THE ROLE OF BIOMARKERS IN THE DIAGNOSIS AND OUTCOME IN PATIENTS WITH SEPTIC SHOCK

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Summary

Sepsis is a main cause of death in critically ill patients. Despite the use of modern antibiotics and resuscitation therapies, severe sepsis mortality is 25% to 30% and mortality due to septic shock approaches 40% to 70%. Sepsis is the systemic response to infection and it involves a complex interaction between the pathogen and the host's immune system that result in the release of inflammatory mediators, vasodilation, increased vascular permeability, diffuse endothelial disruption, activation of coagulation pathways and thrombosis of end organ capillaries with subsequent organ faiure.

The diagnosis of sepsis is difficult, because clinical signs of sepsis often overlap with other non infectious causes of systemic inflammation. These signs include tachycardia, leucocytosis, tachypnea, and pyrexia which are collectively termed a systemic inflammatory response syndrome (SIRS). Microbiological culture can be used to distinguish sepsis from non infectious conditions. However, this method lacks sensitivity and specificity and there is often a substantial time delay.

The diagnosis of sever sepsis is based clinically on suspected infection (through clinical localizing and systemic symptoms and signs of infection) and clinical evidence of organ dysfunction. The diagnosis of septic shock is established in the presence of suspected infection with sustained hypotension (without a definitive alternate explanation) despite adequate fluid resuscitation.

Contents

List of abbreviations

$AaDO_2$	**Alveolar arterial O_2 tension difference**
ABG	**Arterial blood gas**
ACTH	**Adrenocorticotropic hormone**
ADH	**Antidiuretic hormone**
AIDS	**Acquired immune deficiency syndrome**
ALI	**Acute lung injury**
ALT	**Alanine transaminase**
AM	**Adrenomedullin**
ANP	**Atrial natriuretic peptide**
APACHE	**Acute Physiology and Chronic Health Evaluation**
aPC	**Activated protein C**
aPTT	**Activated partial thromboplastin time**
ARDS	**Acute respiratory distress syndrome**
ARF	**Acute renal failure**
AST	**Aspartate transaminase**
ATIII	**Antithrombin III**
ATN	**Acute tubular necrosis**
ATP	**Adenosine triphosphate**
BBB	**Blood-brain barrier**
BCs	**blood cultures**
BNP	**Brain natriuretic peptide**
BUN	**Blood urea nitrogen**
BWF	**biphasic waveform**
C3a	**Complement 3a**
C4bBP	**C4b-binding protein**
CAP	**Community acquired pneumonia**
CD	**Cluster of differentiation**
CK-MB	**Creatine kinase MB isoenzyme**
CNS	**Central nervous system**
CO	**Cardiac output**
CO_2	**Carbon dioxide**
CoA	**Co-enzyme A**
Cr	**Serum creatine**
CRP	**C reactive protein**
CT	**Computed tomography**
CVOs	**Circumventricular organs**
CVP	**Central venous pressure**

CVVH	**Continuous veno-venous haemofiltration**
DC	**Dendritic cells**
DIC	**Disseminated intravascular coagulation**
DNA	**Deoxyribonucleic acid**
dsRNA	**Double stranded ribonucleic acid**
DVT	**Deep venous thrombosis**
ECG	**Electrocardiography**
ED	**Emergency department**
EEG	**Electroencephalography**
ELAM-1	**Endothelial-leukocyte adhesion molecule-1**
EMG	**Electromyography**
EPCR	**Endothelial cell protein C receptor**
ET-1	**Endothelin-1**
F/TV	**Frequency/ tidal volume**
FDA	**Food and drug administration**
FIO_2	**Fraction of inspired oxygen**
GCS	**Glasgow coma scale**
G-CSF	**Granulocyte colony stimulating factor**
GFR	**Glomerular filtration rate**
GI	**Gastrointestinal**
GM-CSF	**Granulocyte/macrophage colony-stimulating factor**
Hb	**Hemoglobin**
$HCO3^-$	**Serum bicarbonate concentration**
HLA-DR	**Human leucocyte antigen-DR**
HMGB-1	**High mobility group box -1**
ICAM-1	**Intercellular adhesion molecule-1**
ICU	**Intensive care unit**
IFN- α	**Interferon- α**
IFN- β	**Interferon- β**
IFN- γ	**Interferon- γ**
IL	**Interleukin**
IL-1ra	**Interleukin-1 receptor antagonist**
iNOS	**Inducible nitric oxide synthetase**
INR	**International normalized ratio**
LBP	**Lipopolysaccharide binding protein**
LC-CRP	**Lipoprotein complexed C-reactive protein**
LHR	**likelihood ratio**
LMWH	**Low-molecular weight heparin**
LPS	**Lipopolysaccharide**

LTA	**Lipoteichoic acid**
LV	**Left ventricle**
MAP	**Mean arterial pressure**
MARS	**Mixed antagonists response syndrome**
MCP	**Monocyte chemotactic protein**
MIF	**Macrophage migration inhibitory factor**
MIP	**Macrophage inflammatory protein**
MMP	**Matrix-metalloproteinase**
MODS	**Multiple organ dysfunction syndrome**
mRNA	**Messenger ribonucleic acid**
MV	**Mechanical ventilation**
NAD	**Nicotinamide adenine dinucleotide**
NFκB	**Nuclear factor kappa B**
NMBs	**Neuromuscular blockers**
NO	**Nitric oxide**
N-ProCT	**Amino-terminal Procalcitonin Cleavage Peptide**
OSF	**Organ System Failure**
$PaCO_2$	**Partial pressure of carbon dioxide in arterial blood**
PAI-1	**Plasminogen activator inhibitor-1**
PaO_2	**Partial pressure of oxygen in arterial blood**
PAP	**Plasmin antiplasmin complex**
PCT	**Procalcitonin**
PCT-Q	**Semi-quantitative procalcitonin test**
pCysC	**Plasma cystatin C**
PEEP	**Positive end expiratory pressure**
PMNLs	**Polymorphonuclear leukocytes**
PrC	**Protein C**
pro-AM	**Pro- adrenomedullin**
PRRs	**pattern recognition receptors**
PT	**Prothrombin time**
RBCs	**Red blood cells**
rhAPC	**Recombinant Human Activated Protein C**
RNA	**Ribonucleic acid**
ROS	**Reactive oxygen species**
rT3	**Reverse Triiodothyronine**
SBP	**Systolic blood pressure**
SBT	**Spontaneous breathing trial**
SD	**Standard deviation**
SIRS	**Systemic Inflammatory Response Syndrome**

SOFA	**Sequential organ failure assessment score**
SSC	**Surviving Sepsis Campaign**
ssRNA	**Single stranded ribonucleic acid**
sTREM-1	**Soluble triggering receptor expressed on myeloid cells-1**
SvO_2	**Mixed venous oxygen saturation**
T_3	**Triiodothyronine**
T_4	**Tetraiodothyronine (Thyroxine)**
TAFI	**Thrombin activatable fibrinolysis inhibitor**
TAT	**Thrombin antithrombin complex**
TF	**Tissue factor**
TFPI	**Tissue factor pathway inhibitor**
TGF	**Transforming growth factor**
TIMPs	**Tissue inhibitor of matrix metalloproteinases**
TLR	**Toll like receptors**
TM	**Thrombomodulin**
TNF	**Tumor necrosis factor**
TnI	**Troponin I**
t-PA	**Tissue-type plasminogen activator**
TREM-1	**Triggering receptor expressed on myeloid cells-1**
TSH	**Thyroid stimulating hormone**
TSST	**Toxic shock syndrome toxine**
UFH	**Unfractionated heparin**
u-PA	**Urokinase-like plasminogen activator**
VAP	**Ventilator associated pneumonia**
VCAM-1	**Vascular cell adhesion molecule-1**
VLDL	**Very low density lipoprotein**
WBC	**White blood cells**

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Introduction

Sepsis is the main cause of death in surgical intensive care units (ICUs), with a continuously increasing incidence and a mortality rate depending on sepsis severity and the days of hospital stay. Therefore, both an early diagnosis and a timely prognosis of sepsis are of great importance to control efficacy of antibiotic and surgical therapy, to manage further diagnostics and interventions and to optimize cost containment by adequate resource allocation ***(Tschaikowsky et al., 2011).***

Early and appropriate antibiotic therapy is critical in sepsis. Likewise, limiting exposure when infection is absent will become exceedingly important as drug resistance increases. These complexities have led to the search for a biomarker or set of biomarkers with compelling sensitivity and specificity for effectively identifying the disease, patients at risk for untoward outcomes and reliably guiding treatment ***(Ventetuolo and Levy, 2008).***

The pathophysiology of sepsis and septic shock involves a complex interaction between the pathogen and the host's immune system that result in the release of inflammatory mediators, vasodilation, increased vascular permeability, diffuse endothelial disruption, activation of coagulation pathways and thrombosis of end organ capillaries. The cascade of inflammation and thrombosis can be triggered by endotoxins contained within the cell wall of gram negative bacteria or exotoxin released by gram positive bacteria ***(Filbin, 2010).***

Septic shock falls under the category of distributive shock, which is characterized by pathologic vasodilation and shunting of blood from vital organ to nonvital tissues such as skin, skeletal muscles and adipose tissue. Endothelial dysfunction and vascular maldistribution of distributive shock results in global tissue hypoxia or inadequate delivery of oxygen to vital tissues. In addition, mitochondria can become dysfunctional, thus compromising oxygen utilization at the tissue level. Furthermore, activation of the coagulation cascade and fibrin deposition cause microthombi to form in end organ capillaries. These factors lead to organ dysfunction and eventual failure ***(Landry and Oliver, 2001) (Trzeciak and Rivers, 2005).***

The diagnosis of sepsis is difficult, because clinical signs of sepsis often overlap with other non infectious causes of systemic inflammation. These signs include tachycardia, leucocytosis, tachypnea, and pyrexia which are collectively termed a systemic inflammatory response syndrome (SIRS). SIRS is very common in critically ill patients, being found in various conditions including trauma, surgery and hypoxic injuries. Microbiological culture can be used to distinguish sepsis from non infectious conditions. However, this method lacks sensitivity and specificity and there is often a substantial time delay ***(Benjamin et al., 2007).***

Blood cultures are based on the detection of viable micro-organisms present in blood. Blood cultures are used to detect viable pathogens and have the advantage of allowing the evaluation of their antimicrobial susceptibility. This aspect is important, as several studies have shown that inadequate antimicrobial therapy is an independent risk factor for mortality

for severely ill patients with life-threatening infections ***(Mancini et al, 2010).***

In patients with sepsis, blood cultures are positive in not more than 30% to 40% and also may be found in patients without sepsis. Microbiologic proof of infection is expensive and may be difficult in patients with prior antibiotic treatment. Positive results may indicate colonization or contamination without pathophysiologic relevance. In 35%, sepsis cannot be proved microbiologically despite the presence of clinical signs and suspicion of a focus ***(Reinhart et al, 2006).***

Recent data and cumulative analysis indicate that biomarkers improve diagnosis of sepsis and may help to predict the prognosis of septic patients. In the scene of sepsis biomarkers, procalcitonin (PCT), C-reactive protein (CRP) and interleukin-6 (IL-6) are the most investigated markers in clinical trials. In recent published studies, procalcitonin is of better value for diagnosis and prognosis of sepsis when compared with markers such as CRP or with proinflammatory cytokines such as IL-6 ***(Hoffmann et al., 2009).***

Concentration of CRP has been used to follow septic patients but it is poor diagnostic and prognostic indicator because of the time taken to produce a reaction and the duration of the increase in serum concentration. Then attention has turned to the use of PCT assay for diagnosis and decision making ***(Diane, 2006).***

PCT is a marker of the inflammatory response. In systemic inflammatory conditions and sepsis, inflammatory mediators

trigger the production of PCT. PCT level increases within 3 to 6 hours of the stimulus. Higher PCT levels are associated with poorer prognosis and are found in patients with sepsis, severe sepsis, and septic shock ***(Becker et al., 2008) (Schneider and Lam, 2007).***

The US Food and Drug Administration (FDA) has approved the use of PCT in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock ***(Jensen et al., 2006).***

IL-6 is an important mediator in septic shock and has long been acknowledged to predict severity and outcome in this disease. As a marker of infection, it is relatively nonspecific, because it is elevated in a variety of inflammatory states. As one of the initial cytokines released in inflammation, IL-6 may be an early predictor of more downstream effects, such as organ dysfunction ***(Chawla et al., 2007).***

Pathophysiology of Sepsis

Introduction

Definitions developed by the American College of Chest Physicians and the Society of Critical Care Medicine in 1992 to describe various components of this complicated clinical state.

Infection

A microbial phenomenon characterized by an inflammatory response to the presence of micro-organisms or the invasion of normally sterile host tissue by these organisms.

Bacteremia

The presence of viable bacteria in the blood. Bacteremia can either be transient, sustained or intermittent.

Systemic Inflammatory Response Syndrome (SIRS)

The systemic inflammatory response to various severe clinical insults, including but not limited to infection. Various other clinical insults include pancreatitis, ischemia, multiple trauma and tissue injury. SIRS requires two or more of the following conditions:

- Temperature >38 ◦C or <36 ◦C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg
- White blood cells (WBC) >12,000/mm_3, <4000 cells/mm_3, or >10% immature (band) forms ***(Bone et al., 1992).***