PRESEPSIN AS A NEW MARKER IN MANAGEMENT OF SEPSIS

Essay

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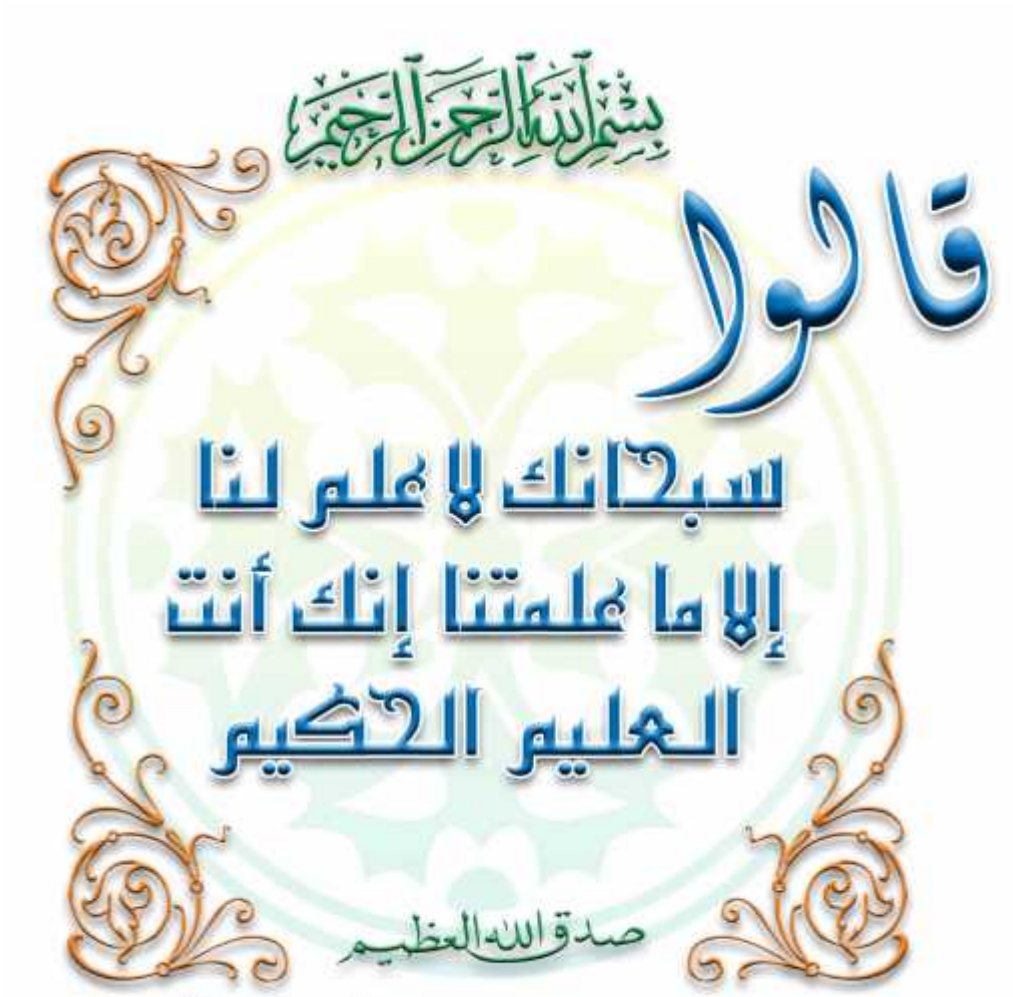

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Dr. Asmaa Magdy Shaban

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
AA	Amino acids
ACCESS	**AC**ontrolled **C**omparison of **E**ritoran Tetrasodium and Placebo in Patients with **S**evere **S**epsis
ACCP	American College of Chest Physicians
ACTH	adrenocorticotropic hormone
AIDS	acquired immunodeficiency syndrome
APACHE	Acute physiology and chronic health evaluation
APC	Activated Protein-C
aPTT	activated Partial thromboplastin time
ARDS	Acute respiratory distress syndrome
ATP	adenosine triphoaphate
ATS	American Thoracic Society
BBB	Blood Brain Barrier
C	Complement fragment
C5a	Complement fragment 5a
C5aR	Complement fragment 5a receptor
CARS	Compensatory anti-inflammatory response syndrome
CD	Cluster of differentiation
CLEIA	chemiluminescent enzyme immunoassay
CLP	Cecal ligation and puncture
CNS	Central nervous system
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
CVC	Central venous catheter
CVP	Central venous pressure
CVVH	Continuous venovenous hemofiltration
DAMPs	Damage-associated molecular patterns
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
DNA	deoxyribonucleic acid

Abbreviation	Meaning
EC	Endothelial cells
ED	Emergency Department
EGDT	Early goal-directed therapy
ELISA	Enzyme-linked immunosorbent assay
ESICM	European Society of Intensive Care Medicine
ET	Endotoxin
FDA	US Food and Drug Administration
FIO_2	fractional inspired oxygen
FMLP	formyl-Met-Leu-Phe (a three amino acid)
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte-monocyte colony stimulating factor
GPI	Glycosyl-phosphatidylinositol
H_2O_2	hydrogen peroxide
HBP	Heparin-binding protein, azurocidin
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HMG	hydroxymethylglutaryl
HMGB1	High- mobility group box 1
HVHF	High volume hemofiltration
ICAM-1	Intercellular adhesion molecule-1
ICU	Intensive Care Unit
IL	Interleukin
IL-1ra	Antagonist of the interleukin-1 receptor
INR	International normalized ratio
IVIG	Intravenous immunoglobulin
kDa	Kilodalton
LBP	Lipopolysaccharide-binding protein
LDL	Low-density lipoprotein
LPS	Lipopolysaccharide
LTA	lipoteichoic acid
MAP	Mean arterial blood pressure
mCD14	Membrane CD14
MCP-1	Monocyte chemoattractant protein-1

Abbreviation	Meaning
MD2	Co-protein of TLR-4
MDL-1	Myeloid DAP12-associating lectin
MHC	Major histocompatibility complex
MIF	Macrophage migration inhibition factor
Mo	Monocytes
MODS	Multiple organ dysfunction syndromes
MRSA	Methicillin-resistant staph aureus
NAD	Nicotinamide adenine dinucleotide
NGAL	Neutrophil gelatinase-associated lipocalin
NO	Nitric oxide
NOD	Nucleotide-oligomerization domain
PACs	Pulmonary artery catheters
PAMPs	Pathogen-associated molecular patterns
PaO_2	arterial oxygen tension
PAOP	Pulmonary artery occlusion pressure
PARs	Protease-activated receptors
PASS	Procalcitonin and Survival Study
PBFC	Polymyxin B fiber column
PCO_2	carbon dioxide partial pressure (tension)
PCR	polymerase chain reaction
PCT	Procalcitonin
PD	Peritoneal dialysis
PD-1	Programmed death-1
PG	Polyglycan
PGN	Peptidoglycan.
PHi	Gastric intramucosal PH
PLTP	Proteins like phospholipid transfer protein
PMNs	Polymorphonuclear leukocytes
PNH	Paroxysmal nocturnal haemoglobinuria
PRRs	Pattern recognition receptors
PTX3	Pentraxin 3
RAGE	Receptor for advanced glycation end-products
rhAPC	Recombinant human activated protein C

Abbreviation	Meaning
RIG-I	Retinoic-acid-inducible gene I
RNA	Ribonucleic acid
SAFE	Saline versus albumin fluid evaluation
SBP	Systolic blood pressure
SCCM	Society of Critical Care Medicine
sCD	Soluble Cluster of differentiation
sCD14-ST	soluble CD14 subtype (Presepsin)
$ScvO_2$	Central venous oxyhemoglobin saturation
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SIS	Surgical Infection Society
SNP	Single nucleotide polymorphism
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
SvO_2	Mixed venous oxyhemoglobin saturation
TCR	T-cell receptor
TGF	Transforming growth factor
TLRs	Toll-like receptors
TNFα	Tumor necrosis factor alpha
TREM	Triggering receptor expressed on myeloid cell
US	United States
VCAM-1	Vascular cell adhesion molecule-1
VISEP	Volume Substitution and Insulin Therapy in Severe Sepsis
VLDL	Very-low density lipoprotein
WBC	White blood cell

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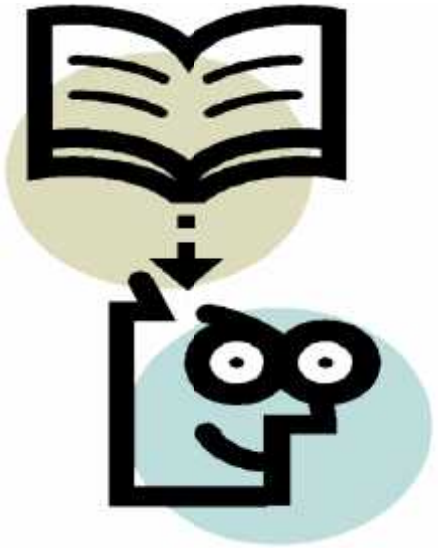
Introduction



INTRODUCTION

Sepsis is a clinical state, which is complicated with severe infection and characterized with systemic inflammation and disseminated tissue damage, which needs explanation of SIRS condition primarily to be fully understood. SIRS is a clinical syndrome that result from dysregulated inflammatory response to non infectious insult, such as autoimmune disorders, vasculitis, pancreatitis, burns or surgery, which requires two or more features of the following abnormalities to be present:

* Body temperature > 38.5 or < 36 ^{0}C.

* Heart rate > 90 beat/ min.

* Respiratory rate > 20 breaths / min or $PaCO_2$ < 32 mmHg.

* Altered leukocyte count > 12000 or < 4000 / mm^3 **(Annane and Cavaillon**, **2005)**.

A consensus conference in 1991 defined sepsis as the combination of an infection with two or more features of SIRS, along with either a culture proven or visually identified infection . An update to that original definition, published in 2003, expand the criteria to include other signs and symptoms commonly seen in critical illness **(Levy et al, 2003)**. Septic shock is defined as sepsis associated with hypotension, despite adequate fluid resuscitation **(Dellinger et al, 2008)**.

Sepsis and septic shock are some of the most common conditions handled in the intensive care areas, and despite modern antibiotic therapy in conjugation with cardiovascular and respiratory support,

mortality remains between 30 and 60% **(Dombrovskiy et al, 2007)**. According to the last guidelines, published in 2013 by the surviving sepsis campaign (SSC), early recognition of these conditions with speed and appropriateness of therapy in the initial hours is likely to influence outcome of septic patients **(Dellinger et al, 2013)**.

Biomarkers to diagnose sepsis may allow early intervention which, although primarily supportive, can reduce the risk of death. Biomarkers can have an important role in the presence, absence or severity of sepsis, and can differentiate bacterial from viral and fungal infection, and systemic sepsis from local infection. Other potential uses of biomarkers include roles in prognosis, antibiotic therapy, evaluating response to therapy and recovery from sepsis, predicting sepsis complications and development of organ dysfunction. However, the exact role of biomarkers in the management of septic patients remains undefined **(Marshall and Reinhart, 2009)**.

Actually, there are some findings about diagnostic biomarkers but none has sufficient capability to diagnose all etiological kinds of sepsis or specificity- sensitivity to be routinely employed in clinical practice. Currently, procalcitonin (PCT) and C-reactive protein (CRP) have been most widely used in clinical practice.CRP has been used for many years but its specificity has been challenged. PCT has been proposed as a more specific and better prognostic marker than CRP, although its value has also been challenged **(Nakamura et al, 2009)**. It remains difficult to differentiate sepsis from other non-infectious causes of SIRS and studies are being continued to define a reliable biomarker.

In these days, a new biomarker, presepsin or sCD14-ST, is proposed in the field of sepsis. It was firstly defined in 2005 and has been a new

important marker for diagnosis and prognosis of sepsis in recent years **(Yaegashi et al, 2005)**. CD14 (cluster of differentiation) is a glycoprotein express on the surface membrane of monocytes/ macrophages and service as a receptor for complexes of lipopolysaccharides (LPS) and LPS binding protein (LPP). Activating proinflammatory signaling cascade on contact with infectious agents, CD14 has a role as a pattern recognition molecule in the innate immune response against microorganisms. During inflammation plasma protease activity generates soluble CD14 (sCD14) fragments: one of them called sCD14 subtype (sCD14-ST) or presepsin **(Shirakawa et al, 2011)**.

Presepsin is normally present in very low concentration in the serum of healthy individuals and has been shown to be increased in response to bacterial infections according to the severity of disease. Preliminary studies suggest that the level of presepsin significantly differs in healthy individuals, in patients with local infection, SIRS, sepsis or severe sepsis. It also sought to be more specific and sensitive biomarker for the diagnosis of sepsis compared to other biomarkers and its level in blood increases faster than them **(Endo et al, 2012)**.

Aim of the Work