Ain Shams University
Faculty of Medicine
Department of Anesthesia and Intensive Care

EARLY AND INNOVATIVE INTERVENTIONS FOR SEVERE SEPSIS AND SEPTIC SHOCK

An Essay

Submitted for partial fulfillment of Master Degree in Intensive Care Medicine

Presented by

Dr: Mohamed Ali Zaki Aboraia
M.B.,B.Ch of medicine and surgery
Ain Shams University

Under Supervision of

Prof./ Sahar Kamal Mohamed Abo Elela
Professor of Anaesthesia and Intensive Care
Ain Shams University

Dr./Maged Mohamed Raafat Mostafa
Lecturer of Anaesthesia and Intensive Care
Ain Shams University

Dr./ Aktham Adel Ihsan Shoukry
Lecturer of Anaesthesia and Intensive Care
Ain Shams University

Faculty of Medicine
Ain Shams University
2009

جامعة عين شمس
كلية الطب
قسم التخدير و الرعاية المركزة

Early and innovative interventions for sever sepsis and septic shock

التدخلات الأولية والمبتكره لعلاج التسمم الشديد بالدم والصدمة بتسمم الدم .

An Essay

Submitted for partial fulfillment of
Master Degree in Intensive Care Medicine

رسالة توطئة للحصول على درجة الماجستير فى الرعاية المركزة

مقدمة من الطبيب / محمد على زكى ابوريا
بكالوريوس الطب والجراحة- جامعة عين شمس
طبيب مقيم رعاية مركزة- المعهد القومى للكلى

تحت إشراف

الأستاذ الدكتور : سحر كمال محمد ابو العلا
استاذ التخدير والرعاية المركزة
كلية الطب – جامعة عين شمس

الدكتور / ماجد محمد رأفت مصطفى
مدرس التخدير والرعاية المركزة
كلية الطب- جامعة عين شمس

الدكتور / اكثم عادل إحسان شكرى
مدرس التخدير و الرعاية المركزة
كلية الطب- جامعة عين شمس

بسم الله الرحمن الرحيم

CONTENTS

ACKNOWLEDGMENT

I would like to express my deep thanks and gratitude for ***Prof. Dr. Sahar Kamal Abo Elela,*** *Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for her great support, guidance and encouragement.*

It was an honor to work under supervision of ***Dr. Maged Mohamed Raafat,*** *lecturer of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, and I'm deeply thankful for his support.*

I'm also deeply thankful and appreciating for the continuous support and creative elaborations provided by ***Dr. Aktham Adel Ihsan Shoukry,*** *lecturer of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, as without his remarkable comments and guidance, this work would not be completed.*

At such a moment, I should never forget to express thanks to my parents and family for their endless care and support. Without it, I wouldn't be able to perform such work.

ABBREVIATIONS

ACTH	: Adrenocorticotrophic hormone
ADP	: Adenosine diphosphate
ALI	: Acute lung injury
AMP	: Adenosine monophosphate
APACHE	: Acute Physiology and Chronic Health Score
APC	: Activated protein C
ARDS	: Acute respiratory distress syndrome
ATP	: Adenosine triphosphate
ATIII	: Antithrombin III
BNP	: B-type natriuretic peptide
CARS	: Counter inflammatory response syndrome
cGMP	: Cyclic guanosine monophosphate
CRP	: C-reactive protein
CSF	: Colony stimulating factors
CVP	: Central venous pressure
DIC	: Disseminated intravascular coagulopathy
DO_2	: Oxygen delivery
DTH	: Delayed type hypersensitivity
GPI	: Glycosyl-phosphatidyl inositol
HDL	: High density lipoprotein
HSP	: Heat shock proteins
ICAM-1	: Intercellular adhesion molecule 1
ICU	: Intensive care unit
IFN-γ	: Interferon γ
IgE	: Immunoglobulin E
IgG	: Immunoglobulin G
IL	: Interleukin
K_{ATP}	: The ATP-sensitive potassium
LBP	: Lipopolysaccharide-binding protein
LDL	: Low density lipoprotein
LPS	: Lipopolysaccharide
LTA	: Lipoteichoic acids

ABBREVIATIONS (Cont.)

MCP-1	: Monocyte chemo-attractant protein 1
MODS	: Multi organ dysfunction syndrome
MOF	: Multi organ failure
MyD88	: Myeloid differentiation factor 88
NDP	: Nucleotide diphosphates
NO	: Nitric oxide
NOS	: Nitric oxide synthase
PAF	: Platelet activating factor
PAR-1	: Protease-activated receptor 1
PGE1	: Prostaglandin E-1
PGE2	: Prostaglandin E-2
PGN	: Peptidoglycan
PKA	: AMP-dependent protein kinase
PMN	: Poly-morphonuclear leukocytes
ROS	: Reactive oxygen species
$ScvO_2$	: Central venous oxygen saturation
SIRS	: Systemic inflammatory response syndrome
SvO_2	: Venous Oxygen Saturation
TF	: Tissue factor
Th	: T-helper cell
TIRAP	: Toll–IL-1-resistance adaptor-like proteins
TLR	: Toll-like receptor
TM	: Thrombomodulin
TNF-α	: Tumor necrosis factor-alpha
V/Q	: Ventilation/perfusion
VCAM-1	: Vascular cell adhesion molecule
VLDL	: Very low density lipoprotein
VO_2	: Oxygen uptake
vWF	: Von Willebrand factor

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Sepsis is the most common cause of death among hospitalized patients in non-coronary intensive care units. Recent US and European surveys have estimated that severe sepsis accounts for 2-11% of all admissions to hospital or intensive care units. Thus, an important goal in critical care medicine is to develop novel therapeutic strategies that will impact favorably on patient outcome. The development of novel therapies for sepsis is critically dependent on an understanding of the basic mechanisms of the disease ***(Aird, 2003).***

The American College of Chest Physicians and the Society of Critical Care Medicine established a set of definitions to facilitate early detection and treatment of sepsis and to standardize patient requirements for research protocols;

1. Systemic inflammatory response syndrome (SIRS): Presence of 2 or more of the following:

a. Temperature > 38^{o}C or < 36^{o}C.

b. Heart rate > 90 beats/min unless the patient is taking medications to reduce the rate (a beta-blocker or calcium channel blocker) or the heart is paced.

c. Respiratory rate > 20 breaths/min (or $PaCO^{2}$ < 32 torr) or mechanically ventilated.

d. Leukocyte count > 12000/mm^3 or < 4000/mm^3, or presence of 10% or more immature band forms.

2. Sepsis: Presence or presumed presence of an infection accompanied by evidence of SIRS.

3. Severe sepsis: Presence of sepsis, plus organ hypoperfusion or dysfunction.

4. Septic shock: Presence of sepsis and refractory hypotension.

Patient may be in septic shock with a normal blood pressure if the baseline blood pressure is elevated (e.g., someone with a history of hypertension, diabetes or vascular disease) or there is concomitant myocardial dysfunction. The initial presentation of severe sepsis and septic shock is often nonspecific, and its severity is unpredictable. Patients who arrive with a relatively benign or clinically unapparent infection can progress within hours to a more devastating form of disease ***(Otero, et al. 2006)***.

Transition from sepsis to septic shock occurs most often during the first 24 hours of hospitalization. It carries with it an increase in morbidity and also in mortality: 20%–46%. The decrease in tissue oxygen delivery and the cardiovascular insufficiency that accompany this transition may not be detected by vital signs nor SIRS criteria. It is at this critical juncture that outcomes can be much improved ***(Rivers et al., 2005).***

Delays in the identification, transfer and management of critically ill patients have been associated with higher mortality rates and increased utilization of hospital resources. Within the last years, advances in the treatment of severe sepsis and septic shock have provided new therapies to treat this disease ***(Otero, et al. 2006)***.

The timeliness of treatment became a more important issue and it was shown a significant mortality benefit when hemodynamic optimization was provided within the first few hours of disease presentation ***(Estenssoro et al., 2005).***

This "golden hour" and "silver day" perspective of early resuscitation, which traditionally has been applied to trauma, can now be applied to severe sepsis and septic shock. In turn, the "silver day" represented the first day's remaining hours, during which aggressive correction of shock and organ dysfunction was found to decrease health-care resource utilization and improve outcomes ***(Rivers et al., 2005).***

PATHOPHYSIOLOGY OF SEPSIS

Sepsis is defined as an inflammatory response to microorganisms or the invasion of normally sterile host tissue by these organisms. The pathophysiology of severe sepsis is highly complex and involves several important themes; first, it is the host response, rather than the nature of the pathogen, that primarily determines patient outcome. Second, monocytes and endothelial cells play a central role in initiating and preserve the host response. Third, sepsis is associated with the concomitant activation of the inflammatory and coagulation cascades. Finally, in a concerted effort to fend off and eliminate pathogens, the host response may inflict collateral damage on normal tissues, resulting in pathology that is not diffuse, but rather remarkably focal in its distribution ***(Aird, 2003).***

(I) Causes of Sepsis:

Sepsis and septic shock may caused by gram-negative or gram-positive bacteria, fungi, viruses and parasites. The most common causes of sever sepsis are:

1. Gram-negative bacilli; mainly E coli, Klebsiella species and Pseudomonas aeroginosa, they vary between 30-80% of cases.

2. Gram-positive cocci; mainly Staphylococci and Strepto-cocci, they vary between 6-24% of cases.

3. Fungi; mostly Candida that accounts for only about 5% of all cases of severe sepsis.

However, the contribution of gram-positive bacteria to sepsis has increased, and in the early 1990s it accounted for more than 50% of all cases of septicemia, with *Staphylococcus aureus (S.aureus*) and *S.epidermidis* being responsible for more than half of the cases of sepsis due to gram-positive bacteria. The increasing rates are probably caused by the increasing use of catheters and other invasive equipment in ICU. Although the abdomen was the major source of infection in sepsis from 1970-1990, in past decade pulmonary infections have emerged as the most frequent site of infection ***(Bochud et al., 2001)***

(II) Host Response to Injury and Sepsis:

The injury response is a dynamic process that follows a general pattern. The early response to injury has been defined clinically as the systemic inflammatory response syndrome (SIRS); it is the proinflammatory phase of the host response to injury, it is mediated primarily by cells of the innate immune system, and describe the early and common systemic response to a wide variety of insults even infectious or non infectious, and it is clinically characterized by two or more of the following manifestations:

1. A body temperature greater than 38°C or less than 36°C.
2. A heart rate more than 90 beats per minute (tachycardia), unless the patient is taking medication to reduce the heart rate or the heart is paced.

3. A respiratory rate greater than 20 breaths per minute (tachypnea).
4. A white blood cell count greater than 12.000 cells per mm^3, or less than 4.000 cells per mm^3, or the presence of greater than 10% immature band forms.

In some patients, a counter inflammatory response (CARS) can develop after the initial SIRS response. The CARS response has been classified as a compensatory, anti-inflammatory response, as it is often associated with the development of immune suppression and the overproduction of anti-inflammatory cytokines by T cells, and thus places the injured host at risk of developing nosocomial or opportunistic infections ***(Levy et al., 2003).***

An additional component of the injury response is secondary SIRS**,** Which can develop if opportunistic infections set in. This secondary inflammatory response occurring after the initial resuscitation period, and may also been defined as the two-hit response model or hypothesis, The two-hit response or secondary SIRS may be driven primarily by the host response to the infection (fig 1). If this response is excessive, this in turn might lead to the development of Multi Organ Dysfunction Syndrome (MODS) and death in some patients **(*Mannick et al., 2001).***