HYPERGLYCAEMIA AS A PREDICTOR OF MORTALITY AND PROLONGED LENGTH OF STAY IN SEVERE SEPSIS AND SEPTIC SHOCK PATIENTS PRESENTED TO RED ZONE OF EMERGENCY DEPARTMENT, HOSPITAL UNIVERSITI SAINS MALAYSIA: A RETROSPECTIVE STUDY

By

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LIST OF ABBREVIATIONS

ACTH	Adrenocarticotropin hormone
AG	Admission glucose
BE	Base excess
cAMP	Cyclic adenosine monophosphate
CARS	Counter inflammatory response syndrome
Cl	Confidence interval
CRP	C-reactive protein
CVP	Central venous pressure
DBP	Diastolic blood pressure
ED	Emergency department
EGDT	Early goal directed therapy
FFA	Free fatty acid
FG	Fasting glucose
MEDS	Mortality in Emergency Department sepsis
mMEDS	modified Mortality in Emergency Department Sepsis
MODS	Multiple organs dysfunction syndrome
NIMGU	Non-insulin mediated glucose uptake

GLUT	Glucose transporter
HbA_{1c}	Glycosylated plasma proteins
HDU	High Dependency Unit
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-pituitary-adrenal axis
HR	Heart rate
ICU	Intensive Care Unit
IGF	Insulin-like growth factor
IL	Interleukin
IMGU	Insulin mediated glucose uptake
IqR	Inter-quartile range
HUSM	Hospital University Science Malaysia
LOS	Length of stay
OR	Odd ratio
$PaCO_2$	Partial pressure carbon dioxide
PaO_2	Partial pressure oxygen
ROS	Radical oxygen species
SBP	Systolic blood pressure
SCCM	Society of Critical Care Medicine

SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
Spo2	Oxygen saturation
TNF-α	Tumour necrosis factor alpha

ABSTRAK

Pengenalan: Hiperglisemia yang dikesan diperingkat awal semasa kemasukan ke wad merupakan penanda risiko morbiditi dan mortaliti bagi pelbagai penyakit kritikal akut. Namun tiada sebarang kajian sebelum ini dijalankan untuk mengkaji hiperglisemia di peringkat awal di kalangan pesakit sepsis teruk dan kejutan septik yang dirawat di jabatan kecemasan.

Objektif: Untuk mengkaji sama ada hiperglisemia yang dikesan semasa presentasi awal pesakit ke jabatan kecemasan mempunyai nilai prognostik di kalangan pesakit sepsis teruk dan kejutan septik; dan seterusnya membuat perbandingan dengan lain-lain parameter prognostik.

Kaedah: Kajian ini merupakan kajian retrospektif bagi pesakit sepsis teruk dan kejutan septik yang dirawat di Zon Merah, Jabatan Kecemasan, Hospital Universiti Sains Malaysia bagi tahun 2008- 2011. Pengumpulan data dilakukan dengan mengenalpasti pesakit melalui rekod pendaftaran pesakit. Data demografi, bacaan awal glukosa darah kapillari dan lain-lain parameter yang berkaitan dengan morbiditi dan mortaliti bagi pesakit sepsis teruk dan kejutan septik diambil dan direkodkan.

Hasil: Data dikumpulkan dari 495 pesakit dengan sepsis teruk dan kejutan septik. Prevalens hiperglisemia stres adalah 14.9%; dan hiperglisemia diperingkat awal secara keseluruhan adalah 40.2%. Hiperglisemia awal mempunyai nilai prognostik dalam menentukan risiko kematian di kalangan pesakit bukan diabetes (Chi-square 32.7% vs 59.1%, p-value 0.001). Tidak ada korelasi yang signifikan ditemui antara hiperglisemia awal dengan tinggal berpanjangan di hospital. Namun apabila analisis multivariat dilakukan hanya markah mMEDs yang tinggi, tahap laktat yang tinggi dan penggunaan

ventilator mekanikal mempunyai kaitan untuk menentukan mortaliti dan; untuk tinggal berpanjangan di hospital hanya markah mMEDs yang tinggi mempunyai nilai prognostik.

Kesimpulan: Hiperglisemia awal mempunyai nilai prognostik dalam menentukan mortaliti bagi pesakit bukan diabetes tetapi tidak di kalangan pesakit diabetes. Tiada korelasi boleh dibuat antara hiperglisemia awal dan tinggal berpanjangan di hospital. Menentukan tempoh tinggal di hospital merupakan perkara yang kompleks dan tidak boleh ditentukan dengan hanya menggunakan faktor tunggal. Jika dibandingkan dengan faktor-faktor prognostik lain seperti mMEDS, laktat dan penggunaan ventilator; hiperglisemia didapati mempunyai nilai prognostik yang lemah.

ABSTRACT

Introduction: Initial or at-admission hyperglycaemia is a risk marker of morbidity and mortality in many acute critical illnesses. There has been no study to evaluate hyperglycaemia in severe sepsis and septic shock in the emergency department setting.

Objectives: To investigate whether hyperglycaemia detected during patient initial presentation to emergency department has prognostic value in the outcome of severe sepsis and septic shock patients and compare it with other prognostic factors.

Methods: A retrospective study in patients with severe sepsis and septic shock presented to the Red Zone of Emergency Department of Hospital University of Science Malaysia during 2008- 2011 was done. Data were collected by tracing patients medical records based on the attendance registry. Demographic data, initial capillary blood glucose and other factors which may predict the outcomes of severe sepsis and septic shock were collected and recorded.

Results: Data were collected from 495 patients with severe sepsis and septic shock. The prevalence of stress hyperglycaemia was 14.9% and the overall initial hyperglycaemia was 40.2%. Initial hyperglycaemia did have significant prognostic value in determining mortality in non-diabetic patients (Chi-square 32.7% vs. 59.1%, p-value 0.001). No significant correlations were found between initial hyperglycaemia with prolonged hospital stay. However when multivariate analysis were done only high mMEDs score, lactate level and mechanical ventilator were associated with mortality and for prolonged length of stay only mMEDs score.

Conclusion: Initial hyperglycaemia has prognostic value in determining mortality in non-diabetic but not in diabetic patients. No correlation can be made between initial

hyperglycaemia and prolonged length of stay, as predicting length of stay is a complex nature and cannot be determined by single factor. When compared with other prognostic factors such as mMEDS score, lactate and ventilator use; hyperglycaemia was found to be inferior.

1.0 INTRODUCTION

In these recent decades, the reported worldwide incidence of sepsis has increased dramatically, mostly due to the advancing age of population, an increased number of invasive procedure being done and immunosuppressive therapy (Martin et al., 2003). It has been estimated that 90.4 cases of severe sepsis per 100,000 population in the European Union countries (Davies et al., 2001). While in the United States it is estimated 3.0 cases per 1000 population per year or roughly 20 million cases per year (Angus et al., 2001). Half of these patients are treated in the Intensive Care Unit (ICU), which constitute about 10% of all ICU admissions (Angus et al., 2001).

In Malaysia, sepsis is one of the three most common diagnoses leading to ICU admissions. A report from the Malaysia Registry of Intensive Care for the year of 2012 had shown that direct admission to ICU from the emergency department had increased from 16.7% in the year of 2008 to 27.9% in 2012 (Tong et al., 2013). With such report, we are expecting to see more severe sepsis and septic shock cases presented to our emergency department.

Not only are we expecting increasing number of severe sepsis and septic shock patients in our community, but the fact that the mortality rate for such patients has remained high between 30-40% over these past few decades despite the use of aggressive antimicrobial agents and advanced life support care surely put more burdens and exhaust our healthcare resources (Angus et., 2001, Friedman et al., 1998).

Many strategies and measures have been proposed to reduce the mortality rate for severe sepsis and septic shock patients, but the most novel of all is the early goal directed therapy (EGDT) when applied early in the emergency department rather than

initiating the treatment later in the ICU or wards (Rivers et al., 2001). They reported a 16% absolute risk reduction for in-hospital mortality.

Subsequently in 2004, an international group of experts in the diagnosis and management of infection and sepsis, representing 11 organizations, published the first internationally accepted guidelines that clinician could use to improve the outcomes in severe sepsis and septic shock patients. These guidelines represented phase II of the Surviving Sepsis Campaign (SSC), a global effort to increase awareness and improve outcome in severe sepsis (Dellinger et al., 2004). These guidelines latest updated in 2012, advocates early recognition, broad-spectrum antibiotics, hemodynamic optimization and lung protective strategies (Dellinger et al., 2013).

Sepsis has a tendency to rapidly progress to a more severe stage with multi-organ failure. Late recognition and initiation of treatments contribute to its high mortality rate. A Canadian study on the analysis of sepsis hospitalization and factors contributing to its mortality, reported that patient whom sepsis was identified in the emergency department had lower risk of dying compared with patient whom sepsis was not identified in the emergency department (Husak et al., 2010).

To identify and diagnose sepsis impose a great challenge for clinician especially in a busy and hectic emergency department. Sepsis manifests itself in vastly variable presentations. It depends on the site of infection, the causative organism, the underlying health status of the patient, and the treatment patients may have received prior to consultation. From the same study, it was reported that only 26.4% of patients identified as having sepsis prior to admission were identified of having sepsis and had diagnosis of sepsis recorded in their emergency department chart (Husak et al., 2010). A

thorough clinical history and examination with a high index of suspicious are all needed to identify sepsis and thus to treat it accordingly.

A reliable risk stratification tools could improve the outcome of sepsis by increasing awareness of the seriousness of the disease, deciding the best choice of treatment and hasten the transfer of such patients from the emergency department to the definite care placement through a more effective communication among health care professionals. Various laboratory tests and scoring systems have been developed and studied to predict the outcome of sepsis.

Example of diagnostic and prognostic biomarkers that available and have been studied are, procalcitonin (Harbarth et al., 2001), C-reactive protein (CRP) (Ho and Towler, 2009), various interleukins (ILs) (Harbarth et al., 2001), eosinophil count (Ho and Towler, 2009), pro-vasopressin (copeptin) (Guignant et al., 2009), interferon- γ (IFN-γ) (Wu et al., 2009) and resistin (Koch et al., 2009) just to name a few. While these biomarkers have variable degree of specificity and sensitivity in differentiating sepsis from other systemic inflammatory response syndrome (SIRS); and inconsistence predictive value in mortality, many of them are not widely available to many emergency departments except maybe the CRP.

More common and readily available sepsis biomarkers in the emergency department such as lactate, base excess and white cell count are also widely studied. They too have variable prognostic values in sepsis outcome. Lactate has shown to have a moderate predictive value in severe sepsis and septic shock outcome (Arnold et al., 2009, Nguyen et al., 2004). Base excess alongside lactate has shown to be an acceptable prognostic marker in severe sepsis (Silva et al., 2005). As for CRP and leukocyte count, studies have revealed that they are not generally accepted as a predictor of mortality

even though they have been used as diagnostic markers for sepsis (Hisamuddin and Azlan, 2012, Alberti et al., 2005, Lee et al., 2008, Kofoed et al., 2007).

Shapiro et al in 2003 published a new simple scoring system designed to be applied in emergency department in predicting the outcome of sepsis patient. The Mortality in Emergency Department Sepsis (MEDS) score uses parameters that are readily available in emergency department as to compare with the more complex score system like the Acute Physiology and Chronic Health Evaluation II (APACHE II), where they are more appropriate to be applied in the ICU (Shapiro et al., 2003). The MEDS score in several studies has proved to be adequately predicting mortality in sepsis patients (Hermans et al., 2012, Sankoff et al., 2008, Lee et al., 2008).

Considering, the workload and fast turnover of patients in many emergency departments, a risk stratification tool that is easily available, give instant result, accurate and low cost would be the ideal tool. One of the potential risk stratification tools in detecting the severity of septic patients that previously may have been overlooked is the blood glucose level. Many studies have associated high initial or at-admission blood glucose level with adverse outcome in patients in severe trauma (Yendamuri et al., 2003, Laird et al., 2004), severe head injury (Walia and Sutcliffe, 2002, Oswald and Yudkin, 1987), severe burn (Gore et al., 2001), myocardial infarction (Stranders et al., 2004, Oswald and Yudkin, 1987) and stroke (Capes et al., 2001).

Any insult or stress to the human body be it infective or not, will trigger the systemic inflammatory response all the same that involves a complex process involving the humoral and cellular responses; and activation of the complements and cytokines cascades. Having this in mind, this study wishes to further investigate and explore the

relationship between the initial blood sugar level with the outcome of severe sepsis and septic shock patients.

2.0 LITERATURE REVIEW

2.1 Body response to insults

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced the concept and definition for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock and multiple organs dysfunction syndrome (MODS) (Bone et al., 1992). The idea behind defining SIRS was to define a clinical response to a non- specific insult of either infectious or non-infectious origins. SIRS is defined as 2 or more of the following variables:

- Fever of more than 38°C or less than 36°C
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or a $PaCO_2$ level of less than 32 mm Hg
- Abnormal white blood cell count (>12,000/µL or <4,000/µL or >10% bands)

SIRS is nonspecific and can be caused by biologic (microorganisms), physical (mechanical insult, radiation), chemical (poisons, acids), metabolic (hypoxia, malnutrition), immunologic (autoimmune diseases) or a combination of several insults. SIRS is not always related to infection. When SIRS is due to infection it is known as sepsis. Severe sepsis is associated with organ dysfunction, hypo-perfusion, or hypotension. Sepsis-induced hypotension is defined as "the presence of a systolic blood pressure of less than 90 mm Hg or a reduction of more than 40 mm Hg from baseline in the absence of other causes of hypotension." Patients meet the criteria for septic shock if

they have persistent hypotension and perfusion abnormalities despite adequate fluid resuscitation.

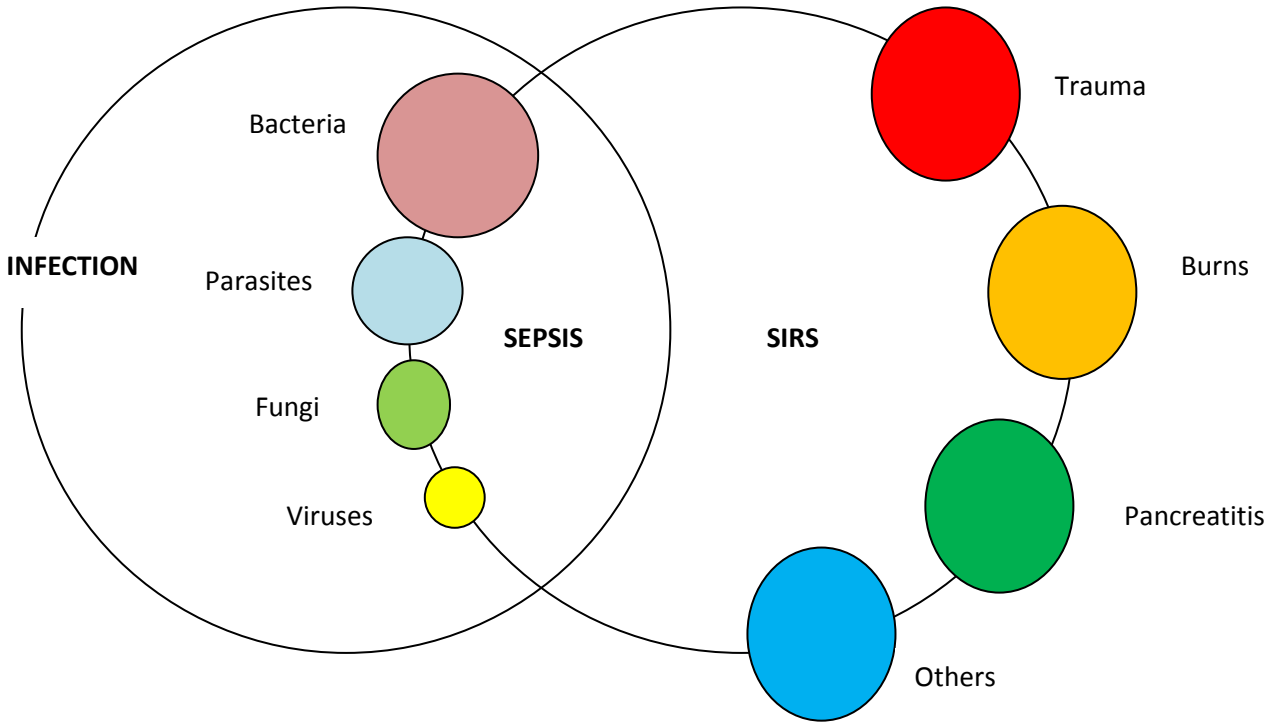

Figure 1: Inter-relation of SIRS with the causes (Bone et al., 1992).

SIRS independent of the aetiology, has the same pathophysiologic properties, with minor differences in inciting cascades (Bone et al., 1992). Many consider the syndrome as a body self-defence mechanism. Inflammation is system of the defensive reactions of the vascularized tissues of the organism to the pathogenic insult of different origin. The goal of inflammation is to eliminate the cause, to eliminate destructed tissue and, through regeneration or repair, to restore metabolism and function of the organs to the state of dynamic balance. The inflammatory cascade is a complex process that involves humoral and cellular responses, complement, and cytokine cascades.

The cumulative effect of this inflammatory cascade is an unbalanced state with inflammation and coagulation dominating. To counteract the acute inflammatory response, the body is equipped to reverse this process via counter inflammatory response syndrome (CARS) (Ward et al., 2008). IL-4 and IL-10 are cytokines (CARS mediators) responsible for decreasing the production of TNF-a, IL-1, IL-6, and IL-8 (SIRS mediators). Usually the pro-inflammatory and the anti-inflammatory responses are in balance which determines the successful of the healing process. However if there is overwhelming production of both SIRS and CARS mediators cause many pathological changes in vital organs and system including metabolic changes.

2.2 Hyperglycaemia and the stress response to critical illness

Stress response is a body mechanism when subjected to external aggression such as surgery, burns, sepsis or shock. This response involves hypermetabolism and hypercatabolism, one such metabolic change is hyperglycaemia (McCowen et al., 2001). An elevated blood glucose level in critically ill patients is termed stress hyperglycaemia. It is usually restricted to patient without previous evidence of diabetes. However patients with diabetes might also develop stress hyperglycaemia. Dungan et al. argue that change in glucose from baseline and not the absolute glucose concentration might be of value, irrespective of whether a patient has pre-existing diabetes. They propose 2 diagnostic categories of stress hyperglycaemia- hospital related hyperglycaemia according to the American Diabetes Association (ADA) conferences definition; fasting blood sugar > 6.9 mmol/L or random blood sugar > 11.1 mmol/L without evidence of previous diabetes and pre-existing diabetes with deterioration of pre-illness glycaemic control (Dungan et al., 2009).

The exact underlying mechanism of stress hyperglycaemia is not entirely understood, but several potential mechanisms have been proposed. These include the availability of substrate such as lactate, enhanced gluconeogenesis and decreased of glycogenolysis due to excessive counter-regulatory hormones and peripheral insulin resistance.

2.2.1 The availability of gluconeogenic substrates

Gluconeogenic substrates such as lactate, alanine and glycerol are released in abundance during stress (Siegel et al., 1979, Cerra, 1987). For example the lung produces a large amount of lactate in patients with acute lung injury; the gastro-intestinal tract, wounds and injured tissues also produce lactate during stress (Kellum et al., 1997, Curtis and Cain, 1992, Willmore, 1986). In sepsis especially in severe sepsis and septic shock, cellular anaerobic metabolism and microvascular tissue hypoxia or ischemia will lead to increased lactate formation. However in sepsis, increased level of lactate is not only due to increased in lactate production but also due to reduced lactate clearance and altered energy substrate oxidative pathway metabolic (Levraut et al., 1998).

Critical illness enhances alanine and glutamine release from skeletal muscles breakdown. This catabolic response is mediated by number of regulators; the main one is the glucocorticoids. While the role of cytokines such as TNF-α is thought to be through the release of glucocorticoids. Glucocorticoids inhibit protein synthesis (Vary and Kimball, 1992) and promote proteolysis (Hasselgren et al., 1989) and subsequently amino acids are released into the bloodstream. Acidosis which is usually observed in

sepsis is also known to promote protein breakdown, although the mechanism is not completely clear (Hasselgren et al., 1987).

The administration of glucose precursors to hyperglycaemic patients with trauma has been shown to stimulate gluconeogenesis and the net hepatic glucose output nevertheless remains unaltered (Tappy et al., 1995). This indicates that the auto-regulation of hepatic glucose production is preserved during critical illnesses, although at a higher level of glucose production (Mizock, 2001).

2.2.2 The counter-regulatory hormones

The activation of the hypothalamic-pituitary-adrenal (HPA) axis with the release of cortisol from the adrenal gland is the hallmark of stress associated with critical illness including during sepsis (Marik and Zaloga, 2002). In addition to increased cortisol secretion the stress response is also characterized by a marked increase in other counter-regulatory hormones like glucagon, growth hormone and epinephrine. These hormones apart from increasing the production of glucose via glycogenolysis and gluconeogenesis, contribute to significant insulin insensitivity through poorly understood mechanism likely related to alteration in insulin signal pathway. Counter-regulatory hormones also enhance lipolysis and increase level of free fatty acids (FFA) in the circulation, which may contribute an additional defect to the normal insulin function (Press, 1988). The overall endocrine reaction to stressful events like in sepsis shifts the metabolism towards catabolism.

2.2.2(i) Cortisol hormone

During acute phase of critical illness, the HPA axis response by releasing adrenocorticotropin hormone (ACTH) probably secondary to increased in corticotrophin-releasing hormone and inflammatory mediators. ACTH and an activated rennin-angiotensin system will give rise to a raised secretion of aldosterone and cortisol hormones (Van den Berghe, 2000). Apart from that, tumour necrosis factor-α (TNF-α) also directly enhances the release of cortisol. Elevated cortisol concentration in the body will sharply increases the blood levels of glucose, amino acid and FFA (catabolic effects) to ensure the availability of substrates to vital organs such brain and heart during stressful event. These mechanisms seemingly provide the metabolic substrates and host defence needed for survival, thus may considered as adaptive and beneficial (Van den Berghe, 2000).

2.2.2(ii) Glucagon hormone

Glucagon roles is to maintain euglycemia during fasting and acute illness by stimulating hepatic glucose output. It increases hepatic glucose output mainly by inducing glycogenolysis (Chhibber et al., 2000).

2.2.2(iii) Catecholamines

The levels of endogenous catecholamines are normally elevated. In addition, exogenous vasopressors are used in hypotension may further increase catecholamines blood level in sepsis patients. Epinephrine via β- adrenergic stimulation inhibits insulin-mediated glucose uptake especially in the skeletal muscles (Deibert and DeFronzo,

1980). The β-adrenergic stimulations disrupt the insulin-signalling pathway by both cyclic adenosine monophosphate (cAMP) and cAMP- independent mechanisms (Lonnroth and Smith, 1983). It is suggested this inhibitory action occurs at multiple sites as the insulin function is disturbed at receptor levels (Linde et al., 1989) and also through tyrosine kinase (Eriksson et al., 1992).

2.2.2(iv) Growth hormone

During acute phase of critical illness, growth hormone baseline is high and more frequent peaks are observed as it is thought to be vital for the biologic effects (Ross et al., 1991). Growth hormone executes most of its anabolic effects via insulin-like growth factor-1 (IGF-1) and its levels are low in critical illness (Andersen et al., 2004).

2.2.2(v) Counter-regulatory hormones in synergism

Shamoon and associates explained the short term effects in normal individuals of the combined infusion of hydrocortisone, glucagon and epinephrine. They observed increased glucose production and decreased glucose clearance, the effect was more prominent when all three hormones were administered together than when they were infused separately, suggesting synergistically effect (Shamoon et al., 1981).

A possible explanation for this synergism is that glucagon increases intracellular cAMP, especially in the liver by a non β-receptor mechanism. This could amplify the action of epinephrine which acts via β-receptor mechanism. Cortisol acts synergistically with epinephrine via cortisol- induced inhibition of catechol-O-methytransferase and blockade of catecholamine reuptake. The glucocorticoids also prevent β_2-adrenergic

receptor down-regulation by increasing both β_2-receptor expression and β_2-receptor gene transcription (Shamoon et al., 1981).

2.2.3 Peripheral insulin resistance

In normal body function, glucose concentration in the blood is tightly regulated even though the rate of glucose uptake and oxidation varies extensively. Three glucose transporter isoforms have been indentified to have an essential role in glucose uptake. GLUT1 is responsible for the non insulin-mediated glucose uptake (NIMGU) and is situated mainly in the erythrocytes and central nervous system. GLUT4 requires insulin to be immobilised to the cell membrane and is located mainly in the skeletal muscles. Whereas GLUT2 is a bidirectional transporter located in the liver and kidneys.

Insulin resistance could be due to defective GLUT4 transporter. Pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumour necrosis factor-α (TNF-α) have deleterious effect on the insulin dependent glucose transporter in which they decrease the expression and phosphorylation of insulin cell surface receptors leading to liver adipocytes and muscle insulin resistance (Aljada et al., 2002). Catecholamines have been shown to inhibit insulin binding, tyrosine activity and translocation of GLUT-4 (Chiasson et al., 1981). Meanwhile glucocorticoids impair insulin mediated glucose uptake by down-regulating various signalling proteins leading to impairment of translocation GLUT-4 glucose transporter (Dimitriadis et al., 1997). Growth hormone causes insulin resistance through reducing insulin receptors and impairing its activation via phosphorylation on tyrosine residues (Smith et al., 1997). The insulin resistance is directly proportional to the severity of stress response (Mizock, 2001).

2.2.4 Detrimental effects of hyperglycaemia in the critically ill.

Hyperglycaemia in critical illness, is not only a marker of severity of illness and the predictor of poor outcome, but also has many kinds of adverse effects on vital organs (Mizock, 2001). Glucose has been shown to be a powerful pro-inflammatory mediator (Dandona et al., 2003) and tight glucose control with insulin below 110 mg/dL has proven to confer anti-inflammatory effects in critically ill patients (Hansen et al., 2003). This pro-inflammatory effect occur both in acutely and chronically hyperglycaemia (Esposito et al., 2002). Esposito and co-workers have demonstrated that subjects with impaired glucose tolerance had higher baseline TNF-α and IL-6 levels compared with their normal controls. Another study has shown that hyperglycaemia dose-dependently stimulates TNF-α and IL-6 production in-vitro (Morohoshi et al., 1996). At the same time, both TNF-α and IL-6 are strongly implicated in the development of insulin resistance (Wogensen et al., 1992). Insulin is on the other hand has anti-inflammatory effects.

Another adverse effect of hyperglycaemia is on the innate immune system. Hyperglycaemia impairs the ability of the host to combat infection, through several mechanisms. Many studies have reported lower chemotaxis of neutrophils in hyperglycaemia condition (Delamaire et al., 1997, Mowat and Baum, 1971). One of the most informative studies on this matter was done by Wierusz-Wysocka et al. They clearly demonstrated a significant reduction in chemotactic migration with increasing glucose concentration up to 300 mg/dL in non-diabetic volunteers (Wierusz-Wysocka et al., 1988).

In hyperglycaemic state, for example in poorly controlled diabetes, phagocytosis has been considered to be negatively influenced by increased blood glucose level

(Turina et al., 2005). In diabetic patients, direct correlation has been observed between either blood glucose levels or the glycosylated plasma proteins (HbA_{1c}) and the polymorphonuclear cell's phagocytic capacity (Alexiewicz et al., 1995, Marhoffer et al., 1992).

Studies have shown that high blood glucose level inhibits the formation of radical oxygen species (ROS) (Dhindsa et al., 2004, Ortmeyer and Mohsenin, 1996, Perner et al., 2003). ROS is a group of reactive substances containing an oxygen molecule with an unpaired electron like superoxide (O_2^-) and hydroxyl radical (OH^-). These toxics neutrophil components are responsible for the disruption of the ingested cellular material (Forman and Torres, 2002). Furthermore, study by Ortmeyer and Mohsenin when cells were placed back into normoglycemic media, physiologic ROS production levels return to normal, confirming the reversible nature of this effect (Ortmeyer and Mohsenin, 1996).

Experiments conducted in peritoneal dialysis groups demonstrated that accelerated induction of apoptosis in neutrophils with exposure to glucose-rich media. Generally apoptosis provides a delicate balance between the aggressive biological behaviour and the safe turnover of potentially harmful immune cells (Turina et al., 2005).

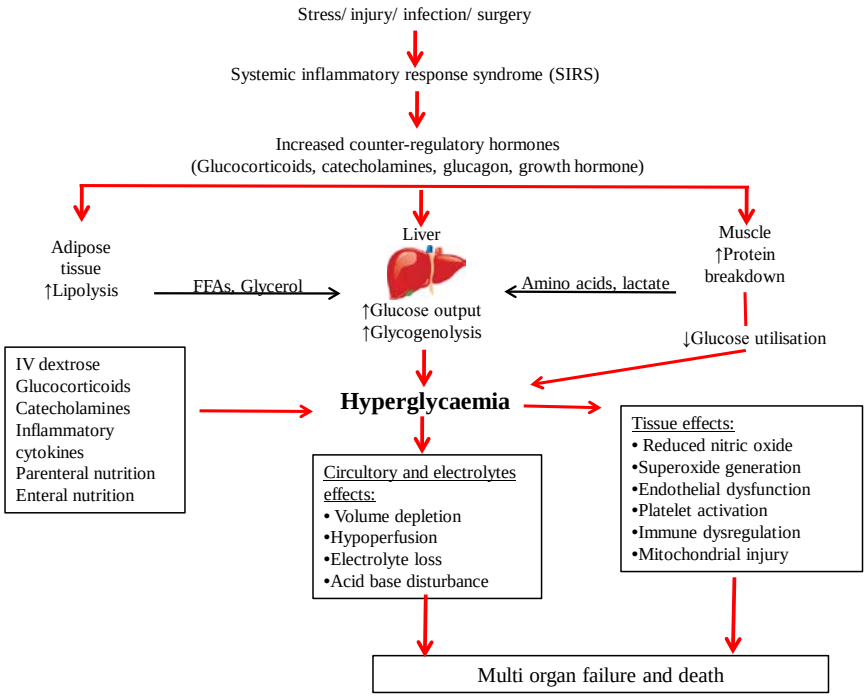

Figure 2: Summary of the pathogenesis and effects of stress hyperglycaemia. Adapted from (Farrokhi et al., 2011).

2.3 Hyperglycaemia as prognostic factor in patients with critical illness

Several studies have documented that hyperglycaemia affects outcomes in patients with various clinical conditions requiring intensive care, such as myocardial infarction, cerebrovascular disorders or traumatic brain injury. The plasma glucose level on admission has been shown to be an independent predictor of prognosis after myocardial infarction (Stranders et al., 2004, Suleiman et al., 2005). The presence of hyperglycaemia following an ischemic and hemorrhagic stroke is associated with a two to threefold increased mortality and significant impairment in functional recovery (Capes et al., 2001).

2.3.1 Hyperglycaemia in myocardial infarction

Stranders et al (2004), documented that an increase of 18 mg/dL (1 mmol/L) in admission blood glucose level in previously non-diabetic subjects post-myocardial infarction was associated with an increase in mortality risk of 3% in univarate analysis and 4% in adjusted analysis (Stranders et al., 2004). This was 6% and 5% respectively in diabetic patients. They also reported long term prognosis for previously non-diabetic patients with admission blood glucose of more than 200mg/dL (11.0 mmol/L) significantly worse than patients with lesser blood glucose level. This was comparable to that of patients with previously known diabetes. Mortality rates in previously non-diabetic patients and diabetic patients with such blood glucose level were 42.6% and 43.1% respectively.

Another study by Suleiman et al (2004) on glucose level in non-diabetic patients with acute myocardial infarction, concluded that both fasting and admission glucose levels have relation with 30-day mortality with fasting glucose (FG) is superior to admission glucose (AG) in the assessment of short term risk (Suleiman et al., 2005). Compared with patients with normal FG and AG, the adjusted ORs for 30-days mortality were 0.71 in patients with elevated AG and normal FG (95% CI, 0.15 to 3.4; P= 0.67), 3.4 for patients with normal AG and elevated FG (95% CI, 1.1 to 10.4; P= 0.03), and 9.6 for patients with both elevated FG and AG (95% CL, 3.5 to 26.0; P < 0.0001).

2.3.2 Hyperglycaemia in stroke

The association between blood glucose level and stroke has been summarised by Capes et al (2000) in their meta-analysis study. After stroke of either subtype ischemic

or hemorrhagic, the unadjusted relative risk of in-hospital or 30-day mortality associated with admission glucose level > 6 to 8 mmol/L (108 to 144 mg/dL) was 3.07 (95% CI, 2.50 to 3.79) in non-diabetic patients and 1.30 (95% CI, 0.49 to 3.43) in diabetic patients (Capes et al., 2000). After ischemic stroke, admission glucose level > 6.1 to 7.0 mmol/L (110 to 126 mg/dL) was associated with increased risk of in-hospital or 30-day mortality in non-diabetic patients only (relative risk= 3.28; 95% CI, 2.32 to 4.64). After hemorrhagic stroke, admission hyperglycaemia was not associated with higher mortality in either diabetic or non-diabetic patients. Non-diabetic stroke survivors whose admission glucose level was >6.7 to 8 mmol/L (121 to 144 mg/dL) also had a greater risk of poor functional recovery (relative risk 1.41; 95% CI, 1.16 to 1.73).

2.3.3 Hyperglycaemia in trauma

Hyperglycaemia is also noted after injury in both diabetes and non-diabetes, and the severity of injury seems to correlate with the level of hyperglycaemia. Study by Laird et al (2004) shows that blood glucose level $\geq$ 200mg/dL is associated with significantly higher infection and mortality rate in severely injured patients independent of injury characteristics (Laird et al., 2004).

Other study by Yendamuri et al (2003) documented that the hyperglycaemia independently predicts increased intensive care unit and hospital length of stay and mortality in the trauma population even at lower level of hyperglycaemia (Yendamuri et al., 2003). Similar with the previous studies they also confirmed the association of hyperglycaemia with infection morbidity. Patients with mild hyperglycaemia (> 135mg/dL or > 7.5 mmol/L) had increased mortality rate compared with patients with normal admission glucose concentrations (15.5% vs. 2.0%, $p < 0.01$); while patients

with moderate hyperglycaemia (> 200mg/dL or > 11.1 mmol/L) had even greater mortality rate compared with corresponding normoglycaemic patients (34.1% vs. 3.7%, $p < 0.01$).

2.3.4 Hyperglycaemia in burn

The effects of hyperglycaemia in severely burn patients shown a significant correlation with greater incidence of positive blood culture and less percentage of skin-graft taken in the hyperglycaemic patients compared with the normoglycaemic group (Gore et al., 2001). Higher percentage of mortality in the hyperglycaemic group was also observed (27% vs. 4%, $p \leq 0.05$).

2.3.5 Hyperglycaemia in general illness

Meanwhile for a more heterogeneous population, stress hyperglycaemia is also associated with increased mortality, prolonged hospital stay and higher rate of admission to ICU in patients that were admitted to general wards (Umpierrez et al., 2002). In this particular study patients with new hyperglycaemia had 16% mortality compared to patients with history of diabetes mellitus (3%) and normoglycaemia (1.7%; both p-value < 0.01). Meanwhile for ICU admission new hyperglycaemia had 29% admission compared with known diabetes 14% and normoglyceamia 9% (p-value < 0.001 vs. known diabetes and < 0.01 vs. normoglyceamia). New hyperglycaemia had mean of 9.0 ± 0.7 days stay in hospital, known diabetes had 5.5 ± 0.2 days and normoglycaemia 4.5 ± 0.1 (both p-value < 0.001).

2.4 Hyperglycaemia in sepsis

Hyperglycaemia has also been indicated to have deleterious effects on patients with sepsis. Compare with other critical illness, not much data available regarding prevalence of hyperglycaemia in sepsis and their association in mortality or prognostic value in patient outcome. A study in Thailand by Rattanaweeboon et al. (2009) has shown that stress hyperglycaemia in non-diabetic patients with sepsis was high, (n=70, 42.3%). In this study, stress hyperglycaemia was defined as fasting plasma glucose of more than 100mg /dL (5.5 mmol/L) or random plasma glucose level of more than 140 mg/dL (7.8 mmol/L) (Rattanataweeboon et al., 2009). They concluded that even though the prevalence of stress hyperglycaemia among septic patient is high, they did not find significant association between stress hyperglycaemia and mortality outcome.

The authors of the study attributed the small sample size and less severe hyperglycaemic cut-off value for their non significant correlation of hyperglycaemia and mortality outcome findings. Their sample of patients included all sepsis patients and only half of them were severe sepsis or septic shock patient. This also may affect their outcome as the degree of hyperglycaemia may be a marker of more severe illness (Egi et al., 2008, Laird et al., 2004, Stranders et al., 2004).

A study by Leonidou et al, reported that stress hyperglycaemia had higher percentages of mortality in severe sepsis compared with patients with normal glucose levels (42.5% vs. 13.7%) and known diabetes patients (42.5% vs. 24.6%). They also demonstrated that the non-survivors among the stress hyperglycaemia group had significantly higher level of fasting blood glucose (182.4 mg/dL vs. 141.3 mg/dL, p-value < 0.05) and glucose at admission (224.0 mg/dL vs. 181.4 mg/dL, p-value < 0.05) than the survivors. No significant differences in blood glucose levels were found

between the survivor and non-survivor in the normal glycaemia and diabetes mellitus groups. Even though they concluded that hyperglycaemia is a common finding in severe sepsis (42.2%), they were unable to clearly demonstrate whether hyperglycaemia itself is a cause of increased mortality or just a marker of increased risk of mortality (Leonidou et al., 2008).

On the other hand among paediatrics septic shock patients, there was correlation between blood sugar level and mortality rate. Study by Branco et al. (2005) found that in non-survivors, the peak glucose level was 262 ± 110 mg/dL, which was higher ($p <$ .01) than that found in survivors (167.8 ± 55 mg/dL). The best peak glucose level for predicting death in children with sepsis was 178 mg/dL (sensitivity, 0.714; specificity, 0.724), and the relative risk of death in patients with peak glucose levels of ≥178 mg/dL was 2.59 (range, 1.37-4.88) (Branco et al., 2005).

Studies have confirmed the prognostic value of blood glucose level in many critical illnesses such as trauma, stroke and myocardial infarction, but in sepsis this is not entirely explored and investigated. Hence this current study aimed to determine the correlation between blood sugar level in predicting the outcome of severe sepsis and septic shock patients, and subsequently to seek whether blood sugar level can be a reliable prognostic tool in determining the outcome of such patients in emergency department.

3.0 RESEARCH HYPOTHESIS AND OBJECTIVES

3.1 Research hypothesis

Hyperglycemia has a predictive outcome of mortality and morbidity in severe sepsis and septic shock patients in Emergency Department

3.2 General research objective

To investigate whether, hyperglycemia detected during patient initial presentation to Emergency Department has a prognostic value in the outcome of severe sepsis and septic shock patients.

3.3 Specific research objective

1. To determine the prevalence of hyperglycemia in severe sepsis and septic shock patients presented to Emergency Department.
2. To study the demographic characteristics of severe sepsis and septic shock patients presented to Emergency Department.
3. To determine the association between hyperglycemia detected during the initial blood glucose measurement and the outcome of severe sepsis and septic shock patients in Emergency Department in term of mortality and length of hospital stay.
4. To compare hyperglycemia during initial blood glucose with other prognostic variables in predicting the outcome of severe sepsis and septic shock patients.

4.0 OPERATIONAL DEFINITION

1. Infective state:

Patient presents to ED with complain of infection symptoms in any form. Vital sign at triage such as temperature, blood pressure, pulse rate or SpO_2 were used to screen patients for recruitment.

2. Triage:

A process for sorting injured people into groups based on their need for or likely benefit from immediate medical treatment. Triage is used on the battlefield, at disaster sites, and in hospital emergency rooms when limited medical resources must be allocated. Malaysia triage system is a three-tier system where the cases are categorized by acuity. The three zones are red, yellow and green.

Malaysia Triage Category:

Triage category	Response	Description of category
Red zone (critical cases)	Assessment and treatment immediately (assessment and treatment often simultaneous)	Condition that are threats to life or imminent risk of deterioration and require immediate aggressive intervention OR The patient's condition is serious enough or deteriorating is rapidly that there is the potential of threat to life, or organ system failure if not treated within 15 minutes of arrival OR

		The potential for time critical treatment (e.g. thrombolysis, antidote) to make a significant effect on clinical outcome depends on treatment commencing within a few minutes of the patient's arrival in the ED
Yellow zone (semi- critical cases)	Assessment and treatment start within 30 minutes	The patient's condition may progress to life or limb threatening, or may lead to significant morbidity, if assessment and treatment are not commenced within 30 minutes of arrival OR There is potential for adverse outcome if time critical treatment is not commenced with 30 minutes OR Humane practice mandates the relief of severe discomfort or distress
Green zone (non-critical cases)	Assessment and treatment start within 90 minutes	The patient's condition may deteriorates, or adverse outcome may results, if assessment and treatment is not commenced with 1 hour of arrival in ED. Symptoms moderate or problem OR There is potential for adverse outcome if time-critical treatment is not commenced within hour OR Likely to require complex work up and consultation and/or in-patient management OR