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The role of corticosteroids in the early management of sepsis in the

Lebanese population

By

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DEDICATION

I dedicate this thesis to almighty ALLAH who provided me with the strength without which I would have never been able to finish this work, and who guided my way throughout this project and all along my life.

I also dedicate this thesis to my loving parents, Nada and Fawaz. My beloved mother who devoted all her life to me and my siblings, always had high expectations of me and continuously encouraged, supported and prayed for me. And my beloved father who always believed that I was special and helped me fight for my dreams no matter how difficult they were to attain.

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The Role Of Corticosteroids In The Early Management Of Sepsis In The Lebanese Population

Rayan Fawaz EL-Ratel

ABSTRACT

The use of corticosteroids in the management of sepsis has been quite controversial. This thesis was motivated by a pursuit to gain a better understanding about the safety and efficacy of using corticosteroids in sepsis. In order to achieve our objective, this thesis will capitalize on an intervention that has been previously implemented in a private hospital in Lebanon. The intervention entailed adding corticosteroids to the management protocol of a group of septic patients. Also to better understand the importance of this intervention, this thesis will specifically compare clinical outcomes of the group of patients who received the intervention (which took place between February 2018 and April 2019), to another group of septic patients admitted prior to the implementation of the intervention (patients admitted between January 2016 and February 2018).

This study is in no way an interventional study, it will build on and analyze a previously conducted intervention in a retrospective manner.

Keywords: Sepsis, septic shock, Intensive care unit, corticosteroids

TABLE OF CONTENTS

Chapter   **Page**

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AMA: American Medical Association

BMJ: British medical journal

CLRs: C-type lectin receptors

CS: corticosteroid

DAMPs: damage-associated molecular patterns

Diabetes Mellitus: DM

DIC: disseminated intravascular coagulation

ED: emergency departments

ESICM: European Society of Intensive Care Medicine

GCS: Glasgow Coma Scale

ICU: intensive care unit

IL: interleukin

LODS: Logistic Organ Dysfunction System LPS: lipopolysaccharide

MAP: Mean Arterial Pressure

NLRs: NOD-like receptors,

PAMPs: pathogen-associated molecular patterns

PRRs: pattern recognition receptors

qSOFA: quick Sequential Organ Failure Assessment

SCCM: Society of Critical Care Medicine

SIRS: Systemic inflammatory response syndrome

SOFA: Sequential Organ Failure Assessment score

TLRS: Toll-Like Receptors

TNF: Tumor Necrosis

Chapter One

Introduction

1.1 Background

Sepsis, derived originally from the Greek word "Sepo", means the decomposition of animal- or plant-based organic materials by bacteria (Fethi Gül et al., 2017). It has been recently defined by the American Medical Association (AMA), as "a life-threatening organ dysfunction caused by a dysregulated host response to infection" (Singer et al., 2016, p. 804).

Sepsis can evolve into septic shock when it is accompanied by persistent hypotension and/or need for vasopressors despite adequate fluid resuscitation (Hotchkiss et al., 2016).

Much effort has been put to establish consensus about the definition of sepsis and septic shock and many papers have been published for this purpose. Most clinical practitioners believe that there is no agreement on the definition of sepsis in clinical practice (Fethi Gül et al., 2017).

"Sepsis-1" and "Sepsis-2" are older definitions of sepsis yet they have several deficiencies

(Singer et al., 2016). "Sepsis-1" defined and diagnosed as any infection accompanied by systemic inflammation (proven by the presence of at least 2 of systemic inflammatory response syndrome (SIRS) criteria) to be sepsis (Simpson, 2018). This definition is deficient because not all infections accompanied by a systemic inflammatory reaction are to be diagnosed as sepsis (Simpson, 2018). "Sepsis-2" definition maintained the previous diagnostic criteria but defined sepsis as a clinical syndrome combined with organ injury (Fethi Gül et al., 2017). This created mismatching between the new definition of sepsis and the preserved diagnostic criteria which revolve around inflammation (and not organ failure or damage), making it necessary to develop a new definition (Fethi Gül et al., 2017). "Sepsis-3" definition established by The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) is the most recent definition of sepsis. It aimed to provide a better reflection of the current understanding of sepsis pathophysiology (Sartelli et al., 2018).

In this thesis, we will be using the clinical definition of sepsis provided by Sepsis-3 where it is defined as, "a life-threatening organ dysfunction caused by a dysregulated host response to infection." and septic shock as "Sepsis with persisting hypotension requiring vasopressors to maintain MAP (Mean Arterial Pressure) $\geq$ 65 mm Hg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation." (Fethi Gül et al., 2017). For the clinical aspect, sepsis can be identified by a Sequential Organ Failure Assessment (SOFA) score of two or more along with a dysregulated host response to an infection (Singer et al., 2016).

Sepsis has a significant epidemiological burden worldwide (Hajj et al., 2018). Globally, the frequency of sepsis as estimated by Surviving Sepsis Campaign in 2002, is 18 million cases annually (Jaimes, 2005). The estimation of sepsis frequency however is subject to several weaknesses such as low diagnostic rate and difficulties in tracking sepsis in many countries (Slade et al., 2003). Moreover, it has been conveyed that the reported rates of sepsis currently depend on different definitions or on different hospital disease identification or billing codes (Vincent, 2016). Therefore, defining and diagnosing sepsis remain factors that affect the estimation of sepsis (Vincent, 2016).

Regarding the etiology of sepsis, respiratory infections are the most common causes of sepsis and septic shock (around 50% of all cases) and genitourinary and abdominal infections come thereafter (Martin, 2012). Sepsis was originally considered to be caused mainly by Gram-negative bacteria because earlier studies established such an association however it has been later revealed that the most common causative pathogens in sepsis are Gram-positive bacteria (Ramachandran, 2015; Martin et al., 2003). Among the most frequently isolated bacteria in sepsis are *Staphylococcus aureus* (S. aureus), *Streptococcus pyogenes* (S. pyogenes*), Klebsiella spp., Escherichia coli* (E. coli), and *Pseudomonas aeruginosa* (P. aureginosa).

The pathophysiology of sepsis is primarily based on the activation of the innate immune response, mainly of macrophages (Ortiz-Ruiz and Dueñas-Castell, 2018, para. 6). Macrophages recognize pathogen-associated molecular patterns (such as lipopolysaccharide "LPS") or damage-associated molecular patterns (such as DNA) and bind to them through pattern-recognition receptors, Toll-like receptor 4 (TLR-4) for instance (Mogensen, 2009; Ortiz-Ruiz and Dueñas-Castell, 2018, para. 6). This will result

in the activation of macrophages and release of cytokines which are key factors in the pro-inflammatory response (Goulopoulou et al., 2016; Ortiz-Ruiz and Dueñas-Castell, 2018, para. 6). The pro-inflammatory response generated is of major importance in pathogen elimination however it can result in organ damage (Ortiz-Ruiz and Dueñas-Castell, 2018, para. 6).

As the pro-inflammatory response begins massive amounts of cytokines (such as IL-1, Il-6, IL-8, TNF-α, etc.) are released (Ortiz-Ruiz and Dueñas-Castell, 2018, para. 6). These cytokines activate and recruit additional pro-inflammatory cells like monocytes and neutrophils to the affected area (Kany et al., 2019; Ortiz-Ruiz and Dueñas-Castell, 2018, para. 6). TNF-α is one of the most important cytokines released as it may play a pivotal role in multiple organ failure (Aikawa, 1996; Ortiz-Ruiz and Dueñas-Castell, 2018, para. 6). Other factors involved in the pro-inflammatory response such as acute-phase reactants and C5a, can activate the coagulation cascade which results in a range of clinical manifestations such as: hypercoagulability Disseminated Intravascular Coagulation (DIC) (Ortiz-Ruiz and Dueñas-Castell, 2018, para. 6).

Among the risk factors which may predispose patients to develop sepsis, are: patients staying for longer periods in ICUs, the increasing elderly population, immune suppression resulting from malignant diseases and their invasive treatment, increasing transplantation practices and the use of related immunosuppressive drugs, respiratory diseases and pneumonia, antibiotic resistance and nosocomial infections (Martin et al., 2003; Kang et al., 2011).

Treatment protocols often recommend the use of broad-spectrum antibiotics even before the acquisition of blood cultures (Dolin et al. 2019). Additional supportive treatment such

as vasoactive drugs and mechanical ventilation may be provided as needed (Lamontagne, 2018). Treatment is then tailored and adjusted based on clinical signs and laboratory data (Lamontagne, 2018).

Intravenous corticosteroids are a component in the management of sepsis, however their use has been subject to many controversies (Yao et al., 2019). Corticosteroids can attenuate these cytokines which are released in sepsis, suggesting a plausible role for corticosteroid use in sepsis management (Long and Koyfman, 2017).

It is possible that corticosteroids can help ameliorate the dysregulated inflammatory immune response caused by sepsis (Franchimont et al., 2002) and exacerbate hypotension (Hylands et al., 2017). Some clinicians believe that this biological rationale is convincing, while others disagree and do not recommend the use of corticosteroids (Lamontagne, 2018).

Currently most guidelines recommend the administration of systemic corticosteroids only if sepsis progresses into refractory shock (Lamontagne, 2018) defined as the presence of hypotension, with end-organ dysfunction, requiring high-dose vasopressor support often greater than 0.5 µg/kg/min norepinephrine or equivalent (Nandhabalan et al., 2018). These guidelines however have not considered the new emerging evidence (Lamontagne, 2018).

Corticosteroids (CS) have demonstrated a decrease in 28-day mortality in at least 27 studies (Annane et al., 2015). Despite the fact that the decrease in mortality may be as small as 2%, members of the BMJ Rapid Recommendation panel guideline believe that most patients want to avoid death and will value even a small, uncertain decrease in mortality (Lamontagne, 2018).

The optimal corticosteroid dosing regimen (drug, dose, and duration of treatment) remains uncertain (Rochwerg et al., 2017). Hydrocortisone was the most commonly used corticosteroid in the randomized controlled trials evaluating CS use in sepsis and septic shock (Lian et al., 2019). Less commonly studied CS's in the context of sepsis and septic shock were dexamethasone, methylprednisolone, and prednisolone (Lamontagne, 2018).

Very few studies provided in-depth analysis of sepsis in Lebanon (Abou Dagher, 2015). Overall mortality rate of sepsis and septic shock in Lebanon has been reported by a study to be 30.9% and the 28-day mortality to be 20.6% (Chehade et al., 2015). The same study reported that the most common sources of infection in Lebanese septic patients are genitourinary (40.2 %) followed by pulmonary (19.6 %), then integumentary (10.3 %), and that Gram-negative bacteria, specifically *Escherichia coli* are the causative agents for most sepsis cases (Chehade et al., 2015).

1.2 Significance of this Research

This study is NOT an interventional study. This study will evaluate a small-size intervention that has been performed between February 2018 and April 2019 in a private hospital in the North of Lebanon. The intervention entailed treating older septic patients with corticosteroids early on and before developing shock.

Data about sepsis in older patients is scarce in developing countries, especially in Lebanon. To our knowledge, no similar study has been conducted in Lebanon before.

1.3 Targeted participant population and justification

Our target population is older septic patients (older adults and elderly), who were subject to an intervention (which took place between February 2018 and April 2019) and those who have been admitted before the intervention started (i.e. patients admitted between January 2016 and February 2018). Older septic patients and elderly septic patients are patients aged above 55 years.

1.4 Study impact

This study will have no direct benefit to the patients since it has a retrospective design. However, this study will shed light on the role of corticosteroids in the early management of Sepsis in older patients. This will promote a better understanding on their role in treating sepsis and hence potentially result in better management of sepsis.

1.5 Study objectives

1.5.1 Primary objective

The primary objective of this thesis is to evaluate the impact of an intervention (that took place between February 2018 and April 2019) where corticosteroids have been administered to a small group of septic patients **on their mortality rates (7- and 28- day mortality rates).** This thesis will also compare the mortality rate of these patients (post-intervention group) to septic patients admitted before the intervention took place (in the period between January 2016 and February 2018) and have not received corticosteroids (pre-intervention group).

1.5.2 Secondary objective

The secondary objective of this thesis is to evaluate the impact of the aforementioned intervention (that took place between February 2018 and April 2019) on other clinical outcomes (related to respiratory function, coagulation status, renal function, hepatic function, cardiovascular system and central nervous system) in those patients who received the intervention). This thesis will then compare the clinical outcomes in this group of patients (post-intervention group) to septic patients admitted before the intervention took place (January 2016 – February 2018) and have not received corticosteroids (pre-intervention group).

1.6 Hypothesis

- Early management of sepsis with Dexamethasone can decrease 7- and 28- day mortality rates.
- Early management of Sepsis with Dexamethasone can improve other clinical outcomes in septic patients.

1.7 Project timeline

Table 1: Timeline of the project

Time	Action
June, 20	Submission of research protocol to IRB
June, 25	Proposal Defense
June, 30	Submission of letter to the hospital for approval
July, 1 until July 14	Retrieving and Collecting Data
July, 14 until July 20	Results synthesis and Analysis
July, 22	Thesis defense

Chapter Two

Variation of Sepsis Definition

The definition of sepsis is a problematic due to the heterogeneity and complexity of the disease process (Gyawali et al., 2019; Fethi Gül et al., 2017). Initial definitions of sepsis, established by the international consensus conference in 1991, defined sepsis as systemic inflammatory response Syndrome (SIRS) combined with infection (Fethi Gül et al., 2017). Sepsis has been recently re-defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Bullock and Benham, 2019). The recent definition describes organ dysfunction as an acute increase in total Sequential Organ Failure Assessment score (SOFA score) two points or more after an infection (Tridente, 2018). A new bedside index, called the qSOFA was also introduced by the Sepsis-3 Task Force, to recognize patients with suspected infection who are likely to develop sepsis outside of critical care units (Sartelli et al., 2018). The Recently updated definition provided by the consensus improved specificity compared with the previous descriptions (Fethi Gül et al., 2017).

Most physicians do not agree on a single definition of sepsis which may influence their ability to diagnose and communicate about sepsis (Poeze et al., 2004). As there is no gold standard for defining sepsis, three international consensus conferences using expert

opinions were held in 1991, 2001 and 2016 to generate the current definitions (Lemachatti, 2017).

2.1 Sepsis-1

Sepsis was defined as the existence of two or more Systemic inflammatory response syndrome (SIRS) criteria (Table 2), in addition to known or suspected infection whereas severe sepsis was defined as clinical sepsis accompanied by organ dysfunction, hypoperfusion or hypotension (Berg, 2018). This definition was deficient because Systemic inflammatory response syndrome findings are rather sensitive, and under stressful conditions in which tachycardia, hyperventilation and leukocytosis are observed, these criteria may result in wrong diagnosis with sepsis (Kaukonen et al., 2015). Another deficiency in this definition is that it is based on the presence of inflammation (Fethi Gül et al., 2017). Inflammation is non-specific and may manifest in many conditions from mild trauma to severe autoimmune disease, therefore it carries little meaning (Vincent JL, 1997).

Table 2: Criteria of Systemic inflammatory response syndrome (SIRS)

Systemic Inflammatory Response Syndrome
Temperature >38.3°C, or <36°C
Heart Rate >90 bmp
Respiratory rate >20 breaths/min
White cell count <4 or >12 g/L
Blood glucose >7.7 mmol/L not diabetic
New altered mental state

Source: McClelland, H., & Moxon, A. (2014). Early identification and treatment of sepsis. Nursing Times, 110(4), 14-

2.2 Sepsis-2

In 2001, the second international consensus conference was held (Balk, 2014). The conference changed the definition of sepsis where it was described as a clinical syndrome combined with organ injury, however it maintained the list of diagnostic criteria from Sepsis-1 (Fethi Gül et al., 2017). The gap between the new definition which included organ injury and the unchanged list of diagnostic criteria, resulted in confusion related to sepsis diagnosis (Fethi Gül et al., 2017).

2.3 Sepsis-3

After recognizing the need to reexamine the previous definitions of sepsis, the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) organized the third consensus meeting and published their report in 2016 (Singer et al., 2016). The third consensus report defines sepsis as a 'life-threatening organ dysfunction caused by a dysregulated host response to infection' and septic shock as "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality" (Singer et al., 2017).

The 2016 SCCM/ESICM meeting compared the SIRS criteria used in the previous definitions to a new suggested scoring system which is the Sequential Organ Failure Assessment (SOFA) (Marik and Taeb, 2017). The authors concluded that SOFA has a superior predictive validity for in-hospital mortality over SIRS and accordingly recommended its use to assess the severity of organ dysfunction in potentially septic patients (Marik and Taeb, 2017; Seymour et al., 2016). Although SOFA may have

comparable predictive capacity as Logistic Organ Dysfunction System (LODS) (another previously established scoring system for sepsis), the task force considered SOFA to be easier to calculate and therefore recommended its use in diagnosing sepsis (Singer et al., 2016; Seymour et al., 2016). SOFA is used to determine the extent of sepsis-related organ dysfunction and to assess the level of dysfunction in five systems: respiratory, cardiovascular, coagulation, renal and neurologic (De Freitas et al., 2014; Fethi Gül et al., 2017).

The consensus also introduced the rapid bedside quick SOFA tool (qSOFA) to identify patients at emergency departments (ED) who are likely to develop sepsis (Fethi Gül et al., 2017). The qSOFA score is not a part of the new definition of sepsis, rather, it can be regarded as a bedside tool to be used instead of SIRS to detect sepsis in the ED (Van der Woude et al., 2018).
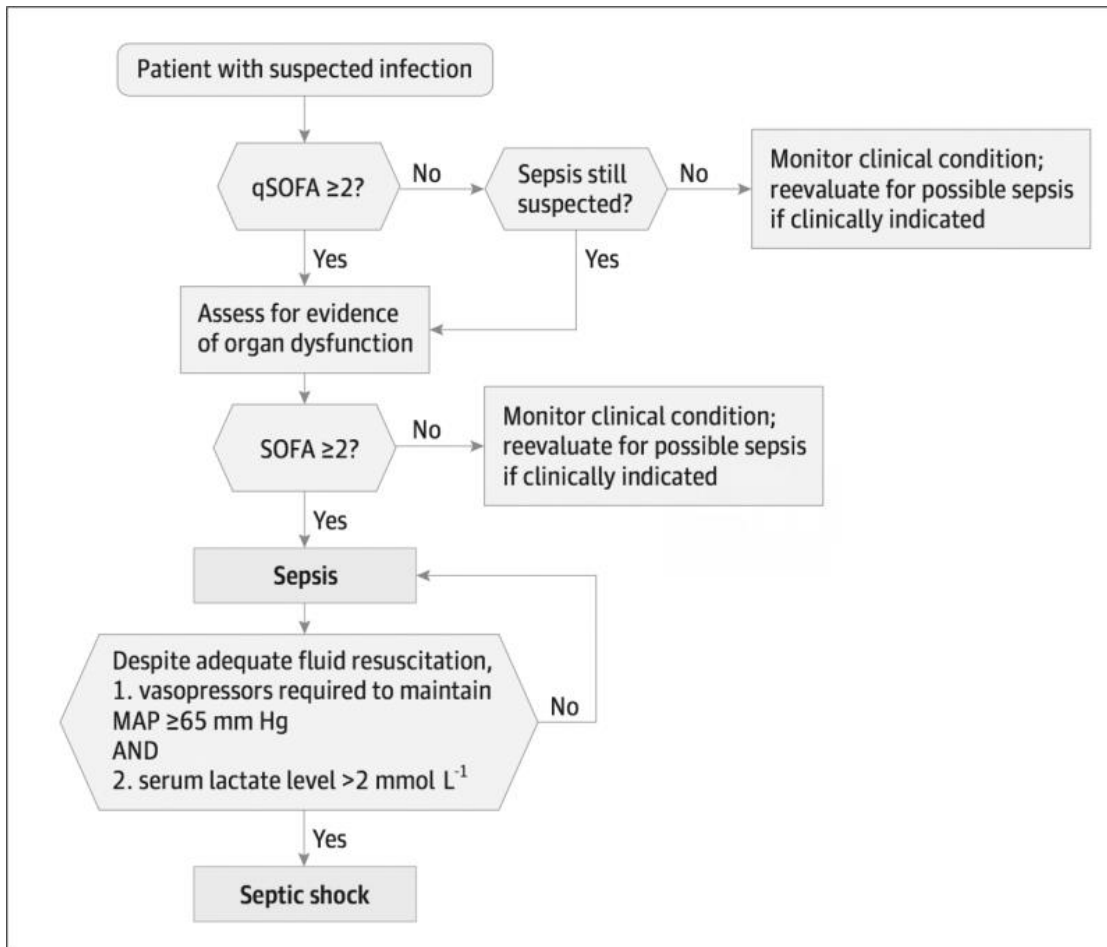
Figure 1: Operationalization of Clinical Criteria Recognizing Patients with Sepsis and Septic Shock

Despite the efforts the task force put to better reflect the current understanding of sepsis pathophysiology through Sepsis-3 definition of sepsis (Fethi Gül et al., 2017), the new definition had its own weaknesses (Sinha and Ray, 2018).

Sepsis-3 definition requires patients to have organ dysfunction to be diagnosed with sepsis, which may hinder early recognition and treatment of infections before organ dysfunction appears (Sartelli et al., 2018). Moreover, the new definition does not utilize lactate as a marker of organ dysfunction (Besen et al., 2016), though it is well documented to be a

sensitive marker of sepsis severity (Kushimoto et al., 2016). Hyperlactatemia is however required to diagnose septic shock, based on the new definition (Lee and An, 2016). Therefore, if lactate levels are not available, the diagnosis of septic shock can be difficult and patients having septic shock will be considered as having only sepsis (Sartelli et al., 2018). Other shortcomings of this definition may be missing on the pediatric population as it does not have data from this population (Abraham et al., 2016). Moreover, the new definition did not run sub-group analysis (covering developing countries for example) and was based solely on Databases from American hospitals (Fethi Gül et al., 2017).

Table 3: The sequential Organ Failure Assessment score

The Sequential Organ Failure Assessment (SOFA) score

SOFA score	1	2	3	4
Respiration			-----with respiratory support-----	
PaO_2/FiO_2 (mm Hg)	<400	<300	<200	<100
Coagulation				
Platelets $\times 10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin (mg dL^{-1})	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular				
Hypotension	MAP <70	Dopamine ≤5 or dobutamine (any)	Dopamine >5 or norepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
Central Nervous System				
Glasgow Coma Score	13–14	10–12	6–9	<6
Renal				
Creatinine (mg dL^{-1}) or urine output (mL)	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200

MAP: mean arterial pressure; vasoactive mediations administered for at least 1 hr (dopamine and norepinephrine µg kg^{-1} min^{-1}).

Source: Gül, F., Arslantaş, M. K., Cinel, İ., & Kumar, A. (2017). Changing definitions of sepsis. Turkish journal of anaesthesiology and reanimation, 45(3), 129.

Chapter Three

Pathophysiology

The immune response is composed of two components: innate and adaptive immunity (Ding et al., 2018). The acute inflammatory response is mostly associated with innate immunity which includes neutrophils and macrophages, while secondary infection is associated with the adaptive immunity, which includes T-cells, B-cell, and dendritic cells (Ding et al., 2018).

The activation of innate immunity involves pattern recognition receptors (PRRs) that recognize antigens (pathogen-associated molecular patterns [PAMPs]) and biomolecules from damaged tissues (damage-associated molecular patterns [DAMPs]) (Jang, 2015). PRRs include toll-like receptors (TLRs), nucleotide-binding oligomerization domain-(NOD-) like receptors (NLRs), and C-type lectin receptors (CLRs) (Jang, 2015).

Sepsis pathogenesis significantly relies on the activation of the innate immune response (Kendrick and Jones, 2008). During sepsis, the activation of innate immune system by PAMPs and DAMPs results in process known as the "cytokine storm", i.e. the release of multiple inflammatory cytokines, which causes a severe and persistent inflammatory response (Rittirsch, 2008). The exaggerated inflammatory response leads to cell and tissue

damage that initiate organ dysfunction and eventually result in multiple organ failure (Ding et al., 2018).

Toll-like receptor 4 (TLR4) plays a critical role in the sepsis model as it promotes organ damage (Deng et al., 2013). TLR4 is a trans-membrane protein with extracellular segments that are rich in leucine repeats forming a horseshoe-like shape (Gay and Gangloff, 2007). Toll-Like receptors recognize PAMPs on bacteria, fungi, and viruses (Kim et al. 2007). The activation of TLR4 is aimed at clearing a potential infection, however, the consequence may be organ dysfunction as the immune response can cause collateral damage to host tissue (Anderberg et al., 2017). TLR4 is expressed on immune cells and renal tubule epithelium, glomerular, and vascular epithelial cells (Li et al., 2019). It has been well studied that the activation pathway of TLR4 in response to infection contributes to acute kidney injury (AKI) (Anderberg et al., 2017). In addition, TLR4 activation is associated with left ventricular dysfunction and myocardial ischemia (Schilling et al., 2011; Fallach et al., 2010).

Chapter Four

Epidemiology of Sepsis

The epidemiology of sepsis varies widely between countries due to the way sepsis is identified and to the regions where it is studied (Mariansdatter et al., 2016). Some of the best information is provided by the Sepsis Occurrence in Acutely ill Patients (SOAP) database (which included 198 Intensive care units in 24 European countries, n=3,147) which reported that rate of occurrence of sepsis among ICU patients ranged from 18% (Switzerland, n=114) to 73% (Portugal, n= 69) and that of severe sepsis from 10% (Switzerland, n=114) to 64% (Portugal, n=69) (Vincent et al., 2006; Vincent et al., 2008).

Table 4: Number of patients, frequency of sepsis, and intensive care unit (ICU) and hospital mortality rates according to country (sorted alphabetically)

Country	No. of Centers	No. of Patients (%)	ICU Mortality, n (%)[a]	Hospital Mortality, n (%)[a]	Frequency, n (%)	SAPS II Score, Mean ± SD	ICU Mortality, n (%)[a]	Hospital Mortality, n (%)[a]	Severe Sepsis, n (%)
					Characteristics of Sepsis Patients (n = 1177)				
Austria	8	68 (2)	14 (21)	16 (24)[b]	26 (38)	42.5 ± 17.2	6 (23)	8 (31)	18 (27)
Belgium	19	703 (22)	86 (12)	120 (17)	188 (27)	38.7 ± 15.0	39 (21)	57 (31)[c]	125 (18)
Eastern Europe[d]	15	174 (6)	41 (24)	53 (31)[b]	83 (48)	40.2 ± 15.0	24 (29)	31 (37)	74 (43)
France	21	332 (11)	63 (19)	70 (21)	136 (41)	43.4 ± 18.0	37 (27)	44 (32)	99 (30)
Germany	21	329 (11)	39 (12)	51 (16)[e]	102 (31)	41.6 ± 15.8	16 (16)	20 (20)	78 (24)
Greece	10	109 (4)	18 (17)	23 (21)	47 (43)	47.1 ± 20.2	14 (30)	16 (34)	41 (38)
Italy	24	237 (8)	61 (26)	73 (31)[e]	89 (38)	43.4 ± 15.3	31 (35)	39 (45)[c]	75 (32)
Netherlands	7	144 (5)	33 (23)	43 (31)	56 (39)	43.8 ± 16.8	18 (32)	25 (47)[c]	49 (34)
Portugal	6	69 (2)	24 (35)	28 (41)	50 (73)	46.2 ± 14.8	16 (32)	19 (38)	44 (64)
Scandinavia[f]	16	209 (7)	29 (14)	51 (24)	74 (35)	41.1 ± 15.7	14 (19)	45 (39)	52 (25)
Spain	13	202 (6)	44 (22)[g]	49 (26)[h]	70 (35)	38.3 ± 17.0	21 (30)	26 (38)[b]	57 (28)
Switzerland	4	114 (4)	9 (8)	16 (14)	20 (18)	38.4 ± 15.4	2 (10)	4 (20)	11 (10)
UK and Ireland	34	457 (15)	122 (27)	154 (34)	236 (52)	42.6 ± 17.6	75 (32)	95 (41)	207 (45)
Total	198	3147	583 (19)[g]	747 (24)	1177 (37)	42.3 ± 16.6	313 (27)	413 (36)[i]	930 (30)

[a]Valid percentages are presented after exclusion of missing values; [b]2 values missing; [c]3 values missing; [d]Czech Republic, Poland, Romania, Slovenia, Slovakia, Hungary, Serbia and Montenegro, and Israel; [e]4 values missing; [f]Denmark, Finland, Sweden, and Norway; [g]1 value missing; [h]12 values missing; [i]13 values missing.

Source: Vincent, J. L., Sakr, Y., Sprung, C. L., Ranieri, V. M., Reinhart, K., Gerlach, H., ... & Payen, D. (2006). Sepsis in European intensive care units: results of the SOAP study. Critical care medicine, 34(2), 344-353.

Another large database, the Nationwide Inpatient Sample (NIS), that was used to estimate

national trends in the frequency and outcomes of hospitalizations for sepsis in the United

States between 2000 and 2007, reported that the frequency of hospitalizations with severe

sepsis increased from 143 per 100,000 US adults in 2000 to 343 per 100,000

in 2007, an average annual increase of 16.5% (Kumar et al., 2011).

The increase in the incidence of sepsis was however accompanied with a decrease of in-

hospital mortality rates of severe sepsis from 39.6% in 2000 to 27.3% in 2007 (Kumar et

al., 2011). A decrease in mortality rate from sepsis has been also reported by a multi-

centered study in Australia and New Zealand (Kaukonen et al., 2014). In the United States,

sepsis accounts for more than 50% of hospital deaths, and mortality increases as the disease

becomes more severe: 10–20% for sepsis, 20–40% for severe sepsis, and 40–80% for septic

shock (Martin, 2012).

Data regarding the epidemiology of sepsis in developing countries is scarce, and the

available evidence suggests that developing countries seem to have 3-fold to 4-fold

increased incidence of mortality from sepsis-related infections (Kemper et al., 2016). A

large database in Brazil (n=724,458), reported an overall sepsis mortality rate of 46.3%

(Neira et al., 2018). Such rates have been observed in other developing countries such as

Mexico with a mortality rate of 30.4%, Columbia with a mortality rate of 21.9% (Rodríguez

et al., 2011) and China with a mortality rate of 33.5–48.7% (Liao et al., 2015) from sepsis.

In Lebanon sepsis carries a total mortality rate of 30.9%, and a 28-day mortality rate of

20.6% which is slightly higher than the developed world (Chedade et al., 2015).

Moreover, factors that increase risk of sepsis include: very young age (< 1 year) and and age above 70 years, impaired immunity (because of malignancies and chemotherapy, long-term treatment with steroids or treatment with immunosuppressants), surgery or other invasive procedure in the past 6 weeks, breaches of skin integrity (such as cuts, burns, blisters or skin infections), misuse of intravenous drugs and use of indwelling lines or catheters (Gauer and Robert, 2013).

Gender seems to play a role in the risk to develop sepsis However, its influence is still highly controversial (Pietropaoli et al., 2010). Epidemiologic studies continuously report higher incidence of sepsis in males as compared to that in females (Pietropaoli et al., 2010). Moreover, septic males have been reported to have a higher mortality rate when compared to septic females (Nasir et al.,2015). Animal studies suggest that females have advantageous immune responses to infections (Angele et al., 1997).

Moreover, the incidence and prevalence of sepsis rise with age (Angus et al., 2001). Age is an independent factor that increases the risk for death in patients with severe sepsis with the highest mortality in old elderly (patients more than 85 years of age) (Nasa et al., 2012).

Other factors such as black race, low socioeconomic status and increased burden of chronic health conditions are significant increase the risk to develop severe sepsis. Clinical and genetic factors' contribution to susceptibility to severe sepsis remains unclear.

Chapter Five

Management of Sepsis

Early management of sepsis requires respiratory stabilization where supplemental oxygen should be administered to all patients and mechanical ventilation should be provided when supplemental oxygen fails to improve oxygenation (Gauer and Robert, 2013). Moreover, cornerstones of management of sepsis are early antibiotics, source control, and cardiovascular support or hemodynamic support (via fluid resuscitation and or vasopressors as needed) (Sartelli et al., 2017).

Regarding resuscitation, although the Current SSC sepsis bundle recommends 30 mL/kg to be initiated in the first hour and to be completed in the first 3 hours in septic patients presenting with hypotension or Lactate > 4, this recommendation has been described as "reckless" (Marik et al., 2017). This is because one size cannot fit all patients and some patients, those with acute lung injury for example may be harmedif they received the 30 ml/Kg (Marik et al., 2017). patients with hypotension should receive a bolus of 500 mL of saline over 15 minutes and additional fluids should be administered based on response (Evans, 2018). Crystalloids are recommended as the initial choice for fluid resuscitation in sepsis with albumin as an adjuvant when patients require substantial amounts of crystalloids (Perner et al., 2012; Caironi et al., 2014; Avila et al., 2016). If patients are not responsive to adequate fluid resuscitation and hypotension persisted, admission to a critical care facility and the use of vasopressors will be required (Levy et al., 2012). Hypotension resulting from vasodilation causes indicates tissue hypoperfusion which may be also demonstrated by clinical signs such as cold or clammy skin, altered mental status, oliguria

or anuria and lactic acidosis (Gauer and Robert, 2013). Studies have demonstrated the importance and benefit of prompt use of antimicrobials that target the suspected causative pathogens (Kumar et al., 2006). The exact timing of administration of antimicrobials is to be identified, however every effort should be made to administer antimicrobials as soon as possible, ideally within 1 hour of admission (Evans, 2018). Although studies have not yet shown the benefit of taking cultures before administration of antimicrobials, identification of cultured pathogens and their corresponding antibiotic sensitivities is important in further management (Evans, 2018).

Source control is recommended in patients with sepsis and risks versus benefits should be weighed when deciding on the best recommended method (Salomão et al., 2011). The three core elements of source control are: Debridement (evacuation of infected solid tissue), drainage (removal of infected fluid through the opening of an abscess, by incision or by the insertion of a drain) and device removal (Marshall and Naqbi, 2009). History, full examination and appropriate radiological investigations are used to identify a likely source of infection; however, no source could be identified in around 25% of the cases (Evans, 2018).

Chapter Six

Literature Review and Corticosteroids place in sepsis

The logic for the use of corticosteroids in sepsis, is that this class of drugs downregulates the exaggerated and abnormal pro-inflammatory reaction and weakens the anti-inflammatory response while keeping innate immunity in tact (Keh et al., 2003). Pro-inflammatory cytokines have been shown to either suppress cortisol response to ACTH or compete with intracellular glucocorticoid function, potentially resulting in Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in septic patients (Annane et al. 2017). Sepsis-related CIRCI may promote organ failure and result in reduced response to vasopressor therapy in these patients (Prigent and Maxime, 2004).

Moreover, it has been demonstrated that in sepsis with adrenal insufficiency, steroid supplementation was associated with significantly higher rate of success in withdrawal of vasopressor therapy (Shaikh et al., 2012). Exogenous glucocorticoids are vastly available medications knowing that they are of low cost and have a verified capability to inhibit the inflammatory cascade (Annane et al., 2017).

However, ever since 1976, the use of corticosteroids for sepsis has been debated (Long and Koyfman, 2017). The HYPRESS for example, a multicenter trial which assigned patients with sepsis (excluding those with shock) to receive either a continuous infusion of 200 mg of hydrocortisone for 5 days, followed by dose tapering until day 11 ($n = 190$), or placebo ($n = 190$) (Annane et al. 2017). No difference in rates of progression to septic shock within 14 days between patients who received hydrocortisone was noted(difference −1.8%; 95%

CI −10.7% to 7.2%; p = 0.70) (Annane et al. 2017). This study however had several limitations: First, informed consent was mandatory before patients could take part in the study, so that patients who developed septic shock early may have been missed. Second, mortality in the study population was closer to the mortality reported in clinical trials on patients with community acquired pneumonia (CAP) than to the mortality (approximately 30%) reported in those on patients with severe CAP; thus, it cannot be excluded that hydrocortisone would have been more effective in patients with a higher risk of death. Third, analyses were performed post hoc and results should only be considered as hypothesis generating. Fourth Adjustment for clustering within site was not performed because site was a stratification factor for randomization (Keh et al., 2017).

Despite the existing deliberation, almost all studies stated that corticosteroids decrease mortality (Yao et al., 2019). Moreover, it has been suggested by recently published meta-analyses and systematic reviews that a long course of low dose corticosteroids can actually save patients from sepsis and septic shock (Fang et al., 2019; Annane et al., 2015). For instance, the current best available evidence, provided by the study run by Fang et al., demonstrated that a long course of low-dose corticosteroids could improve 28-day mortality (RR, 0.90; 95% CI, 0.82-0.98; I2 = 27%) and intensive care unit (ICU) mortality (RR, 0.85; 95% CI, 0.77-0.94; I2 = 0%) and in-hospital mortality (RR, 0.88; 95% CI, 0.79-0.99; I2 = 38%) (Fang et al., 2019).

Shock reversal is another beneficial outcome that has been also demonstrated (Annane et al., 2004). Several studies suggested that treatment of corticosteroids favors shock reversal at day 7 (Annane et al., 2004; Minneci et al., 2004; Annane et al., 2009; Sligl et al., 2009; Moran et al., 2010; Annane et al., 2015; Rochwerg et al., 2018; Zhu et al., 2018).

Furthermore, three studies by Annane et al published in 2004, 2009 and 2015 reported the reversal of shock at day 28, which displayed a positive effect that favors corticosteroids (Annane et al., 2004; Annane et al., 2009; Annane et al., 2015).

Corticosteroids have been also shown to decrease the length of ICU-stay of septic patients (Yao et al., 2019. A recent meta-analyses of corticosteroids revealed that corticosteroids have no immediate benefit on the length of stay in the hospital (Lyu et al., 2018) but may decrease the length of stay in the ICU (Fang et al., 2019).

Nevertheless, the severity of adverse events is likely to increase mortality and affects the application of corticosteroids for participants with sepsis (Yao et al., 2019). However, regardless of the dose and course duration of treatment with corticosteroids, the incidence of gastrointestinal bleeding did not significantly increase (Yao et al., 2019). Several studies showed no remarkable effect on superinfection or secondary infection after corticosteroids course of high dose, as well as a long course of low dose corticosteroids (Annane et al., 2004; Annane et al., 2009; Sligl et al., 2009; Annane et al., 2015; Lyu et al., 2018; Rochwerg et al., 2018; Fang et al., 2019).

Currently, guidelines for sepsis management (updated in 2013) support the use of corticosteroids by stating that their use accompanied by adequate fluid resuscitation and vasopressor treatment can restore hemodynamic stability (Dellinger et al., 2013). The most recent guidelines further supported the use of corticosteroids, specifically hydrocortisone therapy at 200 mg per day (Rhodes et al., 2017).

For our knowledge, the early use of corticosteroids in sepsis has been evaluated in very few studies. As such, data about the ideal regimen and corticosteroid to be used in early

sepsis management also remains indefinite. One study evaluating the role of early treatment of septic shock patients demonstrated a significant decrease in 7- and 28- day mortality of patients, significant improvement in PaO2/FiO2 ratio during the first day of treatment and a significant decrease in the duration of vasopressor therapy (Cicarelli et al., 2007). Early treatment with dexamethasone was defined in this study as the treatment before the patient progresses into refractory shock (Cicarelli et al., 2007). Another study that evaluated the role of treatment of septic shock patients early, described in this study as "within few hours of developing shock" has shown significant improvement in the rate of shock reversal and in the Hospital-mortality rate of the corticosteroid group when compared to the placebo (Sprung et al.1984). This study concluded that corticosteroids do not improve the overall survival of patients with severe, late septic shock but may be useful when administered early in the course (Sprung et al.1984).

6.1 Gaps in Research

As such we believe more research is needed to highlight the role of administration of corticosteroids in stages early on, i.e. specifically before progressing into septic shock. Moreover, further research is needed to identify the optimal therapeutic regimen (which corticosteroid, frequency and dose).

6.2 Research questions

Therefore, we believe it is necessary to conduct this study to address the following questions:

1. What would be the influence of early use of corticosteroids in patients with sepsis before they develop septic shock?

2. Does dexamethasone decrease 7- and 28- day mortality when used in septic patients before developing shock?

3. Is the regimen used (0.2 mg/kg IV Dexamethasone daily for 3 doses) effective?

6.3 The choice of Dexamethasone

The choice of dexamethasone in the intervention was based on its pharmacokinetic and pharmacodynamic properties. Dexamethasone is among the most potent glucocorticoids available (1mg of Dexamethasone is equivalent to 30mg of Hydrocortisone) (Paul M., 2014). Furthermore, it has been now well documented that that the expression of inducible nitric oxide synthase (iNOS), responsible for the excessive vasodilatation which is characteristic of the hypotension in septic shock, is negatively regulated by dexamethasone in vivo (Titheradge, 1999).

Interestingly Dexamethasone has the longest half-life (200 minutes) and duration of action (36-54 hours) among all corticosteroids (Paul M., 2014). Also, IV Dexamethasone may have a faster onset of action (1hour) compared to IV Hydrocortisone (1-2 hours) (Dexamethasone (systemic), n.d.). This Pharmacokinetic criterion may be significant in a disease where time plays a significant role. Dexamethasone is lipophilic and distributes well (Vd =2L/kg) to the tissues. This is beneficial in sepsis where a more practical administration (less frequent administration) is needed.

Unlike most of the other corticosteroids, and despite having high potency regarding its anti-inflammatory effect, Dexamethasone lacks any mineralocorticoid activity (mineralocorticoid activity relative to Hydrocortisone=0) (Paul M., 2014). This is advantageous since it may allow the avoidance of hypernatremia secondary to

mineralocorticoid effects. Critical illness related hypernatremia is associated with disease severity, kidney injury and dysfunction, mechanical ventilation and ICU length-of-stay and higher in-hospital mortality (Henry T. et al., 2008).

6.4 New Data about Dexamethasone

Of interest for us is to mention here that Dexamethasone, the corticosteroid used in this study have very recently shown its ability to decrease mortality in patients with COVID-19 as well. One of the world's largest randomized, controlled trials for coronavirus treatments; the RECOVERY trial, was launched in March 2020. The dexamethasone arm enrolled 2,100 participants who received the drug at a low-to-moderate dose of 6 milligrams per day for 10 days, and were compared to 4,300 people who received standard care for coronavirus infection (Ledford, 2020). The risk of death among COVID-19 patients who were on ventilators and received dexamethasone was decreased by 20% (Ledford, 2020).

Chapter Seven

Methodology

7.1 Study Setting

In Lebanon, there are 163 Hospitals contracting with the MoPH, 84.66% of the hospitals are private hospitals while 15% are public hospitals (hospitals in Lebanon, 2013). The North region holds the second highest concentration of hospitals in Lebanon (18.84% of the private hospitals and 24% of the public hospitals in Lebanon) (Hospitals in Lebanon, 2013).

The study will be conducted at "New Mazloum hospital" (NMH), located in north Lebanon, Tripoli. NMH is a private hospital established in 1957. NMH is currently undergoing a major revamping as it is transforming into a university hospital, combining hospital services with the education of medical students and with medical research. In 2011, NMH established an agreement with the American University of Beirut (AUB) (Porter, 2013).

NMH operates in Dam wal Farez area, an area with middle to high-income inhabitants. However, on a larger scale, NMH receives most of the admissions from other areas in Tripoli. Tripoli in general is a low-income region, i.e. in Tripoli more than third of the inhabitants live below the poverty line (Gmayel, 2019).

NMH is a medium-sized hospital that operates 110 beds of which 35 are medicine beds and 10 of which are intensive care unit (ICU) and coronary care unit (CCU) beds (Ministry of Public Health, 2019). Moreover, it operates multiple departments, floors and units:

Emergency department (ED), Internal medicine unit (IMU), pediatric, gynecology, neonatal intensive care (NICU) and surgical unit units. The intervention that we will evaluate in this project has been conducted in the ICU, ED and IMU.

7.2 Study Design

This study will have an **observational retrospective pre-/post- interventional design**. It will evaluate already existing data without any contact with patients. Data will be collected in a manner that does not identify patients.

7.3 Sample Size Justification

The definition of Sepsis is highly variable even within the same hospital and sepsis is a rare condition. These factors together oblige us to go back with our screening for a relatively long period before the intervention had been implemented. We will screen files of septic patients admitted from January 2016 up to February 2018. Our target will be a number that is close to 13 pre-intervention cases (which is the number of patients who have received the intervention).

7.4 Description of the intervention and choice of patients receiving it

Doctors performing the intervention (that took place between February 2018 and April 2019), screened the ED, ICU and IMU for septic patients during their daily rounds (morning and afternoon rounds). During their screening, they searched for diagnostic criteria of sepsis in patients. Their diagnosis of sepsis was based on the recent definition of sepsis (Sepsis-3). Whenever they could find patients with evidence of infection (based on previously agreed parameters) (Appendix I) and organ dysfunction, they considered the case a potential candidate for the intervention. Doctors used SOFA to confirm organ

dysfunction. A SOFA score of 2 or more was indicative of organ dysfunction. SOFA score is a severity grading system that provides weights to organ damage based on the severity of the organ involvement (Appendix II). SOFA scoring system has superior predictive validity for in-hospital mortality as compared to other scoring systems used in sepsis, such as SIRS (Seymour et al., 2016).

After the confirmation, the doctor would write the treatment order. It is important however to mention that the dexamethasone dose used in the treatment group was not fixed. The treatment group was further stratified into two subgroups:

a) High-dose dexamethasone that received: a weight-based regimen composed of 0.2 mg/kg single daily doses for three consecutive days (n = 10)

OR

b) Low-dose dexamethasone that received: a fixed dosing regimen composed of 4 – 8 mg single daily doses for three consecutive days (n = 4)

The assignment of the patients to any of the above subgroups was based on the doctor's judgement. Patients who were non-diabetic or had their diabetes controlled received the weight-based regimen. Whereas patients with poorly controlled diabetes received the fixed-dose regimen. The latter were put on an insulin regimen after consulting with the endocrinologist.

Doctors followed the patients up during their stay. In case the patients were discharged they would follow them up telephonically. The follow up duration was 28-days.

All patients received in addition to the above regimens, the clinically appropriate treatment for sepsis: broad-spectrum antibiotics, Intravenous fluids and oxygen as needed.

7.5 This Study

This study will be looking at the impact of the intervention discussed above on the mortality rate and on several clinical aspects. To do so, we will retrieve medical records of septic patients who received corticosteroids during the period of the intervention (February 2018 – April 2019) (post-intervention group). We will also retrieve medical records of septic patients admitted to the hospital prior to the intervention for patients admitted during the year before the intervention (January 2016 – February 2018). Then I will compare the mortality rates and other relevant clinical outcomes between both groups.

A computerized system will be used in their retrieval. This system classifies patient files based on different variables, of interest for us is the reason of hospitalization. Accounting for the large variability of sepsis definition, we will specify the reason for hospitalization to be: "sepsis", "septicemia" and "Septic shock". Moreover, since many patients may have developed sepsis after being admitted for an infection, i.e. the reason of hospitalization may be different than sepsis, we will include in the search: "urospesis", "endocarditis" and "pneumonia", knowing that these infections may be severe enough to develop into sepsis.

All of these files will have the infection component present (the reason of hospitalization is either an infectious disease or sepsis-related). Therefore, we will directly move to the following step and calculate the SOFA score. We will check the inclusion and exclusion criteria of the study (Table 5). We will be using the same inclusion and exclusion criteria that were used during the intervention. We will then collect data for each patient using the data collection sheet.

Chapter Eight

Study procedure

8.1 Manner of recruitment and informed consent

No patients will be recruited and no direct contact with patients will take place. Medical

records of septic patients admitted prior to the initiation of the intervention will be

screened. Hospital approval to access the files will be sought.

Table 5: Inclusion and Exclusion Criteria of this study

Inclusion criteria	Exclusion criteria
Males and females	Patients with a history of immunosuppression
18 years and above	Patients younger than 18 years
Hispanic, white and black ethnicities	Patients with a concurrent use or history of glucocorticoid use for over two weeks within the last year or upon admission to this hospital
Sepsis diagnosis after admission into the intensive care unit (ICU) in New Mazloum hospital and with confirmed sepsis diagnosis i.e. Sofa>or =2 with a map > or =65mmhg after fluid resuscitation not requiring vasopressors such as dopamine or norepinephrine or inotropes such as Dobutamine. Patients should be admitted to the ICU because of sepsis or other reasons that developed into sepsis.	Patients with active pancreatitis, terminal illness (end stage neoplasm with a life expectancy of less than three months) or recent gastrointestinal hemorrhage were excluded. Also patients who progressed into septic shock, i.e. patients with SOFA>or =2 requiring vasopressors to maintain a MAP > 65mmHg and a lactate level of 2mmol/L or more despite fluid resuscitation.

* The inclusion and exclusion criteria in this study are similar to those used during the previously implemented intervention

We will be looking at the impact of the intervention discussed above on the mortality rate and on several clinical aspects. To do so, we will retrieve medical records of septic patients who received corticosteroids during the period of the intervention (February 2018 – April 2019) (post-intervention group). We will also retrieve medical records of septic patients admitted to the hospital prior to the intervention for patients admitted during the year before the intervention (January 2016 – February 2018). Then we will compare the mortality rates and other relevant clinical outcomes between both groups.

In addition to mortality rates (7- and 28- day) I will be assessing the following clinical outcomes pre- and post- intervention:

- The respiratory function by looking at the Arterial blood gases (ABG's)
- The coagulation status by looking at the through platelet count
- The renal function by looking at Serum creatinine (SrCr)
- The hepatic function by looking at Bilirubin level
- The cardiovascular system through the Mean Arterial Pressure (MAP). I will calculate MAP which is based on systolic blood pressure (SBP), using the average daily SBP.
- The central nervous system (CNS) by calculating Glasgow Coma Scale (Appendix III). The Glasgow Coma Scale (GCS) is used to objectively assess the degree of consciousness impairment in all types of acute medical and trauma patients (Jain and Iverson, 2020). The scale evaluates patients based on three aspects of responsiveness: eye-opening, motor, and verbal responses (Jain and Iverson, 2020). Glasgow Coma Scale score is an important parameter that dominates the

association between admission SOFA score and 30-day mortality (Knox et al., 2014).

8.2 Anticipated risks and potential benefits to participants

Since our part of the study is to retrospectively review medical records of already admitted septic patients, there will be no risks

8.3 Steps taken to protect participants

Only de-identified data will be used to preserve patients' confidentiality. Data collected will only be used for this research.

8.4 Outcomes of the study

8.4.1 Primary outcomes

1. Mortality after 7-days of the first dose of dexamethasone
2. Mortality after 28-days of the first dose of dexamethasone

8.4.2 Secondary outcomes

1. Safety of Dexamethasone in septic patients
2. SOFA score variation (numerical)
3. Other clinical outcomes variation

8.5 Statistical Analysis

To analyze data, we will use the Statistical Package for the Social Sciences (SPSS). The primary outcome (mortality) is categorical. Therefore, to be able to detect whether the

differences in mortality rates between both the intervention and control groups are statistically different, we will run a Pearson chi-square. We will look at measures of association, specifically at the relative risk of death and build our 95% confidence interval accordingly. The level of statistical significance we will be using is P-value < 0.05.

Chapter Nine

Results

9.1 Patients included in the study

Records of 26 patients meeting the inclusion criteria of the study were identified, 12 of which belonged to the control group. Those patients have been admitted to the hospital over a period of 2 years (between January 2016 and January 2018) (figure 2). Amongst those 12 patients, 8 were admitted in 2018, while 3 were admitted in 2017 and 1 was admitted in 2016.

The other 14 patients belonged to the intervention group. Those patients have been admitted to the hospital over a period of 9 months (between March and November 2018) (figure 3). A single patient was admitted every month in March, April, June, August, October and November. Considerably more patients were admitted in May (4 patients) and July (4 patients).

There was a difference in the duration needed for finding sufficient control patients when compared to intervention patients. It was difficult to find pre-intervention septic patients who met the universal diagnostic criteria that were used in this study. Misclassification and misdiagnosis were major issues that prevented easy data collection. Many files have been wrongly classified under sepsis and septic shock while they were severe infection cases. Also many patients meeting the diagnostic criteria of sepsis had one or more exclusion

criteria, and therefore could not be included. There was more control over the intervention cases. Moreover, the pharmacist had an informative lecture delivered to the participating physicians to unify the diagnostic criteria and promote screening. With a unified background knowledge amongst the physicians and more targeted and efficient screening it was logical to detect more septic patients in a shorter period of time.

NUMBER OF PATIENTS BY YEAR
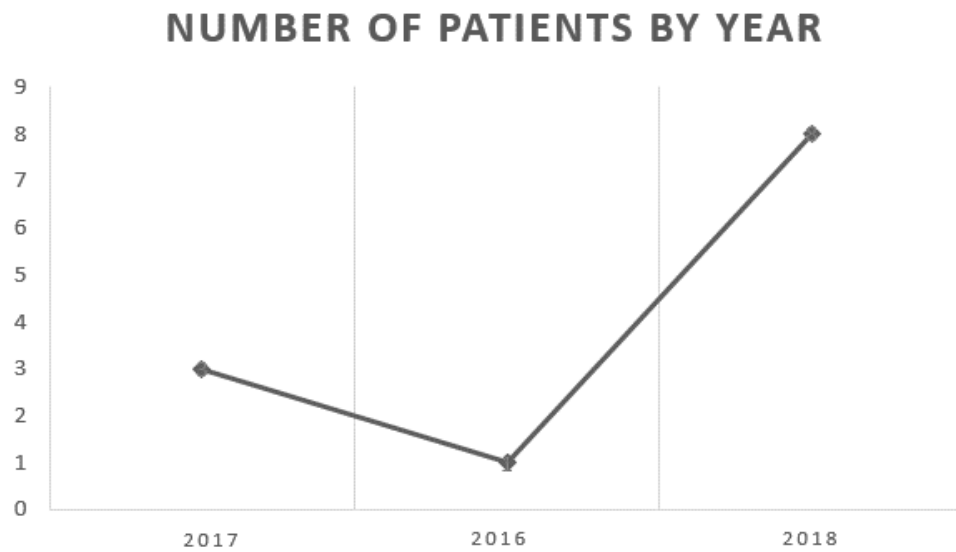
Figure 2: patients included in the control group (n=12) by year
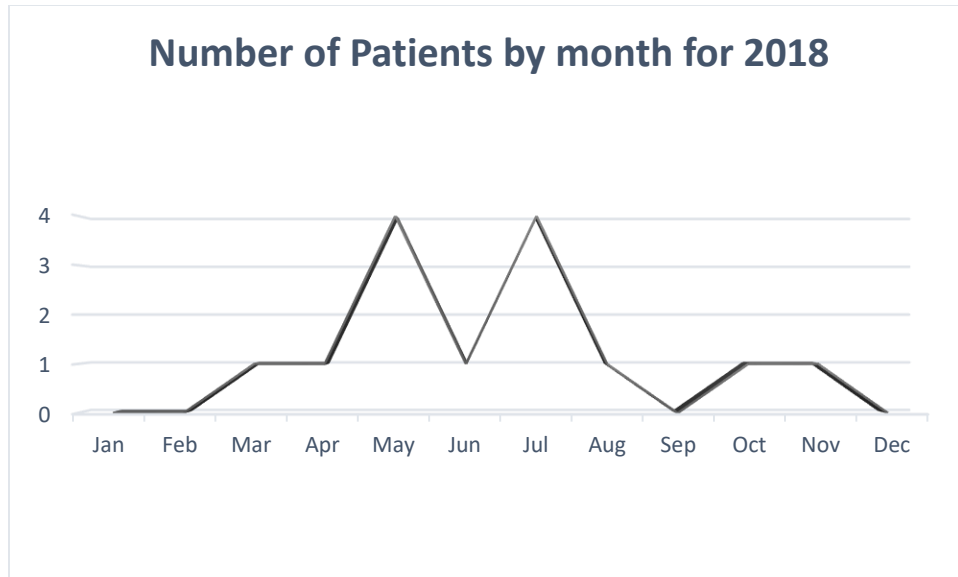
Figure 3: patients included in the intervention group (n=14) by month

9.2 Age and Weight of the sample

The mean age close to 80 and was not statistically significantly different between the control and intervention group (79.08 vs 79.57, p-value=0.900) (Table 6).

The average weight of the control group was slightly lower than that of the intervention group, however the difference was not statistically significant (66.25 vs 72.71, p-value=0.190) (Table 6). None of patients included in the study were morbidly obese or underweight which indicates that the weight of the patients included had no role with the primary outcome (mortality). Therefore, one may conclude that the difference in the average weight between the control and intervention group has no influence on mortality.

Table 6: Age and Weight of the sample by group (control and intervention group)

	Control group (Pre-intervention) (n=12)			Intervention group (During intervention) (n=14)					
	Mean	SD	Range	Mean	SD	Range	t-test	df	p-value
Age	79.08	11.81	57-97	79.57	5.95	65-88	-0.13	15.68	0.900
Weight	66.25	9.32	50-88	72.71	13.97	62-88	-1.36	24.00	0.190

9.3 Gender and ward distribution of the sample

As for the gender, more males were included in the intervention group as compared to the control group. Six (6) out of 12 patients (50%) included in the control group were males, while 9 out of 14 patients (64%) included in the intervention group were males, differences being not statistically significant (p-value = 0.460).

Regarding the ward, more patients in the control group were admitted to the ICU as compared to the intervention group. In the control group, 6 out of 12 patients (50%) were admitted to the ICU, 5 out of 12 patients (42%) to the internal medicine (IM) floor and 1 out of 12 patients (8%) was admitted to the cardiology floor. In the intervention group, 4 out 14 patients were admitted to the ICU (29%), 10 out 14 patients (71%) were admitted to the IM and none were admitted to the cardiology floor. Differences between the control and intervention group were not statistically significantly different (p-value=0.230) (Table 7).

		Control (Pre-intervention group) (n=12)		Intervention gr oup (During intervention) (n=14)				
		n	%	n	%	Chi-Square	df	p-value
Gender	Females	6	50.00	5	35.75	0.54	1.00	0.460
	Males	6	50.00	9	64.28			
Ward	ICU	6	50.00	4	28.57	2.93	2.00	0.230
	IM	5	41.66	10	71.42			
	Cardiology	1	8.33	0	0.00			

9.4 Comorbidities of the sample

Table 8 shows the differences in the comorbidities between both study groups. Patients in the control were less likely to have hypertension as compared to the intervention group (25% vs 71%, p-value=0.018). They were also less likely to have heart failure (33% vs 57%, p-value=0.225), chronic obstructive pulmonary disease (8% vs 7%, p-value=0.910) and kidney disease (8% vs 21%, p-value=0.356). Moreover, they were significantly less likely to have myocardial infarction (25% vs 83%, p-value=0.018). They were however more likely to have cancer (16% vs 14%, p-value=0.867), diabetes mellitus (50% vs 14%, p-value=0.049) and other comorbidities (58% vs 57%, p-value=0.277) (Table 8).

The average number of comorbidities in the control group is less than that in the intervention group, with difference not statistically significant (2.50 vs 3.51, p-value= 0.179).

Table 8: Comorbidities of the control and intervention group

Comorbidities	Control (Pre-intervention group) (n=12)		Intervention group (During intervention) (n=14)		Chi-Square	df	p-value
	n	%	n	%			
Hypertension	3.00	25.00	10.00	71.42	5.57	1.00	0.018
Heart Failure	4.00	33.33	8.00	57.14	1.47	1.00	0.225
History of myocardial infarction	3.00	25.00	10.00	83.33	5.57	1.00	0.018
Diabetes Mellitus	6.00	50.00	2.00	14.28	3.86	1.00	0.049
Chronic obstructive Pulmonary disease	1.00	8.33	1.00	7.14	0.012	1.00	0.910
Cancer	2.00	16.66	2.00	14.28	0.02	1.00	0.867
Liver disease	0.00	0.00	0.00	0.00	NA	NA	NA
Kidney disease	1.00	8.33	3.00	21.42	0.85	1.00	0.356
Other comorbidities	7.00	58.33	8.00	57.14	10.97	9.00	0.277

9.5 Antibiotics used during hospital stay

The most commonly used antibiotic was Avalox (moxifloxacin) (41% vs 42%, p-value=0.951). The second most commonly used antibiotic was Rocephin (Ceftriaxone) (41% vs 28%, p-value=0.484). other antibiotics used were Tazocin (Tazobactam and Piperacillin), Meronem (Meropenem), Tienam (Imipinem and Cilastatin), Invanz (Imipinem), Tygacil (Tygicycline), Liespan (Linezolide) and Cefizox (There were no statistically significant differences between the frequencies of antibiotics used. The

duration of antibiotic treatment was also comparable (6 vs 5 days, p-value=0.565) (Table 9).

Table 9: Antibiotics used during hospital stay of control and intervention group

		Pre-intervention group (n=12)		Intervention group (During intervention) (n=14)				
		n	%	n	%	Chi-Square	df	p-value
	Avalox	5.00	41.66	6.00	42.85	0.004	1.00	0.951
	Rocephin	5.00	41.66	4.00	28.57	0.48	1.00	0.484
	Tazocin	3.00	25.00	2.00	14.28	0.47	1.00	0.490
Antibiotic	Meronem	1.00	8.33	0.00	0.00	2.90	3.00	0.406
	Tienam	1.00	8.33	0.00	0.00	1.21	1.00	0.270
	Invanz	1.00	8.33	2.00	14.28	0.22	1.00	0.635
	Tygacil	1.00	8.33	1.00	7.14	0.01	1.00	0.910
	Linespan	1.00	8.33	0.00	0.00	1.21	1.00	0.271
	Cefizox	0.00	0.00	1.00	7.14	0.89	1.00	0.345
		Mean	**SD**	**Mean**	**SD**	**t-test**	**df**	**p-value**
Duration of treatment		6.333	6.35	5.21	1.76	0.591	12.45	0.565

9.6 SOFA components and scores of the sample

Regarding the components of SOFA score, the first and last values of each parameter will be compared between both study arms. The first value refers back to the first measurement of the parameter after admission. The Last value, is the value of the last measurement of the parameter before discharge or death.

The first PaO2/FiO2 value was higher in the intervention group (304.35 vs 241.10) but the difference was not statistically significant (p-value=0.256). The last PaO2/FiO2 value was also higher in the intervention group and also not statistically significant (404.25 vs 343.00, p-value=0.83). Platelet count first and last values were higher in the intervention group (196.55 vs 267.7, p-value=0.32) and (189.5 vs 284.6, p-value=0.212) respectively. Moreover, the MAP first and last values were higher in the intervention group but the difference was not statistically significant (83.29 vs 76.55, p-value=0.102) and (87.21 vs 81.83, p-value=0.178). Glasgow score first and last values were higher in the intervention group as compared to the control group (13.86 vs 11.00, p-value=0.080) and (14.81 vs 12.18, p-value=0.105). SrCr first value was higher in the control group (1.94 vs 1.77, p-value=0.603). The last SrCr value was however higher in the intervention group (1.70 vs 1.40, p-value=0.467). None of the differences was statistically significant.

Regarding the SOFA score, this score was initially (upon admission) slightly higher in the control group, but the difference was not statistically significant (3.83 vs 3.07, p-value=0.339). As time elapsed, the difference in SOFA score between both groups was approaching statistical significance. Last SOFA value (upon discharge or before death) was still higher in the control group but the difference between both groups was larger and close to approaching significance (3.64 vs 2.00, p-value=0.077). It was apparent that with time SOFA score was decreasing at a faster rate in the intervention group (3.07 to 2.00) as compared to the control group (3.83 to 3.64) (Table 10).

Table 10: First and Last values for SOFA scores and SOFA components of control and intervention group

		Control group (Pre-intervention) (n=12)		Intervention group (During intervention) (n=14)				
		Mean	SD	Mean	SD	t-test	df	p-value
PaO₂/FiO₂	First value	241.10	85.75	304.35	70.91	-1.22	8.00	0.256
	Last value	343.00	NA	404.25	234.42	-0.23	3.00	0.830
	Delta time	4.00	2.44	3.00	2.05	0.879	14.00	0.394
Platelet	First value	196.55	69.00	267.70	202.80	-1.00	19.00	0.328
Count	Last value	189.50	41.80	284.67	231.33	-1.32	11.15	0.212
	Delta time	7.00	7.28	3.78	2.32	1.40	11.61	0.185
MAP	First value	76.55	12.38	83.92	9.69	-1.70	24.00	0.102
	Last value	81.83	10.90	87.21	8.50	-1.38	23.00	0.178
	Delta time	4.33	5.85	1.25	0.50	1.02	8.00	0.333
Glasgow	First value	11.00	4.99	13.86	1.65	-1.89	13.07	0.080
	Last value	12.18	4.87	14.81	0.60	-1.78	10.30	0.105
	Delta time	4.33	5.85	1.25	0.50	1.02	8.00	0.333
SrCr	First value	1.94	0.80	1.77	0.75	0.528	23.00	0.603
	Last value	1.40	1.06	1.70	0.79	-0.74	19.00	0.467
	Delta time	7.70	7.21	2.83	2.03	2.06	10.20	0.065
SOFA	First value	3.83	2.40	3.07	1.26	0.986	16.09	0.339
	Last value	3.64	2.50	2.00	1.47	1.88	15.93	0.077
	Delta time	4.80	3.70	3.23	2.52	1.20	15.11	0.268

Delta represents the time in days between first and last measurement. NA because not all patients underwent ABG's

9.7 Inflammatory and infection Biomarkers of the sample

CRP first and last value were higher in the control group (200.74 vs 161.51, p-value=0.456) and (122.36 vs 76.92, p-value=0.456).

Procalcitonin first and last values were also higher in the control group (200.74 vs 144.63, p-value=0.274) and (122.36 vs 75.29, p-value=0.382). WBC first value were higher in the control group (13.86 vs 17.62, p-value=0.305). The last WBC values were comparable between both groups (12.24 vs 12.76, p-value=0.878) in the control and intervention groups respectively. None of these differences was statistically significant (Table 11).

Table 11: First and Last values for inflammatory and infection Biomarkers of control and intervention group

		Pre-intervention group (n=12)		Intervention group (During intervention) (n=14)				
		Mean	SD	Mean	SD	t-test	df	p-value
CRP	First value	200.74	97.52	161.51	131.30	0.76	20.00	0.456
	Last value	122.36	101.58	76.92	71.98	1.05	15.00	0.167
	Duration between first and last measurement	13.00	14.14	2.00	1.41	1.09	2.00	0.388
Procalcitonin	First value	200.74	97.52	144.63	115.18	1.19	20.00	0.274
	Last value	122.36	101.58	75.29	69.64	1.11	15.00	0.382

	Duration between first and last measurement	8.00	8.67	3.00	2.19	1.38	5.35	0.220
WBC	First value	17.62	9.94	13.86	5.72	1.14	13.51	0.305
	Last value	12.24	7.45	12.76	6.42	0.545	17.00	0.878
	Duration between first and last measurement	6.16	8.32	2.25	1.21	1.64	16.00	0.120

9.8 Sources of cultures and MO isolated

Cultures in both groups were most commonly grown from urine (41.66% vs 50%, p-value=0.671). The most commonly isolated microorganism was Klebsiella pneumonia (25% vs 35%, p-value=0.747). Other less commonly isolated microbes were E.Coli (8.33% vs 0%, p-value= 0.197) and Staphylococcus Areus (8.33% vs 0%, p-value= 0.134) (Table 12).

Table 12: Sources of cultures and MO isolated control and intervention groups

		Pre-intervention group (n=12)		Intervention group (During intervention) (n=12)		Chi-Square	df	p-value
		n	%	n	%			
Source of culture	Cultures grown from urine	5.00	41.66	7.00	50.00	0.18	1.00	0.671
	Cultures grown from sputum	1.00	8.33	0.00	0.00	1.21	1.00	0.271
	Cultures grown from gastric secretions	1.00	8.33	0.00	0.00	1.21	1.00	0.271
MO isolated	E.Coli	1.00	8.33	0.00	0.00	1.66	1.00	0.197
	Klebsiella Pneumonia	3.00	25.00	5.00	35.71	0.104	1.00	0.747
	Staphylococcus Areus	1.00	8.33	0.00	0.00	2.250	1.00	0.134

9.9 Mortality within 7 and 28 days

Table 8 shows the 7-days and 28-days mortality rates which are the primary outcomes of the study. The 7-days mortality rate was significantly higher in the control group (25% vs 0%, p-value=0.047). Moreover, the 28-day mortality rate was significantly higher in the control group (33% vs 0%, p-value=0.019) (Table 13).

Table 13: Mortality within first 7 days and 28 days relative to diagnosis with sepsis control and intervention groups

	Pre-intervention group (n=12)		Intervention group (During intervention) (n=14)				
	n	%	n	%	Pearson Chi-Square	df	p-value
7-days mortality rate	3.00	25.00	0.00	0.00	3.957	1.00	0.047
28-days mortality rate	4.00	33.33	0.00	0.00	5.51	1.00	0.019

Figure 4: Death within 7 days in the control and intervention groups

Control group — 25.00%
Intervention group — 0.00%
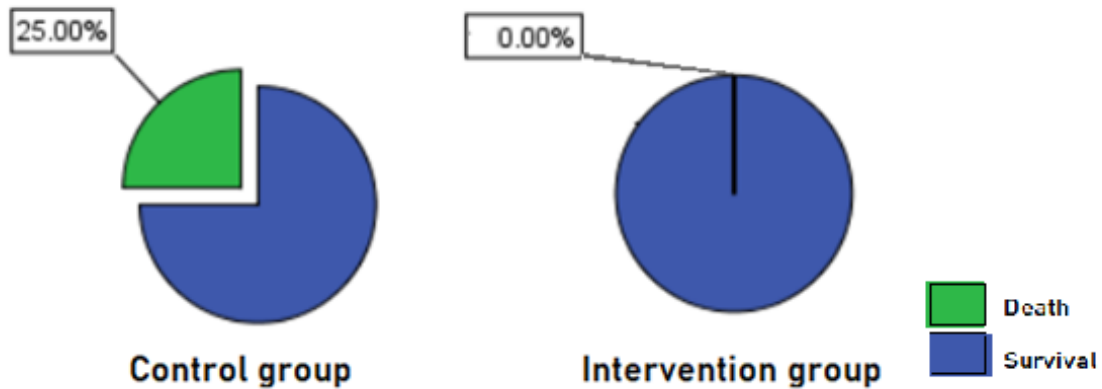
Death
Survival

Figure 5: Death within 28 days in the control and intervention groups
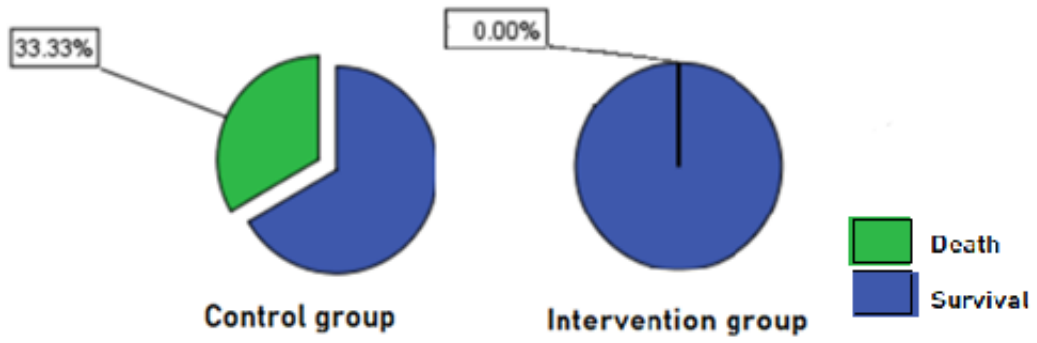
9.10 Adverse events

The only adverse event that occurred and only in the intervention group was hyperglycemia (21% vs 0%, p-value=0.088). No other adverse event occurred in any of the groups (Table 14).

Table 14: Adverse events in the control and intervention group

		Pre-intervention group (n=12)		Intervention group (During intervention) (n=14)				
		n	%	n	%	Chi-square	df	p-value
	Hyperglycemia	0.00	0.00	3.00	21.42	2.912	1.00	0.088
Adverse event	Super-infection	0.00	0.00	0.00	0.00	NA NA	NA	NA
	Neurological adverse events	0.00	0.00	0.00	0.00		NA	NA
	Arthralgia	0.00	0.00	0.00	0.00	NA	NA	NA
	Myopathy	0.00	0.00	0.00	0.00	NA	NA	NA
	Gastro-intestinal	0.00	0.00	0.00	0.00	NA	NA	NA
	Rash	0.00	0.00	0.00	0.00	NA	NA	NA

Chapter Ten

Discussion

10.1 Basic characteristics and comorbidities

This study has an observational retrospective pre-/post- interventional design. The aim of this study was to evaluate the impact of an intervention (that took place between February 2018 and April 2019) where corticosteroids have been administered to a small group of older septic patients and whereby the mortality rates were assessed (7- and 28- day mortality rates).

The target population was older septic patients (older adults and elderly between 57 and 97 years), admitted to (that took place between February 2018 and April 2019) . Older septic patients and elderly septic patients were defined as age above 55 years.

Both study arms were similar in demographic characteristics: age, gender and weight. They were also similar in their distribution over medical units. There was some difference in the comorbidities between the two groups. Patients in the intervention group had on average more comorbidities as compared to the control group however the difference was not significant. The lack of significance may due to the small sample size. It has been reported in literature that the number of comorbidities seems to play a role in sepsis mortality, the higher number of comorbidities is associated with a higher 28-mortality rate (Sinapidis et al., 2018). It has been reported that even the presence of a single comorbidity increases the

risk of sepsis-induced death (Sinapidis et al., 2018). Such findings do not agree with the findings of our study where patients in the intervention group had a lower 28-day mortality despite having more comorbidities.

Moreover, patients in the intervention group were more likely to have history of MI and hypertension but less likely to have DM. Comorbidities pose a significant risk for developing sepsis in older persons (Martin et al., 2003). Compared to younger patients, patients above 75 years of age enrolled in a sepsis study had higher rates of comorbidities (Ely et al., 2003), and those above 65 years of age who were enrolled in another sepsis study were twice more susceptible to have at least 1 comorbid medical condition, compared to younger septic patients (Martin et al., 2003). Management of comorbidities often necessitates the use of medical instruments like urinary catheters and central venous catheters which compromises the natural barriers and generates a portal of entry for infections and therefore for sepsis (Girard et al., 2005).

The influence of coronary artery diseases (CAD) such as MI on sepsis mortality is controversial. While one study reported no difference in hospital-mortality between septic patients with CAD and those with no CAD (Shah et al., 2018) another study reported higher mortality rate in septic patients with CAD (Sinapidis et al.(2018 ,. In our study, septic patients in the intervention group had lower mortality though they significantly had higher rates of history of myocardial infarction.

Moreover, patients in the intervention group were more likely to have hypertension. Hypertension has been independently associated with increased risk of death after sepsis develops (Wang et al., 2014). Wang et al. reported that hypertensive septic patients had 46% higher risk of death at any point of time when compared to non-hypertensive septic

patients (Wang et al., 2014). These findings do not concur with findings of our study where patients in the intervention group having a higher rate of hypertension, had lower 28-day mortality rate.

Furthermore, patients in the intervention group where less likely to have diabetes Mellitus. One meta-analysis evaluating the influence of DM found that DM does not increase and may even decrease the risk of death in septic patients (Wang Et al., 2017). Short-term hyperglycemia that may accompany sepsis was reported as independent risk factor for death in non-diabetic critically-ill patients (Krinsley et al., 2003). When compared to non-diabetic patients, diabetic patients tolerate more short-term hyperglycemia (Wang Et al., 2017). This protective role of DM has not been supported by the findings of our study where the control group having a higher rate of diabetes had a higher 28-day mortality rate.

10.2 Age and Ward

Age is a significant cause of morbidity and mortality in the older septic patients (Nasa et al., 2012). It has been reported that most septic patients in the US, around 65% of all septic patients, are older people (above 65 years) (Starr and Saito, 2014). Studies that aim to diagnose and manage sepsis usually exclude subjects that have several co-morbidities or are very old patients (older than 80 years) (Nasa et al., 2012). Nevertheless, as the population becomes older, this subset of patients will increase and they will be more frequently admitted into the ICUs where it will be challenging to manage them without adequate knowledge and established therapeutic regimens (Nasa et al., 2012). Moreover, age influences mortality as it is an independent risk factor for death in patients with sepsis (Nasa et al., 2012). Elderly patients have a mortality rate due to sepsis that is 1.3–1.5 times higher than in younger patients (Martin et al., 2017). It has been reported for instance that

the Intensive care unit mortality of sepsis in elderly is 60.7% and 78.9% in very old patients as compared to young patients which is 45.6% (Nasa et al., 2012). Furthermore, mortality rates of sepsis increase progressively with age, with the highest mortality in patients more than 85 years of age (Starr and Saito, 2014). Despite the large number of clinical and basic research studies that are being held, there is still no effective therapeutic strategy that saves elderly septic patients (Starr and Saito, 2014). In an attempt to cover this gap in research, participants targeted in our study were 57 and 90 years (79.08 in the control group vs 79.57 in the intervention group).

Regarding the ward, more septic patients have been initially admitted to the ICU in the control group as compared to the intervention. Admitting septic patients from the ED to other floors than the ICU (before admitting them to the ICU) has resulted in a higher mortality rate (Motzkus et al., 2018). Septic patients triaged from the ED to other wards besides the ICU may receive less timely and effective primary care than those directly admitted to the ICU from the ED (Motzkus et al., 2018). We would have favored that all septic patients included in the study, be triaged from the ED to the ICU so that they could have received the same critical care provided to the patients in the control group. However, with the adequate screening the team performing the intervention was providing, sepsis could be detected early on in the course. And knowing that the ICU in NMH is not large (10 ICU beds), the hospital policy prioritized more serious cases than those early detected sepsis cases, to be admitted to the ICU.

10.3 Corticosteroids

Patients in the intervention group (receiving dexamethasone) had significantly lower 7- and 28-day mortality rates as compared to the control group (receiving standard therapy).

Our findings are in accordance with other studies. One recent meta-analysis including 34 trials (n = 8699) reported significantly lower 28-day mortality in groups receiving corticosteroids as compared to control groups receiving placebo (Fang et al., 2019). Other studies with similar findings has been clustered by a Cochrane systematic review published by Annane (Fang et al., 2019). This study included 33 trials randomizing 4428 and demonstrated a decrease in the 28-day mortality rates (RR, 0.87; 95% CI, 0.76-1.00). (Annane et al., 2015).

The corticosteroid used was dexamethasone. The choice of dexamethasone in the intervention was based on its pharmacokinetic and pharmacodynamic properties as described in the Literature Review section. In our study, Dexamethasone demonstrated its ability to significantly decrease mortality in patients aged ≥ 57 and ≤ 97 years. This finding has been demonstrated by other studies targeting younger patients (Cicarelli et al., 2007; Schumer, 1976; Sprung et al., 1984; Zhang et al., 2020).

The doses used in our study ranged from 4 mg (moderate dose equivalent to 106.7 mg Hydrocortisone) to 16 mg (High dose equivalent to 426.7 mg Hydrocortisone). Previously, studies focused on the use of corticosteroids equivalent to 200 mg Hydrocortisone. However, higher doses are becoming increasingly investigated (Huang et al., 2014; Torres et al, 2015) and are demonstrating positive impact on mortality (Cicarelli et al., 2007; Zhang et al., 2020). the advantage in our study is that it provided such a range of doses in a try to identify the most influential dose. Unfortunately due to the small sample size the decrease in 7- and 28- day mortality was not apparent when we ran a subgroup analysis and divided the treatment groups further into high and moderate doses. We believe more

studies with larger sample sizes are needed to identify the appropriate dose of dexamethasone for septic patients.

10.4 SOFA score

Initially, the control and intervention groups had close SOFA scores. As time lapsed (4.8 days vs 2.23 days passed in the control and intervention group respectively) , SOFA score of both groups decreased, however the decrease was faster and to a lower SOFA score in the intervention group and therefore predicting a better outcome (Ferreira et al., 2001). Similar findings have been reported by Annane et al. in 2018, where the corticosteroid group demonstrated a faster decrease in the SOFA score as compared to placebo group (Annane et al., 2018). Likewise, other studies also reported larger declines in SOFA scores in corticosteroid groups when compared to the placebo (Sabry and Omar, 2011; Opert et al., 2005, Cicarelli et al., 2007). Glasgow Coma Scale was slightly lower in the control group as compared to the intervention group. As time lapsed GCS became similar between both groups. It has been reported by Dolan et al., that Glasgow score upon admission it not associated with in-hospital mortality (Dolan et al., 2016).

Chapter Eleven

Limitations

This study had several limitations. Firstly, the sample size was small (n=26). We tried to tackle this limitation by extending the period of the pre-intervention group up to 2 years (before the intervention) started and around 1 year thereafter (after the intervention initiation). It is of advantage that the effect size of this intervention is medium and despite the small sample size significant differences between intervention and control group could be detected. Secondly, when the intervention took place it was single-blinded (the treating physician knew about the intervention while the patient did not) and there was no randomization. We did not have control over blinding and randomization as our role was solely observational where we assessed the outcomes of the intervention. The absence of blinding and randomization may have introduced some bias to the study, however these measures were difficult to be taken especially in the critically ill population included in the study. Moreover, there were stringent inclusion and exclusion criteria to abided by, physicians had to assess the patients, look for inclusion and exclusion criteria and evaluate their risk of developing corticosteroid-hyperglycemia. This evaluation was necessary to decide on the low or moderate corticosteroid dose. In a try to minimize the bias as much as possible, we chose objective outcomes for our assessment such as 7- and 28-day mortality rates, SOFA score and rate of adverse events.

Chapter Twelve

Conclusion

Our study that was performed on small group of septic patients, showed a positive impact of the treatment on 7- and -28 days mortality, and on SOFA score. This small scale study demonstrates the need for a larger implication of the treatment especially in remote areas where the treatment of sepsis is not done according to the up to date guidelines and at many times the recommendation regarding treating septic patients with corticosteroids is not accepted. We recommend that the ministry of health partake into a large scale national program, educating physicians about the guidelines of treating sepsis and septic shock and highlight the positive role corticosteroids may have in septic patients. This role as demonstrated by our study is not limited to hydrocortisone as dexamethasone may be equally effective at reducing mortality in septic patients. Moreover, this positive role is not strictly related to the late administration of steroids, where, as demonstrated by our study, early administration of corticosteroids may prohibit the progression of patients into refractory septic shock.

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Appendices

Parameter		Value	Values associated with sepsis	Normal values	Significance and association with sepsis
Vitals	Fever		>38° C or <36° C	37° C	
	Heart rate		>90bpm	60-90bpm	
	Respiratory rate		>20bpm	12-20bpm	
WBC			>12,000cells/mm^3	4.5-11 *10^3 cells/mm^3	
Procalcitonin (PCT)			PCT >0.5 to <12.8 ng/mL	0.15 ng/mL or less	PCT concentration has been found to be elevated in sepsis. Owing its specificity to **bacterial infections**, PCT has been proposed as a pertinent marker in the rapid diagnosis of bacterial infection
Lactate			>1mmol/L and <2mmol/L	0.5-1mmol/L	Decreased lactate clearance has been found to be associated with increased mortality in sepsis. Lactate assay remains a clinically useful test that can alert a clinician to underlying hypoperfusion.
C-reactive protein (CRP)			50-79 mg/dL	<3mg/dl	Daily measurement of CRP is useful in the detection of sepsis
Cultures	Grown and positive?	Yes/No		---------	In sepsis: considered golden standard of diagnosis. Rate of false positive (~30%) and negatives (~50%)
	Microorganism identified			---------	
Based on the above, Could an infection be identified?			Yes/No		

Appendix II: SOFA score components and reference values

System	Score 0	1	2	3	4
Respiration					
Pao$_2$/Fio$_2$, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10^3/μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio$_2$, fraction of inspired oxygen; MAP, mean arterial pressure; Pao$_2$, partial pressure of oxygen.
[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.
[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Appendix III: Glasgow Coma Scale

BEHAVIOR	RESPONSE	SCORE
Eye opening response	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best verbal response	Oriented to time, place, and person	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best motor response	Obeys commands	6
	Moves to localized pain	5
	Flexion withdrawal from pain	4
	Abnormal flexion (decorticate)	3
	Abnormal extension (decerebrate)	2
	No response	1
Total score:	*Best response*	15
	Comatose client	8 or less
	Totally unresponsive	3

Inclusion criteria	Exclusion criteria
Males and females	Patients with a history of immunosuppression
18 years and above	Patients younger than 18 years
Hispanic, white and black ethnicities	Patients with a concurrent use or history of glucocorticoid use for over two weeks within the last year or upon admission to this hospital
Sepsis diagnosis after admission into the intensive care unit (ICU) in New Mazloum hospital and with confirmed sepsis diagnosis i.e. Sofa>or =2 with a map > or =65mmhg without the need of vasopressors such as dopamine, dobutamine or norepinephrine. Patients should be admitted to the ICU because of sepsis or other reasons that developed into sepsis.	Patients with active pancreatitis, terminal illness (end stage neoplasm with a life expectancy of less than three months) or recent gastrointestinal hemorrhage were excluded. Also patients who progressed into septic shock, i.e. patients with SOFA>or =2 with a MAP < 65mmHg and a lactate level of 2mmol/L or more were excluded.

Appendix V: Data collection sheet

Section A: Patient Demographics and Comorbidities

Comorbidities			Patient characteristics	
1. HTN			1. Patient ID (ID given by the investigator for the patient)	
2. HF			2. Age	
3. DM			3. Ward	
4. COPD			4. Gender	
5. Cancer			5. Admission date 6. Discharge date	
6. Recent trauma			7. Height (cm)	
7. Liver disease (hepatitis/ cirrhosis)			8. Weight (kg)	
8. Kidney disease			9. CrCl (ml/min)	
	Day1		**CrCl (ml/min):**	

		Cockcroft and Gault equation: CrCl = [(140 - age) x IBW*] / (Scr x 72) (x 0.85 for females)
Day2		Normal creatinine clearance for healthy women is 88-128 mL/min
Day3		Note: if the ABW (actual body weight) is less than the IBW use the actual body weight for calculating the CRCL.
Day4		*Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet. *Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.
Day5		1 foot= 30.48cm 1 inch= 2.54cm
Day6		
Day7		
Day8		
Day9		
Day10		
Day11		
Day12		
Day13		
Day14		
11. Reason for hospitalization:		10. Allergies

Section B: Treatment offered

Day and Date	Fluids	Antibiotics
Day1		
Day2		
Day3		
Day4		
Day5		

Day6		
Day7		
Day8		
Day9		
Day10		
Day11		
Day12		
Day13		
Day14		
Was treatment offered adequate and antibiotics tailored based on cultures appropriately? **Comment:**	**Y/N**	

Section C: variables to be monitored

Variables WEEK 1	Day1	Day2	Day3	Day4	Day5	Day6	Day7	Notes
$PaO_2/(FiO_2/100)$								**nl. PaO2:FiO2 = 100 mmHg/0.21 ≈ 500** The lower the ratio, the worse the disease process.
Platelets $*10^3$/Microliter								**nl. 150-400*10^3/Microliter**
Conjugated Bilirubin mg/dl								**nl. Direct biluribin <0.3 mg/dL** mg/dl= Mmol/L/17.1
Average daily **MAP= (SBP + 2 (DBP))** 3								**nl. Range 70 – 110 mmHg**
Glasgow Coma score								**Maximum score is 15 which has the best prognosis**
SCr (mg/dl or Mcmol/L/88.4)								**nl. 0.6 to 1.2mg/dl in males and 0.5 to 1.1mg/dl infemales.**
Urine Output ml/d (= Actual [cc/day] / (weight [kg]*24).								**nl. 800 to 2000 milliliters per day.** Oliguria is urine output < 500 mL in 24 h (0.5 mL/kg/h) in an adult)

SOFA score								
Lactate mmol/L								In sepsis: >1mmol/L and <2mmol/L Normal: 0.5-1 mmol/L Decreased lactate clearance has been found to be associated with increased mortality in sepsis. Lactate assay remains a clinically useful test that can alert a clinician to underlying hypoperfusion
Procalcitonin ng/ml								In sepsis: PCT >0.5 to <6.2 ng/mL Normal: 0.15 ng/mL or less PCT concentration has been found to be elevated in sepsis. Owing its specificity to **bacterial infections**, PCT has been proposed as a pertinent marker in the rapid diagnosis of bacterial infection
CRP								In sepsis: 50-79 mg/dL Normal: <3mg/dl
WBC								In sepsis: >12,000cells/mm^3 Normal: 4.5-11 *10^3 cells/mm^3
Average daily Body Temperature								>38° C or <36° C

Variables WEEK 2	Day8	Day9	Day10	Day11	Day12	Day13	Day14	Notes
PaO$_2$/(FiO$_2$/100)								**nl. PaO2:FiO2 = 100 mmHg/0.21 ≈ 500** The lower the ratio, the worse the disease process.
Platelets *10^3/Microliter								**nl. 150-400*10^3/Microliter**
Conjugated Bilirubin mg/dl (= Mmol/L/17.1)								**nl. Direct biluribin <0.3 mg/dL**
Average daily								**nl. Range 70 – 110 mmHg**
Glasgow Coma score								**Maximum score is 15 which has the best prognosis**
SCr (mg/dl or Mcmol/L/88.4)								**nl. 0.6 to 1.2mg/dl in males and 0.5 to 1.1mg/dl infemales.**
Urine Output ml/d								**nl. 800 to 2000 milliliters per day.**

(= Actual [cc/day] / (weight [kg]*24).								Oliguria is urine output < 500 mL in 24 h (0.5 mL/kg/h) in an adult)
SOFA score								
Lactate mmol/L								In sepsis: >1mmol/L and <2mmol/L Normal: 0.5-1 mmol/L Decreased lactate clearance has been found to be associated with increased mortality in sepsis. Lactate assay remains a clinically useful test that can alert a clinician to underlying hypoperfusion
Procalcitonin ng/ml								In sepsis: PCT >0.5 to <6.2 ng/mL Normal: 0.15 ng/mL or less PCT concentration has been found to be elevated in sepsis. Owing its specificity to **bacterial infections**, PCT has been proposed as a pertinent marker in the rapid diagnosis of bacterial infection
CRP								In sepsis: 50-79 mg/dL Normal: <3mg/dl
WBC								In sepsis: >12,000cells/mm^3 Normal: 4.5-11 *10^3 cells/mm^3
Average daily Body Temperature								>38° C or <36° C

Section D: Pathogens if identified

	Day1	Day2	Day3	Day4	Day5	Day6	Day7
4. Cultures grown daily?	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
5. Type of cultures: -blood -urine -pulmonary/sputum -fecal -through debridement							
6. MO isolated: **G +ve bacteria (**_Staphylococcus aureus_**,** _Streptococcus species_**,** _Enterococcusspecies_) **G –ve bacteria** _(Escherichia coli, Klebsiella species, Pseudomonas aeruginosa)_ **Other, specify**							

Appendix VI: Outcome evaluation tool

Treatment evaluation tools				
Dexamethasone was started at what time relative to time of diagnosis and to antibiotics initiation				
Dosage Regimen followed was as such: (mention any discrepancies) *0.2mgkg/kg IV bolus right at diagnosis* *0.2mgkg/kg IV bolus 24 hours after the first dose* *0.2mgkg/kg IV bolus 24 hours after the second dose*		**Date**	**Time**	**Dose**
	Day1			
	Day2			
	Day3			

Section F: Treatment protocol and primary and secondary outcomes

Was Dexamethasone treatment discontinued? If yes, what was the reason?	**Y/N** ☐ adverse drug reactions ☐ Allergy ☐ Death of the patient ☐ other														

Secondary outcomes: Safety of Dexamethasone	**Type of ADR**	**Date and time of detection:**												
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
	Super-infection													
	Hyperglycemia													
	Neurological (psychosis, syncope, delirium...)													
	New arthralgia/osteoporosis													
	New myopathy													

	Gastro-intestinal bleed														
	Rash														
	Other adverse reactions:														
Primary outcomes: Mortality	**Mortality after 7-days of the first dose of dexamethasone**														
	Mortality after 28-days of the first dose of dexamethasone														
Loss of follow-up	**Y/N**	**Time of loss of follow-up:**		**Reason of loss:**											