ROLE OF PROCALCITONIN HORMONE AS DIAGNOSTIC AND PROGNOSTIC FACTOR IN SEPSIS

Essay
Submitted for Partial fulfillment of
Master Degree in Critical Care

By

Abd El-Rahman Mohamed Thabet Soliman Hammuda
M.B., BCh.

Supervised by

Professor Doctor/ Nahed Salah El-Din Omar
Professor of Anesthesia & Intensive Care
Faculty of Medicine
Ain Shams University

Professor Doctor/ Mohamed Esmail Abd El-Fatah
Professor of Anesthesia & Intensive Care
Faculty of Medicine
Ain Shams University

Doctor/ Magdi Shehata Metias
Lecturer of Anesthesia & Intensive Care
Faculty of Medicine
Ain Shams University

Faculty of Medicine
AIN SHAMS UNIVERSITY
2010

ACKNOWLEDGMENT

First of all, thanks to **ALLAH** the most merciful for guiding me through and giving me the strength to complete this work the way it is.

My deepest gratitude to **Prof. Dr. Nahed Salah Eldin Omar**, professor of Anesthesia and Critical care, Faculty of Medicine, Ain Shams University; Who gave me the opportunity and honor to be under her supervision. Her continuous advice and active guidance were of great value and helped me so much. She always devotes much of her time to me and other young doctors.

I would like to express my sincere thanks and gratitude to **Prof. Dr. Mohamed Esmaeel Abd El-Fatah**, Professor of Anesthesia and Critical care, Faculty of Medicine, Ain Shams University; for his close supervision, valuable suggestions, good support and unlimited help during this work. It was a great honor for me to work under his supervision.

I wish to express my deep appreciation and sincere gratitude to **Dr. Magdi Shihata Metias**, lecturer of Anestheisa and Critical care, Faculty of Medicine, Ain Shams University; Who had generously devoted much of his time and effort for planning and supervision of this study.

Finally, I can not express my deep gratitude and appreciation to my family for their active support, encouragement and patience.

CONTENTS

LIST OF TABLES

List of Abbreviations

ACCP	:	American college of chest physicians.
SCCM	:	Society of critical care Medicine.
SIRS	:	Systemic inflammatory response syndrome.
MODS	:	Multi – organ dysfunction syndrome
AIDS	:	Acquired immunedeficiency syndrome
D.M	:	Diabetes mellitus .
NF – B1	:	nuclear factor – B1 .
TNF	:	Tumor necrosis factor .
PNMS	:	Polymorphonuclear leukocytes .
I.L	:	Interlukeins .
LPS	:	Lipopoly Sacharid .
C5a	:	Complement fragment 5 a
SNP	:	Single nucleotide polymorphism .
PAI–1	:	Plasminogen activator inhibitor – 1
NO	:	Nitric oxide .
CRH	:	Corticotrophin - releasing Hormone
ACTH	:	Adrenocortico – trophic Hormone .
PCT	:	Procalcitonine .

Calc – 1 gene : gene for production of procalcitonine .

C – cells	:	Cells of thyroid gland responsible for PCT production .
$Scvo_2$	:	Superior vena cava o_2 saturation .
Svo_2	:	Mixed venous o_2 saturation frome pulmonary artery sample .
ICU	:	Intensive care unite .

MRSA	:	Methicilline – resistant Staph – aureus .
SSc	:	Serviving Sepsis Compagine .
ARDS	:	Acute respiratory distress syndrome .
SaO_2	:	arterial Oxygen Saturation .
FIO_2	:	Fractional inspired oxygen .
$PaCo_2$	:	Arterial Co_2 pressure
$Paco_2$	:	Arterial Co_2 pressure .
A L I	:	Acute Lung injury .
G I T	:	Gastro intestinal tract .
L M W H	:	Low Molecular weight heparin
D V T	:	Deep venous thrombosis .
U . F . H	:	Un fractionated Heparine

LIST OF FIGURES

INTRODUCTION

procalcitonin (PCT) is a protein of 116 amino-acids with molecular weight of 13 KDa, was discovered 25 years ago as a prohormone of calcitonin produced by C-cells of the thyroid gland and intracellularly cleaved by protolytic enzymes into the active hormone. Circulating levels of procalcitonin in healthy subjects are below detection limit. Since 1993 when its elevated level was found in patient's with bacterial infection, procalcitonin became an important protein in the detection and differential diagnostics of inflammatory states. The production of procalcitonin during inflammation is linked with a bacterial endotoxin and with inflammatory cytokines (TNF, IL-6). Procalcitonin detectable in the plasma during inflammation is not produced in C-cells of he thyroid. The protable site of procalcitonin production during inflammation are the neuroendocrine cells in the lungs or intestine ***(Maruna et al., 2000)***.

Procalcitonin circulating levels in healthy subjects are below the detection limit and are only enhanced in medullar carcinoma of the thyroid or in small cell lung carcinoma. When its elevated levels were reported in patients with bacterial infection ***(Boeken et al., 1998)***.

Procalcitonin became an important protein in the detection and differential diagnosis of inflammatory statess. Today a quarter of a century after procalcitonin discovery and seven years after its inclusion among inflammatory markers, it has became a useful tool in clinical practice although its physiological role still unclear. It's a protein play an undeniable role in the diagnosis of inflammatory states with advantages over other markers ***(Assicot et al., 1993)***.

CHAPTER 1

PATHOPHYSIOLOGY OF SEPSIS

Sepsis is a clinical syndrome defined as a systemic response to infection with maladaptive response of the host organism to the invasion of normally sterile tissue, fluid or body cavity by pathogenic or potentially pathogenic microorganisms. **“Martini A, et al, 2008”**

Sepsis is one of the most common reasons for admission to intensive care units (ICUs) throughout the world. Sepsis and multiorgan dysfunction syndrome (MODs), which is a common sequela of sepsis, use enormous ICU resources and are the leading causes of mortality in the ICU. Since the 1970s, enormous advances have been made in our understanding of sepsis, and these are being translated into new approaches to the management of patients with sepsis. **“Cheng B, et al, 2007”**

With progression to sepsis-associated organ failure “severe sepsis” or hypotension “septic shock” it became frequently fatal and represents a significant health care burden with increase of the incidence of morbidity and mortality rates and cost. **“Engel C, et al, 2007”**

Epidemiology

In recent decades, the reported incidence of sepsis has increased dramatically, largely due to an increased number of invasive procedures being performed, immunosuppressive therapy, and the advancing age of the population. Statistics from the Centers of Disease Control and Prevention

show that mortality from sepsis increased 13-fold from 1950 to 1991. in the United States, approximately 750.000 cases of sepsis occur each year- at least 225.000 of which are fatal. Despite the use of antimicrobial agents and advanced life supportive care, the mortality of the patients with sepsis has remained between 30% to 40% since the 1970s. **"Angus DC, et al, 2007"**

Defining a Syndrome

Before 1992 the terminology used to define the systemic response to infection varied widely. Then members of the American college of chest physicians (ACCP) and the society of critical care medicine (SCCM) developed a set of consensuses definitions for sepsis and related disorders. The consensuses committee believed that standardized terminology would improve the ability of clinicians to make an early diagnosis of sepsis, provide for more reliable reporting of the incidence and severity of sepsis and facilitate early therapeutic interventions. In addition they hoped that acceptance of the definitions would help to standardize research protocols and improve the dissemination and application of clinical information from subsequent studies. "**Levy MM, et al, 2003"**

Systemic inflammatory response syndrome (SIRS) is characterized by two or more of the following: **"Levy MM, et al, 2003"**

(a) A body temperature of greater than 38°C or less than 36°C.
(b) A heart rate is greater than 90 beats per minute and
(c) Tachypnea as manifested by a respiratory rate of greater than 20 breaths per minutes.

(d) An alteration of the white blood cell count of greater than 12.000 cells/mm^3 or less than 4.000 cells/mm^3 or the presence of greater than 10% immature neutrophils.

Sepsis is a SIRS in response to infection and its diagnosis requires at least two SIRS criteria plus infection. **"Levy MM, et al, 2003"**

Sever sepsis is more than just an inflammatory reaction to bacterial infection. Instead it is a viscous cycle of inflammatory changes, endothelial injury and coagulation abnormalities. So it is associated with one or more of acute organ dysfunction. **"Levy MM, et al, 2003"**

Sepsis shock defined as sepsis induced hypotension despite fluid resuscitation in addition to the presence of perfusion abnormalities that includes oliguria, lactic acidosis and acute circulatory failure. **"Levy MM, et al, 2003"**

Fluid un responsive hypotension defined as systolic blood pressure less than 90 mmHg or mean arterial pressure less than 60 mmHg or reduction of systolic blood pressure more than 40 mmHg from base line. Unresponsive to adequate fluid challenge so requiring vasopressors and inotropes. **"David AT, et al, 2008"**

Pathogenesis of sepsis

The normal host response to infection is a complex process that serves to localize and control bacterial invasion and to initiate repair of injured tissue. This inflammatory process is normally accompanied by activation of circulating and fixed phagocytic cells and by generation of

pro-inflammatory and anti-inflammatory mediators. Sepsis results when the inflammatory response to infection becomes generalized, and extends to involve normal tissue remote from the initial site of injury or infection. "**Cinel I, and Dellinger, 2007**"

Sepsis has been referred to as a process of malignant intravascular inflammation. It is considered malignant because it is uncontrolled, unregulated, and self-sustaining. It is considered intravascular because it represents the blood-borne spread of what is usually a cell-to-cell interaction in the interstitial space. It is considered inflammatory because all characteristics of the septic response are exaggerations of the normal inflammatory response. "**Van der Poll T, et al, 2008**"

Sepsis may therefore be described as an autodestructive process that permits the extension of a normal pathophysiologic response to infection to involve otherwise normal tissue. This can result in the multiple organ dysfunction syndrome (MODS). "**Baron RM, et al, 2006**"

Therefore sepsis is considered a complex process that involves interplay between number of microbial and host factors in the form of excessive triggering of body defense mechanisms by invading microorganisms. These defense mechanisms include a complex interaction between immunity, coagulation /fibrinolytic systems. So components of the reaction to sepsis include host, bacterial factors, cellular elements, cytokines and other mediators and hemostatic mediators. **"Tsiotou AG, et al, 2005"**

a. Microbial Factors

Microbial factors are the second determinant of sepsis outcome. Microbes posses several factors that facilitate their growth in a normally sterile environment. These include properties of their capsule or envelope. Cell wall and metabolic factors such as the production of exotoxins. "**Vincent JL, et al, 2006**"

Direct effects of invading microorganisms or their toxic products may also contribute to the pathogenesis of sepsis. Among the potentially offending factors are endotoxin, cell wall components of bacteria (peptidoglycan, muramyl dipeptide, and lipoteichoic acid), and bacterial products such as staphylococcal enterotoxin B, toxic shock syndrome toxin-1, Pseudomonas exotoxin A, and M protein of hemolytic group A streptococci. "**Akira S, et al, 2006**"

There is substantial evidence to suggest that endotoxin is an important exogenous mediator of sepsis in gram negative bacterial infections. Endotoxin, a lipopolysaccharide found in the cell wall of gram negative bacteria, tends to reproduce many of the features of sepsis when infused in humans." **Bianchi ME, 2007**"

Endotoxemia is detectable in septic patients. Furthermore, elevated plasma levels of endotoxin are associated with shock and multiple organ dysfunction. "**Saleh M, et al, 2006**"

b. Host Factors

1. Resistance to infection is a result of a number of host factors which are known as "homeostasis" or host defense mechanisms as like epithelial barriers which are the first line of defense against infection. This barrier

may be breathed by trauma or alteration of mucosal defense results from toxins or hemodynamic alterations. Also factors that prevent local infection includes mucocilliary flow in respiratory tract, pH of stomach of body fluids and secretory immunoglobulins.

2. Immune status of host is a function of inherited and acquired compoenents which has a major role in localizing and limiting the infection with prevention of its extension and propagation. So infection is more common and more dangerous in immuno compromised patients as diabetics, malnourished patients, alcoholics, cancer patients and immunosuppressed patients as AIDS and those on immunosuppressive drugs.

3. Genetic factors of host: emerging improvements in technologies (ie, analysis of common genetic variation) have led to high expectations for determining the contribution of genetics to risk assessment. "**Johnson SB, et al, 2007**"

Many investigators have used the most common form of genetic variation, the single nucleotide polymorphism (SNP), to assess risk in septic patients. SNPs are stable substitutions of a single base that have a frequency of more than 1 percent in at least one population and are strewn throughout the genome, including promoters and intergenic regions. The total number of common SNPs in the human genome is estimated to be more than 10 million. SNPs are genetic markers. At most, only 2 to 3 percent are known to alter the function or expression of a gene. Various SNPs are associated with increased susceptibility to infection and poor outcomes. They include SNPs of genes encoding cytokines (eg, TNF, lymphotoxin-alpha, interleukin 10, interleukin 18, interleukin-1 receptor

antagonist, interleukin 6, and interferon gamma), cell surface receptors (eg, CD14, MD2, toll-like receptors 2 and 4, and Fc-gamma receptors II and III), lipopolysaccharide ligands (lipopolysaccharide binding protein, bactericidal permeability increasing protein), mannose-binding lectin, heat shock protein 70, angiotensin I-converting enzyme, plasminogen activator inhibitor, and caspase-12. "**Abraham E, 2007**"

4. Acquired risk factors. Such as age: young children and elderly have an increased incidence of sepsis most probably due to low level of the immunostatus in comparison with middle age groups. **"Moss M, 2005"**

Sex: gender also influences incidence of sepsis, this may be due to function of androgens induced immunodepression and difference in site of infection between both sex. Exposure and interventions, diseases as diabetes mellitus, liver cirrhosis and renal failure are risk factors for sepsis. **"Moss M, 2005"**

When the body is challenged by foreign agents, homeostatic mechanisms come into play that attempt to rid the body of the foreign antigens without damaging the host. These pathways include the pro-and anti-inflammatory cytokines, which are closely linked to other homeostatic pathways including those of the coagulation/fibrinolytic system, the acute phase and heat-shock response, neutrophil-endothelial cell activation, activation of the hypothalamic-pituitaryadrenal axis, immune and nonimmune cell apoptosis, increased nitric oxide (NO) production, and the oxidant/antioxidant pathway, to name but a few. Sepsis can be considered to be a dysregulation of this tightly integrate homeostatic mechanism. **"Tsiotou, et al, 2005"**