AN EVALUATION OF EMPIRIC ANTIMICROBIAL THERAPY IN PATIENTS WITH SEPSIS ADMITTED TO INTENSIVE CARE UNITS IN MADINAH, SAUDI ARABIA

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وبعد،

قال سبحانه وتعالى
بسم الله الرحمن الرحيم
{وَ قُلْ رَبِّ زِدْنِي عِلْماً} [طـه : 114]
and say, "My Lord, increase me in knowledge."

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LIST OF ABBREVIATIONS

AKI	Acute kidney injury
AMR	Antimicrobial Resistance
AMS	Antimicrobial stewardship
ANN	Artificial Neural network
APACHE II	Acute Physiology and Chronic Health Evaluation II
ATP	Adenosine triphosphate
CAD	Coronary artery disease
CBC	Complete blood count
CKD	Chronic Kidney Disease
CNS	Central nervous system
DAMP	Damage-associated molecular patterns
DIC	disseminated intravascular coagulation
DM	Diabetes mellitus
GCS	Glasgow coma scale
GI	Gastrointestinal
ICU	Intensive care unit
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IRB	Institutional review board
MAP	Mean arterial pressure
MDRO	Multi-drug resistant organism
MEDS	Mortality in Emergency Department Sepsis
MODS	Multiple Organ Dysfunction Score
NOD	nucleotide-binding oligomerization domain

PAI	plasminogen activator inhibitor type 1
PAMP	Pathogen-associated molecular patterns
PIRO	Predisposition, Infection, Response, Organ Dysfunction
REMS	Rapid Emergency Medicine Score
RIG	Retinoic acid inducible gene 1
RPHICU	Royal Perth Hospital Intensive Care Unit
SAE	Sepsis associated encephalopathy
SCCG	Surviving sepsis campaign guidelines
SOFA	Sequential Organ Failure Assessment
TLR	toll-like receptors
TNF	Tumor necrosis factor

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PENILAIAN TERAPI ANTIMIKROB EMPIRIK PADA PESAKIT SEPSIS DIMASUKKAN KE UNIT PENJAGAAN INTENSIF DI MADINAH, ARAB SAUDI

ABSTRAK

Sepsis merupakan salah satu kecemasan perubatan yang sering digambarkan sebagai respons imunologi sistemik terhadap penyerangan bahagian badan steril oleh patogen jangkitan yang kemudiannya menyebabkan kegagalan organ dan kematian. Dalam pengurusan sepsis, selain daripada resusitasi cecair, terapi antimikrob empirik yang mencukupi adalah salah satu pilar penting dalam pengurusan sepsis. Oleh itu, penting untuk menilai kecukupan terapi antimikrob empirik dalam pesakit sepsis yang dirawat di unit rawatan rapi (ICU) dan mengenal pasti faktor-faktor yang menentukan ketidakcukupan terapi tersebut. Objektif utama kajian ini adalah untuk menilai kecukupan terapi antimikrob empirik dalam pesakit yang dirawat di ICU akibat sepsis atau renjatan septik, faktor-faktor yang menentukan ketidakcukupan terapi tersebut, dan kesan terhadap hasil klinikal. Data pesakit yang dirawat di unit ICU akibat sepsis atau renjatan septik, di dua fasiliti tertier penjagaan kesihatan di Al-Madinah Al-Munawwarah telah dikaji secara retrospektif. Kajian ini menggunakan analisis regresi tradisional dan analisis rangkaian neural buatan untuk mengenal pasti faktor-faktor yang menentukan ketidakcukupan terapi antimikrob empirik, faktor-faktor yang meramalkan kematian di ICU, faktor-faktor yang meramalkan masa kediaman di ICU, dan faktor-faktor yang menentukan keparahan penyakit. Hasil kajian ini menunjukkan bahawa lima puluh tiga peratus pesakit menerima terapi antimikrob empirik yang tidak mencukupi, dan kadar kematian pesakit yang dirawat di ICU akibat sepsis atau renjatan septik adalah 49%. Purata masa kediaman di ICU adalah 6 (3-11) hari. Faktor-

faktor yang menentukan ketidakcukupan terapi antimikrob empirik adalah skor APACHE II, jangkitan organisma rintang ubat berbilang (MDRO), sejarah pembedahan, dan komorbiditi. Berkaitan dengan kesan ketidakcukupan terapi antimikrob empirik terhadap hasil klinikal, didapati bahawa ketidakcukupan tersebut menjadi penentu tidak bersandar untuk kematian di ICU. Masa kediaman di ICU bagi pesakit yang menerima terapi antimikrob empirik yang tidak mencukupi adalah lebih tinggi berbanding pesakit yang menerima terapi yang mencukupi. Berkaitan dengan prestasi model rangkaian neural buatan (ANN), hasil kajian ini menunjukkan bahawa model ANN berprestasi lebih baik daripada model regresi dalam meramalkan kecukupan terapi antimikrob empirik, kematian di ICU, tempoh penginapan di ICU.

AN EVALUATION OF EMPIRIC ANTIMICROBIAL THERAPY IN PATIENTS WITH SEPSIS ADMITTED TO INTENSIVE CARE UNITS IN MADINAH, SAUDI ARABIA

ABSTRACT

Sepsis is one of the medical emergencies that is often described as a systemic immunological response to the invasion of sterile body parts by an infectious pathogen which subsequently results in organ dysfunction and death. In the management of sepsis, in addition to fluid resuscitation, providing adequate empiric antimicrobial therapy (EAMT) is considered an important pillar of sepsis management. Therefore, it is important to evaluate the EAMT's adequacy in patients with sepsis admitted to the ICU and the determinants of inadequate EAMT. The main objective of this study was to evaluate the adequacy of EAMT in patients admitted to the ICU with sepsis or septic shock, determinants of inadequate EAMT, the predictors of clinical outcomes, and the discriminatory performance of APACHE II score in predicting ICU mortality. Data of patients admitted to the ICU units due to sepsis or septic shock in two healthcare facilities in Al-Madinah Al-Munawwarah were retrospectively reviewed. The current study used traditional regression analysis and artificial neural network analysis (ANN) to identify determinants of inadequate EAMT, predictors of ICU survival, predictors of ICU length of stay, and determinants of severity of illness. This study reported that fifty three percent of patients received inadequate EAMT, and the ICU mortality rate in patients with sepsis admitted to the ICU was 49%. The median (interquartile range) of length of stay in the ICU was: 6 (3-11) days. Determinants for inadequate EAMT were APACHE II score (OR= 1.087, 95% CI= 1.010-1.170, p value 0.026), multiple drug resistant organism (MDRO) infection (OR= 7.318, 95% CI= 2.839-18.864, p

value <0.001), surgical history (lower limb amputation) (OR= 0.109, 95% CI= 0.025-0.478, p value 0.003), and comorbidity (coronary artery disease) (OR= 3.128, 95% CI= 1.016-9.629, p value 0.047). ANN model revealed that APACHE II score and MDRO infections were the most important determinants of inadequate EAMT. Inadequate EAMT was found to be an independent predictor of reduced ICU survival (HR = 2.714 CI 1.292-5.703 p value 0.008). ICU length of stay in patients received inadequate EAMT were shown to be longer when compared with patients received adequate as inadequate EAMT was found to be an independent predictor of prolonged ICU length of stay (β = 1.489 95% CI 0.284-2.712 p value 0.016). APACHE II score was found to have a good discriminatory performance in the prediction of mortality within the ICU with a ROC-AUC of 0.80. With regards to the performance artificial neural network (ANN) model, the results of current study revealed that ANN model performed as well as or better than the regression models in predicting EAMT adequacy with an overall classification accuracy of 81.6% and ROC-AUC 0.895. Also, DeepSurv model had a better predictive performance (C-Index = 0.83) compared with cox-regression model (C-index = 0.73). ANN also performed as well as or better than regression models in the prediction of ICU length of stay and severity of illness. In conclusion, despite the thorough understanding of sepsis, it still considered one of the leading causes of death in the intensive care units. Our study provided important inputs related to the clinical outcomes of sepsis patients admitted to the intensive care units in Al-Madinah Al-Munawwrah. Also, our study resembles a situational analysis which fills the gap in the literature about the adequacy of EAMT and clinical outcomes of patients with sepsis admitted to the ICU in Saudi Arabia. ANN analysis performed as well as or better than the traditional regression models. This indicates the importance

of the employment deep learning techniques in the accurate prediction of the clinical outcomes of critically ill patients.

CHAPTER 1

INTRODUCTION

1.1 General introduction

Sepsis is defined as an acute medical condition that is associated with end-stage organs dysfunction and death as a result of the systemic immune reaction caused by an underlying infection (Gyawali et al., 2019). It is one of the leading contributors of morbidity and mortality in intensive care units (ICUs) and considered as the most leading cause of death in non-coronary intensive care unit with a mortality rates of approximately 20% – 25% (Bullock and Benham, 2019, Sakr et al., 2018a).

1.2 Sepsis definitions

Sepsis definition has evolved over the past decades (Gyawali et al., 2019). Going form Sepsis-1 definitions which focused mainly on the systemic inflammatory response syndrome (SIRS) host's response to an infection in which included the following terms: sepsis, severe sepsis, and septic shock (Bone et al., 1992). In 2001 a task force addressed the limitation of Sepsis-1 definitions however it did not provided alternatives due to the lack of supporting evidence (Levy et al., 2003). In 2016, the third international consensus developed new definition of sepsis in order to overcome the limitations of Sepsis-1 and Sepsis-2 definitions and to provide better consistency for the results of epidemiologic studies and clinical research, and ease the early recognition and subsequently providing a more appropriate and timely therapy to patients with sepsis (Gyawali et al., 2019, Singer et al., 2016). The latest definition of sepsis have been established and defined based on the international consensus (sepsis-

3) in 2016 included sepsis and septic shock (Singer et al., 2016). Table 1.1 below describe each of these terms.

Table 1.1 Terms, key concepts, and definitions according to sepsis – 3 (Singer et al., 2016)

Term	Definition/criteria
Sepsis	• Defined as life-threatening organ dysfunction caused by a dysregulated host response to infection • Organ dysfunction is identified as an acute change in total SOFA score ≥2 points consequent to the infection: o The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction. o Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside by using quick qSOFA, i.e., alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22/min.
Septic Shock	• Defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

1.3 Epidemiology

There is a significant variation in the reported prevalence of sepsis in the ICU in the literature. A study in India reported that severe sepsis represented 6% of the total ICU admissions (Chatterjee et al., 2017) In addition, higher rates were identified in Italy, France, and Germany 11.4%, 14.6%, and 17.9% respectively (de, 2016, Sakr et al., 2013, fr, 2004). A much higher occurrence rates were reported in United Kingdom, and China 27.1% and 42.5% respectively (Wang et al., 2020a, Padkin et al., 2003). Moreover, an international study which included more than 10000 patients reported that approximately 30% of ICU patients had sepsis (Sakr et al., 2018b). Also, it has been established that the rates of sepsis in the ICU setting varied from 13.6% to 39.3%, this variation can be a result of the inconsistency of sepsis definition used by different studies (Sakr et al., 2018b). This was identified as a shortcoming of the Sepsis-1 and Sepsis-2 definitions as the reported epidemiological results varied. Therefore, Sepsis-

3 definitions were developed to rectify this issue (Singer et al., 2016, Levy et al., 2003, Bone et al., 1992). This allowed the researchers to assess and evaluate the incidence of sepsis, and sepsis related mortality which will be discussed in the following sections.

1.3.1 Trends of sepsis epidemiology and the impact of sepsis definitions

Sepsis epidemiology has been shown to be variable in the literature. Although it was reported that the incidence of sepsis is increasing in trends; however, the mortality rates are reducing. For example, in a 10-years study; sepsis's incidence increased from 4319 cases in 2005 to 25820 in 2015 while the sepsis associated mortality reduced over the years (Canora et al., 2020). Factors that may contributes to this increase in sepsis's incidence include the implementation of disease coding systems, the increase in aging population, frequent utilization of immunosuppression, invasive procedures, and the spread of multi-drug resistant infections (Canora et al., 2020, Rhee and Klompas, 2020, Rhee et al., 2015).

With regards to the mortality rates in patients with sepsis, it is also seems to be highly variable in the literature. For instance, ICU mortality were reported be 27.2% in china (Wang et al., 2020a), 34.4% in Germany (de, 2016), 38.9% in Netherlands (Driessen et al., 2018), and 41.3% in Italy (Sakr et al., 2013). While in the United States approximately 1.7 million adults are affected by sepsis each year, these cases contributes potentially to more than 250000 deaths (Rhee et al., 2019). Also, sepsis associated mortality in Europe and North America is estimated to be around 38% (Vincent et al., 2019). In addition, a meta-analysis showed that 41.9% of patients with sepsis died prior to the hospital discharge (Fleischmann-Struzek et al., 2020).

Evidently, the inconsistent application of sepsis definitions can potentially result in variability of the reported sepsis epidemiology in the literature (Gyawali et al., 2019). This was reported by a study that compared the outcomes of patient with sepsis defined according to Sepsis-1 and Sepsis-3 definitions which showed that the ICU mortality rates were higher in patients diagnosed with sepsis according to Sepsis-3 (de, 2016). Similarly, it was reported that ICU mortality were also higher in patients diagnosed with sepsis according to Sepsis-3 (38.9%) compared with Sepsis-2 (34%) (Driessen et al., 2018). Also, according to a study in the United Kingdom, ICU mortality in patients with Sepsis-3-septic shock was significantly higher (46.7%) compared with Sepsis-2-septic shock (25.6%) (Shankar-Hari et al., 2017).

This indicates that the application of the Sepsis-3 definition in patients with septic shock resulted in the precise selection of smaller but more critically ill subpopulation which fulfils the aim of Sepsis-3 consensus definition to describe septic shock as a more severe illness with an increased likelihood of death compared with sepsis (Driessen et al., 2018). Similar results were also reported by a nationwide study conducted in japan which reported the sepsis-3 septic shock definitions included a more critically ill patients compared with sepsis-2 septic shock definition (Takauji et al., 2020). This also explains why sepsis-3 had better predictive validity for septic shock (Shankar-Hari et al., 2017). Table 1.2 describe the variation of sepsis epidemiology according to the country, measured outcome and definition.

Table 1.2 Sepsis epidemiology according to the definitions

Country	Prevalence of sepsis in the ICU	Mortality	Definition
France (fr, 2004)	14.6%	35% (30-days)	Sepsis-1
Italy (Sakr et al., 2013)	11.4%	41.3% (ICU mortality)	Sepsis-1
Germany (de, 2016)	17.9%	34.4% (overall ICU mortality) 37.3% (Sepsis-1 septic shock) 44.3% (Sepsis-3 septic shock)	Sepsis-1 and Sepsis-3
United kingdom (Padkin et al., 2003)	20.0%	44.7% (Hospital mortality)	Sepsis-1
China (Wang et al., 2020a)	42.5%	27.2% (ICU mortality)	Sepsis-3
International (Sakr et al., 2018b)	29.5%	25.8% (ICU mortality)	Sepsis-3
Croatia (Vucelić et al., 2020)	13.1%	37.9% (ICU mortality)	Sepsis-3
Netherland (Driessen et al., 2018)	NR	34.0% (Sepsis-2) 38.9% (Sepsis-3)	Sepsis-2 and Sepsis-3

NR: not reported

1.3.2 Sepsis in Saudi Arabia

When it comes to sepsis in Saudi Arabia, there are few studies conducted which reported that the prevalence of sepsis among specific population e.g., neonates and pilgrims. In 2004, sepsis occurred in 25.4% of ICU admission during Hajj season 2004 at Makkah hospitals (Baharoon et al., 2009). While in 2012, sepsis occurred in 16% of ICU admission at Buraidah central hospital, Qassim, Saudi Arabia (Gasim et al., 2016). According to the progress report of the national sepsis plan in Saudi Arabia it is estimated the prevalence of sepsis in Saudi Arabia to be 128000 episodes per year (Aljuaid, 2018). Thus, it is important to detect the prevalence, clinical characteristics, outcomes, and determinants of clinical outcomes in patients with sepsis admitted to the ICU at Medina, Saudi Arabia.

1.4 Sepsis pathophysiology

Sepsis involves many mechanism which can affect the body at different levels including: molecular, cellular, and organ levels (Gotts and Matthay, 2016). These mechanisms can be related to the host responses and the nature of the causative pathogen through which it mediates the sepsis's complications (Aird, 2003). Multi organs dysfunction occurs due to several mechanisms including: endothelial dysfunction, coagulopathy, cellular dysfunction, and cardiovascular dysfunction (Evans, 2018).

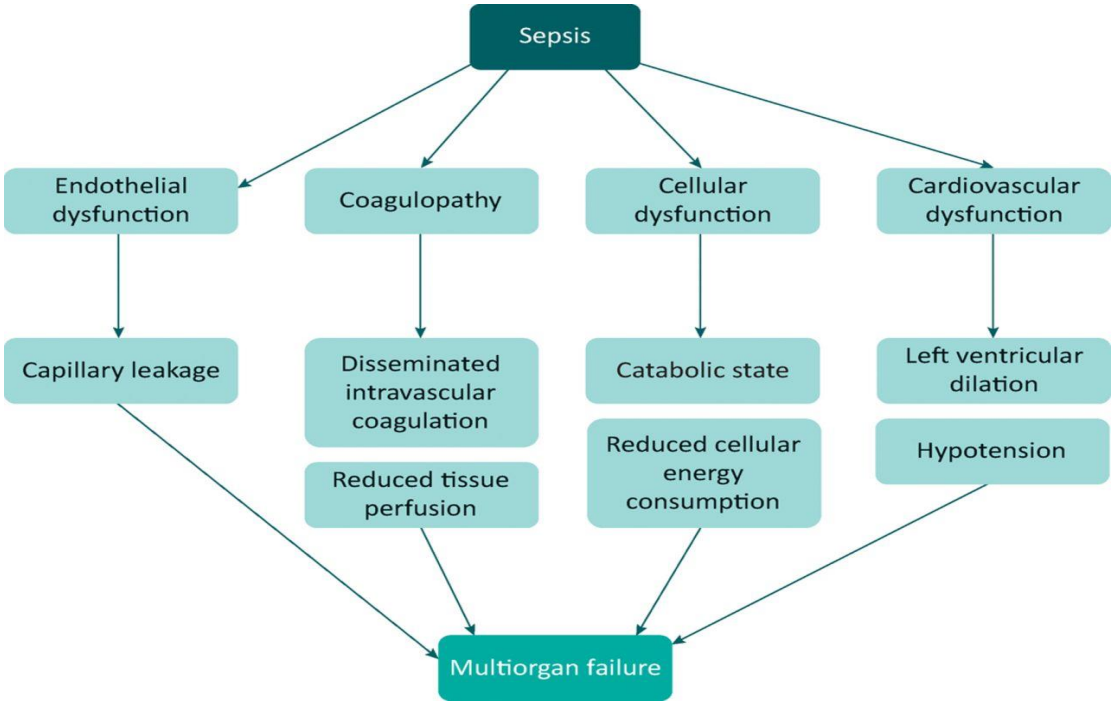

Figure 1.1 Key pathophysiological changes of sepsis that can contributes to multi-organ failure adapted from (Evans, 2018).

1.4.1 Role of inflammatory mediators

When it comes to the initiation of immune response to an invading pathogen, the innate-immune system is considered the first line of defence; When activated, many type of immune cells and components will be involved such as: macrophages, natural killer cells, monocytes, and neutrophils (Carrillo et al., 2017).

The immune system's activation occurs as a result of the interactions between immune system components' specific recognition pattern and the pathogen associated molecular patterns (PAMPs) which includes: fungal β-D-glucose polymers (β-glucans), or bacterial endotoxins (Carrillo et al., 2017). Also, these interaction can occur with the damage associated molecular patterns (DAMPs) that can be molecules or intracellular components released from damaged or dead body cells (e.g. mitochondrial DNA and ATP); subsequently it will bind to specific receptors on macrophages and monocytes including: the toll-like receptors (TLRs), retinoic acid inducible gene-1 receptors (RIG-1), C-type leptin receptors, and nucleotide binding oligomerization domain (NOD)-like receptors (Gyawali et al., 2019, Carrillo et al., 2017).

Subsequently, intracellular signal transduction pathways will be activated and leads to the transcription, production and release of pro-inflammatory cytokines like interlukin-1 (IL-1), interlukin-6 (IL-6), and tumour necrosis factor-α (TNFα) (Zhang and Wang, 2014). These pro-inflammatory cytokines will lead to the activation and growth of leukocytes, endothelial adhesion molecules upregulation, expression of chemokines, production of tissue factor, and activation of the complement system (Almawash, 2018, Zhang and Wang, 2014). Under certain circumstances e.g. sepsis,

dysregulated and exaggerated activation of the abovementioned mechanisms will lead to the damage, dysfunction and death of body's cells and tissues (Almawash, 2018).

1.4.2 Loss of hemostasis

In sepsis, the coagulation system's activation is common and can lead to a wide spectrum of coagulative disorders ranging from mild thrombocytopenia to prompt disseminated intravascular coagulation (DIC) (Carrillo et al., 2017). This can be a result of the interaction of coagulation and inflammation which is also known as immune-thrombosis (Engelmann and Massberg, 2013). Immuno-thrombosis in sepsis can be mediated via different mechanisms such as: the activation of coagulation system through the pro-inflammatory cytokines and chemokines, expression of tissue factor on the endothelial cells and monocytes which leads to the initiation of coagulation and thrombin generation (Iba et al., 2020). In addition, pro-inflammatory cytokines can impair the functions of anticoagulant pathways due to the decreased levels of endogenous anticoagulant substances such as: protein S, protein C, and thrombomodulin (Levi and van der Poll, 2017).

Moreover, the high levels of Interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNFα) and in sepsis patients can results in impaired fibrinolytic system function; this can be a result of increased levels of plasminogen activator inhibitor type-1 (PAI-1) which is considered an important regulator of plasmin (Iba et al., 2019a). This increased fibrin formation and impaired fibrinolysis will lead to the formation of micro-vascular clots, which contributes to tissue ischemia and consequently organ dysfunction (Iba et al., 2019a).

1.4.3 Cellular, tissue, and organ dysfunction

Complication of sepsis (i.e. tissue and organ dysfunction) occurs mainly due to the lack of adequate tissue perfusion with oxygenated blood (Gyawali et al., 2019). Sepsis involves many mechanisms which can affect the body at different levels including: molecular, cellular, and organ levels (Gotts and Matthay, 2016).

The endothelium contribute to an axial role in the vasomotor tone regulation, coagulation, and the balance of inflammatory status (balancing between anti-inflammatory and inflammatory mechanisms) (Aird, 2003). Moreover, endothelial cells are act as a defensive mechanism as it activated against invading microorganism by initiating the coagulation cascade and inflammatory response to fight the invading pathogen (Aird, 2003, Henneke and Golenbock, 2002). In sepsis, the state of excessive and sustained inflammatory response combined with an inadequate anti-inflammatory response (i.e. endothelial cell dysfunction) which can potentially results in tissue damage or death (Aird, 2003). Furthermore, endothelial injury can be associated with micro-thrombi formation and endothelial leaking, both can affect the blood perfusion and expose tubular epithelial cells TEC to inflammatory mediator for longer time (Peerapornratana et al., 2019a). In sepsis, there is a dilation that can involve the three microvasculature's compartments (capillaries, arterioles, and venules), this can be enhanced by the underlying intravascular fluids leakage into the interstitial spaces due to the endothelium integrity (Krishnan and Bansal, 2019).

In addition, sepsis is associated with altered blood flow as it can causes alterations of both the macrocirculation and microcirculation which is characterized by a reduced peripheral vascular resistance, altered distribution of blood flow to the tissue, and microcirculatory perfusion derangement (Zarbock et al., 2014).

Microcirculatory alterations plays an major role in organ injury (Peerapornratana et al., 2019a). These microcirculatory abnormalities can occur through several mechanisms such as: endothelial injury (Verma and Molitoris, 2015, Sprague and Khalil, 2009), autonomic nervous system response (van Doorn et al., 2008), upregulation of inducible nitric oxide synthase enzyme (iNOS) i.e. localized nitric oxide deficiency (Trzeciak et al., 2008), and coagulation cascade activation (De Backer et al., 2011, De Backer et al., 2009).

Sepsis induced hypotension can also contribute to the organ damage or failure as it can decrease the adequate perfusion of oxygenated blood to vital tissues and organs (e.g. lungs, kidney, CNS, and others). All of the abovementioned mechanisms and factors potentially contributes to tissue organ injury and dysfunction (Lelubre and Vincent, 2018).

1.5 Clinical complications of sepsis

Sepsis is a systemic disorder i.e. it can affect various body organs, as a result of the immune response and the inflammatory response mediated by inflammatory cytokines and other inflammatory mediators that are released into the systemic circulation (Hotchkiss et al., 2016). Therefore, the complications of sepsis varies according the affected organ or system (Hotchkiss et al., 2016).

1.5.1 Cardiopulmonary complications

Contractile dysfunction is considered one of the main characteristics of sepsis-induced cardiac dysfunctions (Habimana et al., 2020). The clinical presentation of myocardial dysfunction has a wide spectrum that includes one or all of the following: right ventricular impairment, left ventricular diastolic dysfunction, dilatation of both

ventricles, or left ventricular (LV) systolic dysfunction (Habimana et al., 2020, Pulido et al., 2012). Moreover, Pulmonary microvasculature is critically damaged during sepsis, resulting in acute respiratory distress syndrome (ARDS) (Goligorsky and Sun, 2020).

1.5.2 Renal complications

Sepsis induced AKI was believed to be due to the state of decreased blood perfusion to the kidney and tubular necrosis (Gotts and Matthay, 2016). However, evidence showed that the kidney injury is less likely to be the sole cause of sepsis-induced AKI (Takasu et al., 2013, Ishikawa et al., 2010). Instead, experimental studies showed the role of cytokines and immune mediated injury in causing tubular cellular dysfunctions including dysregulated tubular integrity and induction of tight junction disruption (Takasu et al., 2013, Ishikawa et al., 2010).

This suggests that sepsis induced AKI is believed to have a multifactorial etiologies and involves the three dimensions of sepsis induced organ injury: inflammatory response, adaptive alterations of epithelial tubular cell due to oxidative stress, and altered renal blood flow (Gómez and Kellum, 2019, Zhang, 2015, Pelte and Chawla, 2009). Prior studies have indicated that sepsis is one of the most common causes of AKI which might lead to increased risk of mortality (Peerapornratana et al., 2019b, Alobaidi et al., 2015, Chen et al., 2009, Bagshaw et al., 2007). Evidently, the most common contributing etiology of acute renal failure in ICU settings was septic shock (Uchino et al., 2005).

1.5.3 CNS complications

Sepsis associated neurological complications can present as a wide spectrum of clinical syndromes which includes encephalopathy, neuromuscular disorders, cerebrovascular events, and seizures (Sweis et al., 2016, Gofton and Young, 2012). Additionally, sepsis associated central nervous system dysfunction can present as hyperactive or hypoactive delirium, seizures, and cerebrovascular events that can develop in the acute event of sepsis resulting in poor clinical outcomes and also results in neurocognitive decline in sepsis patients survivors (Sweis et al., 2016). This indicates that sepsis associated encephalopathy (SAE) is considered as a life-threatening worsening of mental status due to underlying sepsis and/or the influence of other factors such as: associated comorbidities, pre-existing neurologic disease, sedation, and antimicrobial treatment. Also, SAE is considered an independent predictor of poor clinical outcomes including: long-term cognitive impairment (Golzari and Mahmoodpoor, 2014, Zampieri et al., 2011).

1.5.4 Metabolic complications

Abnormal blood glucose levels is often seen in patients who are critically ill (Mitsuyama et al., 2022). With this regards, hyperglycemia is considered a common response to acute illnesses (Mitsuyama et al., 2022). Evidently, sepsis is associated with hyperglycaemia and it appears to develop in the early stages of sepsis (Jan et al., 2009, Brierre et al., 2004). Sepsis induced hyperglycemia is believed to be multifactorial i.e. hyperglycemia can develop due to the following: Stress-induced elevations in glucagon, catecholamine, growth hormone, and cortisol which promote hepatic gluconeogenesis and glycogenolysis (Tucholskie, 2008, Brierre et al., 2004). In addition to the insulin resistance induced by pro-inflammatory cytokines (e.g. tumor

necrosis factor-α (TNF-α), interleukin-1, and interleukin-6) (Tucholskie, 2008, Chambrier et al., 2000). All these factors results in sepsis induced hyperglycemia which is reported to be associated with poor prognosis and clinical outcomes in both diabetic and non-diabetic patients with sepsis admitted to the ICU (van Vught et al., 2016).

1.5.5 Gastrointestinal complications

Liver dysfunction is usually seen as a late feature or complication of sepsis, manifesting as jaundice and hyperbilirubinemia (Wang et al., 2014). However, recently it has been revealed that it is an early event in sepsis (Wang et al., 2014, Marshall, 2012). Sepsis can cause liver damage through hemodynamic alterations or via direct, indirect, or both hepatocytes' damage (Nesseler et al., 2012). The incidence of liver dysfunction in patients with sepsis was reported to be ranging from 34% to 46% (Yan et al., 2014). Also, liver dysfunction is considered a complication with a significant impact on the mortality and morbidity in patients with sepsis or septic shock (Woźnica et al., 2018, Wang et al., 2014). Evidently, sepsis associated liver dysfunction is an independent risk factor for developing multiple organ dysfunction and death (Yan et al., 2014).

1.5.6 Coagulopathy and sepsis

Disseminated intravascular coagulation (DIC) is a commonly reported complication in sepsis (Iba et al., 2019c). Many mechanisms can mediates the development of DIC including: coagulation activation, the excessive suppression of fibrinolysis due to plasminogen overproduction, and the consumption of coagulation inhibitors; All these factors/mechanisms can lead to a pro-coagulant state which can

subsequently results in inadequate removal of fibrin and increased fibrin deposition in the microvasculature (Iba et al., 2019b, Zeerleder et al., 2005). Moreover, it can lead to the quickly development of organ dysfunctions, and death (Iba et al., 2019b, Taylor Jr et al., 2001). In addition, in the past decades research has been increasingly pointing out venous thromboembolism as one of sepsis's complications of sepsis as sepsis patients at high risk of developing initial and recurrent venous thromboembolism (Colling et al., 2021). This also justifies the use of thromboprophylaxis in sepsis ICU patients (Minet et al., 2015).

1.5.7 Other complications

Patients with sepsis are considered to be at high risk of complications particularly morbid complications, large part of these complication is due to the sepsis induced organs dysfunction which justifies the utilization of organs dysfunction as a new standard for defining sepsis (Fujishima, 2016, Singer et al., 2016). Septic shock is considered as the most sever sepsis complications as it carries a high mortality rate (Mahapatra and Heffner, 2019). While sepsis can be associated with other complications including: acute kidney injury, chronic kidney disease, myocardial dysfunction, mesenteric ischemia, and acute liver dysfunction (Mahapatra and Heffner, 2019). Furthermore, other complications or issues can be related to the adequacy of treatment used in the management of sepsis for example the antimicrobial resistance and the negative consequences associated with the overuse of antimicrobial agents in ICU settings as the use of broad-spectrum agents in the lack of proven underlying infection can be associated with increased risk of resistant pathogen colonization and infection (Niederman et al., 2021). Also, the overuse of broad-spectrum antimicrobials can increase the incidence of resistance even if resistance risk

factors are absent (Al-Sunaidar et al., 2020). In addition, diagnostic and therapeutic options used in the management of sepsis can be associated with increased risk of complications such as AKI (Petejova et al., 2020). For instance, several potentially nephrotoxic agents are used in the management of patients with sepsis such as empiric antimicrobial agents, human albumin, stress ulcers prophylactic agents (Petejova et al., 2020). With this regards, several nephrotoxic medications are found in the recommended EAMT regimens such as: vancomycin, aminoglycosides and polymyxins, which can cause acute tubulointerstitial nephritis (ATIN) and apoptosis. It is worth mentioning that several antimicrobial agents and other supportive medications often used in the management of critically ill patients can also cause ATIN and accounts for 60–70% of ATIN cases (Petejova et al., 2020, Perazella and Markowitz, 2010). Also, agents used for diagnostic indications such as Iodine contrast which is used for radiocontrast imaging to identify sepsis source or for surgical interventions can contribute to AKI (Petejova et al., 2020, Wilhelm-Leen et al., 2017).

1.6 Risk factors of sepsis

When it comes to the prognosis of sepsis it is still considered poor with a reported mortality from 36% - 55.2% which means that sepsis is considered as the main death cause in the ICU settings (Fathi et al., 2019). Therefore, it is important to understand the risk factors as the identification of sepsis associated risk factors is essential for health practitioners to prevent complications and to identify treatment preferences (Fathi et al., 2019). Furthermore, risk factors that increases the risk of sepsis development can be categorized into risk factors related to the demographic characteristics of patient with sepsis, patient's comorbidities, and patients' clinical characteristics (Fathi et al., 2019).

When it comes to the demographic characteristics and its association with the development of sepsis, it has been shown that age is identified as a risk factor of developing sepsis (Fathi et al., 2019, Wafaisade et al., 2011, Hodgin and Moss, 2008). Furthermore, approximately 60% of sepsis cases occurs in elder patients (more than 65 years old) (Lineberry and Stein, 2014). Besides, the incidence increased with a more than 100 folds with age according to an epidemiological study in the United States (Angus et al., 2001). However, according to meta-analysis showed that included 11 cohort studies that have assessed the risk factors of sepsis, only two studies reported that older age was significantly associated with the development of sepsis (Fathi et al., 2019, Wafaisade et al., 2011, Baršić et al., 1999).

Evidently, there are several identified co-morbidities and demographic characteristics that can be associated with increased susceptibility of sepsis development (Hodgin and Moss, 2008). For instance, patients with two or more co-morbid conditions, and patients with coma and central nervous system infections were significantly more likely to develop sepsis (Farinas-Alvarez et al., 2000). Moreover, Berger and colleagues reported that immunosuppressive disorders, and chronic obstructive pulmonary disease (COPD) were independently associated with increased risk of developing sepsis (Berger et al., 2014).

With regards to the impact of the clinical characteristics on the risk of sepsis development, the use of mechanical ventilation, catheterization, parenteral nutrition, and the utilization of vasoactive medications and fluid resuscitation was identified as factors significantly associated with increased risk of sepsis development (Fathi et al., 2019, Elias et al., 2012, Farinas-Alvarez et al., 2000, Baršić et al., 1999). In addition,

Glasgow Coma Scale (GCS) and higher severity of illness scores were also reported to increase the risk of sepsis development (Fathi et al., 2019).

1.7 Diagnosis of sepsis

In accordance with the sepsis definitions, diagnosis of sepsis is made based on the evidence of infection and associated organs dysfunction (Rhodes et al., 2017, Singer et al., 2016). This indicates that acute organs dysfunction should be ruled out in the contexts were a new infection is suspected (Bloos, 2018). Similarly, infections should to be ruled out in the contexts were new onset of organs dysfunction are present (Bloos, 2018). Therefore, to achieve accurate, prompt and rapid diagnosis of sepsis, an initial history and clinical examination, laboratory workup, microbiological, and imaging studies should be obtained (Schmidt et al., 2018). Simultaneously, airway stabilization and rapid intravenous access are essential to be done. Also, the assessment of tissue perfusion status, organs dysfunction, and culture samples should be done promptly and taken into consideration as these assessments yields potentially valuable inputs regarding the suspected source and complications of sepsis, and subsequently, guide the selection of empiric therapy, ensures the provision of optimal management, resuscitation and guidance for additional monitoring (Schmidt et al., 2018). In addition, the identification and control of the infection source is very important, as it not only facilitates the selection of the optimal antimicrobials. Also, it plays a major role in the evaluation and management of certain types of infections such as abscesses that are operable and for surgical intervention such as surgical or percutaneous drainage, bowel ischemia, gastrointestinal (GI) perforation, urinary or biliary systems infections, necrotising soft tissue and skin infections and infection associated with implanted devices (Thompson et al., 2019).

1.7.1 History and physical examination

Sepsis and septic shock are clinical syndromes that are identified by a group of symptoms, signs, laboratory abnormalities and pathophysiological derangements (Mahapatra and Heffner, 2021).

Early presentations of sepsis include the following changes in the vital sign:

- Fever (body temperature above 38 C), or hypothermia (body temperature below 36 C).
- Tachycardia (heart rate 90 beats per minute or higher) in adult patients or less than two standard deviations for age in pediatric patients.
- Tachypnea (respiratory rate higher than 20 breaths per minute) in adult patients or more than two standard deviations for age in pediatric patients.

In addition, when it comes to medical history assessment in a patient suspected to have sepsis it is important to evaluate risk factors associated with reduced survival or higher incidence of sepsis, and to identify possible sources of infection. For instance, active malignancy, chronic lung disease, diabetes, renal insufficiency, congestive heart failure, and liver disease(cirrhosis) were identified as comorbidities associated with morbidity and reduced survival in sepsis patients (Bullock and Benham, 2019). Moreover, age has been shown to be associated with mortality in sepsis patients. This is can be explained by the association of older age with the reduction of efficiency of adaptive immune system and impaired with B and T cells functions (Iskander et al., 2013). The physical and clinical examination provides critically important inputs which also allows the utilization of clinical screening tools

(Bullock and Benham, 2019). Common clinical findings associated with sepsis are described in Table 1.3 below.

Table 1.3 Summary of clinical findings of sepsis and septic shock (Gauer et al., 2020)

System	Clinical findings
Cardiovascular system	Hypotension; tachycardia; cardiac murmur; poor capillary refill; warm; and flushed skin.
Constitutional system	Fevers or chills; malaise; diaphoresis; and anorexia
Dermatologic/skin	Petechiae; erythematous; rash; ulceration; purulent lesions; splinter hemorrhage; and erythema
Gastrointestinal system	Distention; rigid abdomen; abdominal pain; decreased bowel sounds; diarrhea ± blood ; and emesis
Genitourinary system	Hematuria, pyuria, dysuria, costovertebral tenderness, lower abdominal pain, vaginal discharge or vaginal bleeding
Musculoskeletal	Joint pain; swelling; regional muscle pain, ± edema; crepitus; and weakness in the extremities
Neurological system	Headache; altered mental status; neck rigidity/stiffness; and convulsions
Pulmonary system	Upper: sore throat; and dysphagia, Lower: cough; shortness of breath, Chest pain; and tachypnea/hyperventilation

1.7.2 Laboratory tests

Laboratory diagnostic tests provides a valuable inputs when it comes to the diagnosis and evaluation of sepsis, sepsis associated organs dysfunction, sepsis severity, and provides a baseline for follow-up (Schmidt et al., 2018). Laboratory diagnostic tests includes: complete blood counts with differential, chemistries, liver function tests, and coagulation studies including D-dimer level, urinalysis, arterial or venous blood sampling (Gauer et al., 2020, Schmidt et al., 2018).

1.7.3 Culture and sensitivity

It is essential that a least two sets of blood cultures are taken prior to the initiation of EAMT (Schmidt et al., 2018). Obtaining blood culture after the initiation of EAMT was found to reduce the sensitivity of culture testing with sensitivity of 53%, also post antimicrobial cultures came out negative in 19.4% compared with 31.4% in pre antimicrobial cultures in patients diagnosed with sepsis (Cheng et al., 2019). This indicates the importance of obtaining cultures prior to the initiation of EAMT (Schmidt et al., 2018). Although, cultures and sensitivity testing plays an axial role in both sepsis diagnosis and management. However, large proportion of patients with sepsis are culture negative sepsis (Sigakis et al., 2019, Neviere et al., 2017, Phua et al., 2013a).

In addition, sign and symptoms of infection can aid in identifying the source of infection and subsequently facilitate the initial microbiological evaluation. For instance, common clinical findings associated with central nervous system infections include: signs of meningeal irritation such as altered mental status, nuchal rigidity, Brudzinski's sign, and seizures (Schmidt et al., 2018, Archibald and Quisling, 2013). While clinical findings found in patients with respiratory infections includes: productive cough, chest pain, and consolidative findings (Saleri and Ryan, 2019, Schmidt et al., 2018). While signs and symptoms associated with urinary tract infections include: loin/back pain, dysuria, and urgency (Schmidt et al., 2018). Table 1.4 below describes the signs and symptoms according to the site of infection and the recommended initial microbiologic evaluation.

Table 1.4 Summary of clinical findings according to the source of infection and the recommended initial microbiological evaluation approach (Schmidt et al., 2018)

Source of infection	Clinical findings	Initial microbiological evaluation
Upper respiratory tract	Pharyngeal inflammation plus exudate with or without lymphadenopathy and swelling	Throat swab for aerobic culture
Lower respiratory tract	Productive cough, pleuritic chest pain, consolidative findings	Sputum culture, rapid influenza testing, urinary antigen testing, quantitative culture of protected brush or bronchoalveolar lavage
Urinary tract	Urinary urgency, dysuria, loin/back pain	Urine culture and microscopy showing pyuria
Vascular catheters associated infections	Redness or drainage at catheter insertion site	Blood culture (from the catheter and a peripheral site), catheter tip culture (if removed)
Indwelling pleural catheter	Redness or drainage at catheter insertion site	Culture of pleural fluid (through catheter)
Wound or burn	Inflammation, edema, erythema, pus	Draining pus culture and gram stain, wound culture not reliable
Skin and soft tissue	Erythema, edema, lymphangitis	Blister fluid culture or draining pus; role of tissue aspirates not proven
Central nervous system	Signs of meningeal irritation	CSF cell count, protein, glucose, culture, and gram stain
Gastrointestinal	Abdominal pain, distension, diarrhea, and vomiting	Stool culture for Salmonella, Shigella, or Campylobacter; detection of Clostridium difficile toxin
Intra-abdominal	Specific abdominal symptoms/signs	Aerobic and anaerobic culture of percutaneously or surgically drained abdominal fluid collections
Peritoneal dialysis (PD) catheter	Cloudy PD fluid, abdominal pain	Cell count and culture of PD fluid
Genital tract	Female: Lower abdominal pain, vaginal discharge Male: Dysuria, urinary frequency/urgency, incontinence, cloudy urine, prostatic tenderness	Female: Endocervical and high vaginal swabs onto selective media Male: Urine Gram stain and culture
Bone	Pain, warmth, swelling, decreased use	Blood cultures, MRI, bone cultures at surgery or by interventional radiology
Joint	Pain, warmth, swelling, decreased range of motion	Arthrocentesis with cell counts, Gram stain, and culture

1.8 Management of sepsis

In the management of sepsis, therapies are provided to manage the basic elements of sepsis i.e., infection, organ dysfunction and host response (Bullock and Benham, 2019). These therapies include resuscitation, antimicrobial therapy, and additional supportive therapies.

1.8.1 Initial resuscitation

Early aggressive fluid resuscitation is considered one of the cornerstones in stabilizing sepsis, or septic shock patients (Gyawali et al., 2019). Initial fluid resuscitation with crystalloids IV fluid is recommended over other types of fluids (Evans et al., 2021), this due to many reasons including: the wide availability of crystalloids, cheap prices, and crystalloids have small molecule. On the other hand colloids IV fluid have larger molecules, can induce blood clotting disorders, kidney failure, and allergic reactions (Lewis et al., 2018). Moreover, using colloids was found to have no significant benefit on mortality when compared with crystalloids (Lewis et al., 2018). According to SCCG, intravenous albumin also can be used in patients who received large volume of crystalloids fluid (Evans et al., 2021).

1.8.2 Vasopressors and inotropes

The tissue hypo-perfusion is believed to be multifactorial and contributes to organ damage and dysfunction in sepsis/septic shock. Therefore, it is essential to restore adequate tissue perfusion in sepsis and septic shock patients (Gyawali et al., 2019). Vasoactive agents are indicated to be used in patient with persistent hypotension despite adequate provision of IV fluids (Evans, 2018). Norepinephrine is considered the first line therapy in sepsis, or septic shock patients (Evans et al., 2021).

Also, vasopressin is recommended in patients with inadequate mean arterial pressure (MAP) despite norepinephrine therapy (Evans et al., 2021). In addition, sepsis-induced myocardial dysfunction is considered one of the major factors that contributes to the hemodynamic instability and is associated with poor clinical outcomes of patients with septic shock (Walley, 2018). Therefore, agents that can be used as inotropes also includes: dobutamine + norepinephrine or using epinephrine (Evans et al., 2021).

1.8.3 Empirical antimicrobial therapy

The adequate and timely use of antimicrobials is considered essential and highly recommended in the management of sepsis due to the fact that a delay in the initiation of antimicrobial therapy can be associated with negative clinical outcomes (Ferrer et al., 2014, Kumar et al., 2006). In fact, early adequate empiric antimicrobial therapy (EAMT) was found to significantly reduce the adjusted risk of mortality in patients with sepsis (Seymour et al., 2017). Moreover, EAMT's adequacy has been consistently reported to be a significant determinant of clinical outcomes in patients with sepsis admitted to the ICU (Al-Sunaidar et al., 2020, Andersson et al., 2019, Trifi et al., 2018, Cañas et al., 2015, Garnacho-Montero et al., 2015, Nygård et al., 2014, Yokota et al., 2014, Rodríguez-Baño et al., 2009, Degoricija et al., 2006, Garnacho-Montero et al., 2003). Therefore, the administration of adequate EAMT is considered as one of the most important and effective management strategies in sepsis management (Evans et al., 2021, Martínez et al., 2020, Strich et al., 2020a, Dewi et al., 2018, Rhodes et al., 2017, Liang and Kumar, 2015).

According to the 2016 and 2021 surviving sepsis campaign's international guidelines (SSCG) for management of sepsis and septic shock, intravenous antimicrobial agents should be started as soon as possible/immediately after the

recognition and optimally within 1 hour for both sepsis and septic shock, as it has been shown that the early administration of appropriate antimicrobials was associated with lower mortality rates (Evans et al., 2021, Rhodes et al., 2017). However, there are some concerns regarding the possibility of consistent achievement of this target as it has not been adequately addressed in the literature (Rhodes et al., 2017). Also, the achievement of this goal can be limited by several factors including delayed recognition of sepsis patients, operational complexities, type of the institute the patients are admitted at, and site of referral can potentially limit the possibility of achieving this goal (Rhodes et al., 2017, Amaral et al., 2016). The recommendation of SSCGs have also raised controversies as several studies in the literature indicated that the delay in providing EAMT was significantly associated with poor clinical outcomes such as higher mortality rates and length of stay (Weinberger et al., 2020, Liu et al., 2017, Seymour et al., 2017). However, aggressive antimicrobial management can rise the risks associated with unnecessary antimicrobials use in critically ill patients as setting tight time window for providing EAMT can lead to over-prescribing of antimicrobial even when the evidence of infection is lacking (Weinberger et al., 2020).

This can indicates that the need for immediate EAMT patients with sepsis is considered to be life-saving, but can be also associated with antimicrobial over-use and drive antimicrobial resistance (Niederman et al., 2021). Therefore, Niederman and colleagues described an approach to minimize and control the risk of resistance which include de-escalating EAMT according clinical, microbiologic (culture), and laboratory data (Figure 1.2) (Niederman et al., 2021). De-escalation can be in the form of shorter duration of therapy, less broad-spectrum agents, fewer drugs, or a combination of these interventions (Niederman et al., 2021). This also justifies the