antibiotics.

1) Likely causative organism

- Decide either community or health-acquired infection
- Identify the most likely source of infection
- Consider local epidemiological data: types of antibiotic depend on the local susceptibility pattern. Knowing the resistance profiles in the community, hospital or unit helps in choosing antimicrobials appropriately

2) Patient factors

- Severity of illness i.e. patient with severe sepsis or septic shock require broad spectrum antibiotics

- Prior antibiotic use or prolonged hospitalization. Both factors associated with presence of resistant organisms.
- Immunosuppressive states (malignancy, malnutrition, on steroid or immunosuppressive drugs) may require broad-spectrum therapy including antifungal.
- Presence of renal or hepatic dysfunction. The risk-benefit of the antimicrobial must be determined on a case-to-case basis. Maintenance doses are adjusted according to the severity of organ dysfunction.
- Others : pregnancy or any drug allergy

3) Antimicrobial profile

- Route of administration.

  The intravenous route should always be used in severe sepsis as oral absorption is unpredictable even in drugs with good oral bioavailability.

- Dose and interval.

  Pathophysiological changes in critically ill patients alter the pharmacokinetic (PK) and pharmacodynamic (PD) profile of the antimicrobials. Antibiotics can be categorized into three different classes depending on the PK/PD indices associated with their optimal killing activity.

- Achievable antimicrobial concentrations in tissue.

  Aminoglycosides and glycopeptides have poor tissue penetration. Thus, aminoglycosides should not be used as monotherapy while a higher plasma level of

glycopeptides is recommended to ensure adequate tissue penetration. Both ß-lactams and quinolones have good tissue penetration.

- Post antibiotic effect (PAE)

  This is defined as persistent suppression of bacterial growth even after the serum antibiotic concentration falls below the MIC of the target organism. For examples, aminoglycosides and fluoroquinolones have post antibiotic effect against gram negative bacteria.

- Adverse events

  Risk-benefit of antimicrobials with potential serious adverse events should be considered which depend on cases. If unavoidable, serum levels should be monitored for toxicity (e.g. aminoglycosides).

- Ecological profile

  Limit the use of antimicrobials with known potential for selecting resistant organisms and associated risks of superinfection e.g. third generation cephalosporins (selection pressure for ESBL producing Enterobacteriaceae).

Empirical antibiotic therapy should be re-evaluated after 48-72 hours or when culture results become available. Once a causative pathogen is identified, the spectrum of antimicrobial therapy should be narrowed (de-escalation). If the patient is improving, the recommended duration of antibiotic therapy is 5 to 7 days. There is increased risk of resistance with prolonged use of antibiotics. Certain conditions may require prolonged therapy e.g infective endocarditis. Consider change to the oral route whenever possible.

If there is no clinical response within 48-72 hours, need to rule out:

- The possibility of a secondary infection
- The presence of resistant organisms
- Abscess that are not drained or infected foreign bodies that are not removed
- Inadequate penetration of antimicrobial to the site of infection
- Inadequate spectrum of antibiotic coverage
- Inadequate dosage or interval
- Non-infectious causes e.g. deep vein thrombosis, acute myocardial or pulmonary infarctions, acute pancreatitis, hyperthyroidism, Addisonian crisis, malignancies and central nervous system haemorrhages (Chan *et al.*, 2012).

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2.12 SURVIVING SEPSIS CAMPAIGN (SSC)

International guidelines for management of severe sepsis and septic shock. The initial SSC guidelines were published in 2004. The most current iteration is based on updated literature search incorporated into the evolving manuscript through fall 2012 (Dellinger *et al.*, 2013). It recommends a six hour resuscitation bundle and a 24 hour management bundle to improve outcomes in severe sepsis.

2.13 HSNZ and ICU

Hospital Sultanah Nur Zahirah (HSNZ), Kuala Terengganu formerly known as Kuala Terengganu Hospital. This hospital is located nearby famous Batu Burok Beach, which covered land area of 21.09 hectares. Until year 2014, HSNZ has 821 beds, 28 wards, 9 specialist clinics, 16 operation theatres, 13 delivery theatres and 1 delivery operational theatre as well as 19 clinical specialists. HSNZ has 2,400 staffs.

It is the biggest hospital in Terengganu and become the main referral centre of the state. Their intensive care unit (ICU) has 20 beds and able to accommodate up to 18 ventilated patients. This study was done in ICU HSNZ.

Since 2011, this hospital was using HIS (Health Information System) where all patients' information was available in the computer system. This system was designed to improve access to patient information through a central electronic information system.

HIS's goal is to streamline patient information flow and its accessibility for doctors and other health care providers. These changes in service will improve patient care quality and patient safety over time.

The system provides all record patient information, patient laboratory test results, and patient's doctor information. Doctors can access easily person information, test results, and previous prescriptions. Every staff was provided with their identification code to assess the system. For Intensive Care Unit and operation theatre, on top of HIS system, they are providing with CCIS (Critical Care Information System) which provides the data for continuous patient monitoring.

CHAPTER 3

3.0 METHODOLOGY

3.1 OBJECTIVES

3.1.1 GENERAL OBJECTIVES

The aim of this study was to evaluate the usage of empirical antibiotic for sepsis patients in Intensive Care Unit (ICU), Hospital Sultanah Nur Zahirah (HSNZ).

3.1.2 SPECIFIC OBJECTIVES

- To determine the adequacy of empirical antibiotic administration for sepsis patients in ICU, HSNZ, from 1st January-31st December 2013.
- To determine the frequency of commonly prescribed empirical antibiotic for sepsis patient in ICU.
- To evaluate the impact of adequate empirical antibiotic therapy on the outcome of patients.

3.2 STUDY DESIGN

This study was a non-interventional, cross-sectional study, based on retrospective analysis of data collection. The data were obtained from the CCIS (critical care information system) including patient's medical notes, drug chart, and laboratory results. This study was conducted after obtaining the ethical approval from the Medical Research and Ethics Committee, Ministry Of Health, Malaysia.

3.3 CHARACTERISTICS OF SUBJECTS

3.3.1 INCLUSION CRITERIA

- Adult patients with the age of 18 year old and above
- All patients who fulfilled the criteria of sepsis on admission to ICU
- All patients who received antibiotics within the first 6 hours of ICU admission

3.3.2 EXCLUSION CRITERIA

- Patients with underlying immunodeficiency i.e. malignancy, neutropenia, HIV positive etc.
- Patient with second episode of sepsis

3.4 DETERMINATION OF SAMPLE SIZE

The sample size for this study is determined using a single proportion formula (Lwanga and Lemeshow, 1991). This formula used to estimate the adequacy of empirical antibiotics used for sepsis patient in ICU HSNZ with 95% confidence interval.

$n = (z/\wedge)^2 * P(1-P)$

p = anticipated patients proportion is 91% (MacArthur *et al.*, 2004)

z= value is1.96, for the level of confidence of 95%

d=absolute precision required on the either side of the proportion, taken at 5% to an adequate sample size

Using the formula,

$n = (1.96/0.05)^2 \times 0.91 (1-0.91) = 126$ samples

10% drop out = 14 samples

The calculated sample size required was 140.

3.5 SAMPLING METHOD

This study involved all patients who were admitted to Intensive Care Unit, HSNZ from 1st January 2013 until 31st December 2013 which met the inclusion and exclusion criteria. Lists of patients admitted to ICU with sepsis were collected from ICU admission book. Then, registration numbers of the eligible patient were collected and patient's medical record were traced from the HIS (Hospital Information System) and reviewed retrospectively. Patients' data were collected from medical records, medication charts as well as investigation results. There were 190 patients who fulfilled the inclusion criteria. All patients were listed following the sequence of admission from January until December. 140 consecutive patients were selected for the sampling but 10 of the record were missing, incomplete or cannot be traced. Therefore, only 130 patients were analyzed.

3.6 DATA COLLECTION

We collected all the data as below:

- Patient demographic data
- Underlying medical illness
- Diagnosis upon ICU admission
- Primary site of infection
- Presence of septic shock
- Empirical antibiotic in ICU, dosage and duration

- Culture and sensitivity results
- Antibiotic outcome (de-escalate, change or continue)
- Duration of ICU admission
- Duration of hospitalization
- Patient outcome i.e. alive or death
- Empirical antibiotic was considered adequate when the isolated organism was sensitive or intermediate in sensitivity to at least one of the antibiotic which was given within 24 hours of ICU admission. For patients with polymicrobial infection, all the pathogens must sensitive to the antibiotics. Patient without any organism isolated also considered as adequate. The antibiotic was adequate in terms of spectrum, dose, application modus and duration of therapy based on guidelines from the Malaysian Society of Intensive Care.
- Inadequate antibiotic was considered when the spectrum, dosage, application modus of antibiotics, or the duration of therapy, and/or when the isolated pathogenic bacteria were resistant to the antibiotic.

3.7 DEFINITIONS

- Empirical antibiotic defined as the initial antibiotic regimen started within 24 hours of admission before the culture results are available (Mettler *et al.*, 2007).

- Infection-directed treatment was defined as the administration of antimicrobials for a specific clinically localized source of (e.g., pneumonia, urinary tract, wound, and bloodstream). Clinically localized sources of infection, excluding bloodstream