The Role of the Recent Biomarkers In Sepsis

Essay
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دور الدلالات الحيوية الحديثة في تعفن الدم

رسالة توطئة للحصول على درجة
الماجستير فى الرعاية المركزة

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Summary

Sepsis is a leading cause of death in ICU despite modern antibiotics and resuscitation therapies. SIRS is characterized by 2or more of the following; body temperature $\geq 38^{o}C$ or $\leq 36^{o}C$ HR 90, WBC 12, 000 or 4000 cell per mm^3 if source of infection is suspected or known this is known as sepsis if associated with organs dysfunction is called severe sepsis but septic shock in defined as severe sepsis associated with hypotension despite adequate fluid resuscitation.

Pathogenesis of sepsis involves interaction between multiple microbial factors and host factors and the out come depends on capability of the immune system, endothelium and haemostatic mechanism to contain and eliminate the process. Microbial factors include (gram positive, negative, mixed and fungal infection) and most common sources of infections are respiratory 50%, abdomen and pelvis 25%, urinary tract 10%, skin 5%, IV catheter 5% and others 10%. Host factors as race, age and comorbities.

Pathophysiology of sepsis includes coagulation system activation as activation of pro-coagulant pathway and imbalance of homeostasis; hypothalamic – adrenal axis dysfunction and microcirculatory dysfunction lead to multi organs failure. There are many hypotheses initiate and perpetuate multi organs failure as gut hypotheses, tissue hypothesis, two events hypotheses and integrated hypothesis.

Disease-severity scoring systems are used for stratification of patients for utilization management, performance assessment, and clinical research as SOFA score, MODS score, APACH score, PIRO score and SAP score.but their calculations require types of data that are frequently unavailable.

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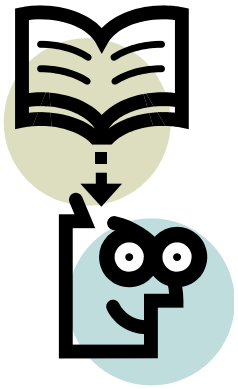
List of Abbreviations

AAG	al-acid glycoprotein
ADAMTS	A Disintegrin- like and metalloprotease with thrombospondin type 1 motif
AIDS	Acquired immuno-deficiency syndromes
ALI	Acute lung injury
AMS	Anti microbial treatments
aPTT	Activated partial thromboplastin time
APACHE score	Acute physiological and chronic health evaluation
APC	Activated protein c
ARDS	Acute respiratory distress syndromes
ARF	Acute renal failure
AT111	Anti thrombin 111
BPI	Bactericidal/permeability-increasing protein
CD	Cluster of differentiation
CIP	Critical illness polyneuropathy
CIRCI	Critical illness related corticosteroid insufficiency
CNP	c-type natriuretic peptide
C-RP	C-reactive protein
CSIF	Cytokines synthesis inhibitory factor
DIC	Disseminated intravascular coagulopathy
DO	Oxygen delivery
EGDT	Early goal directed therapy
FIO_2	Fractional inspired oxygen

GMP	Guanosine monophpsphate
HBP	Heparin binding protein
HMGB	High mobility group box1
HO	Hem oxygenase
ICAM	Intercellular adhesion molecule
IL18BP	Interleukin 18 Binding protein
IL	interleukin
INR	International normalization ratio
LDL	Low density lipoprotein
LPS	lip polysaccharides
LPB	Lip polysaccharide binding protein
MAP	Mean arterial pressure
MDF	Myocardial depressant factor
MODS	Multi organ failure dysfunction syndromes
MMDS	Microcirculatory and mitochondrial distress syndromes
NPV	Negative predictive value
NF-6B	Nuclear factor 6B
NO	Nitrous oxide
NOS	Nitrous oxide synthesis
PAMPS	Pathogen associated molecular pattern
PaO2	Arterial oxygen tension
PAR	Pressure adjusted heart rate
PAI	Plasminogen activator inhibitor
PCT	Plasma Procalcitonin
PIRO	Predisposition insults/injuries response organ dysfunction
PPV	Positive predictive value
PRRS	Pattern recognition receptor
PT	Prothrmbin time

RAI	Related adrenal insufficiency
RCO	Ristocetin co factor activity
Rh APC	Recombinant activated protein C
SAFE	Saline versus albumin fluid evaluation
SAPS	Simplified acute physiological score
SBP	Systolic blood pressure
SCVO2	Central venous oxygen saturation
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SOFA	Sepsis related organ failure
STREM	Soluble triggering receptor expressed on myeloid cells
SVO2	Mixed Venous oxygen saturation
TAT	Thrombin anti thrombin complex
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
TLR	Toll like receptor
TM	Thrombomoduline
TNF	Tumor necrosis factor
T-PA	Tissue –type plasminogen activator
UPA	Urokinase –type plasminogen activator
VAP	Ventilator associated pneumonia
VCAM	Vascular cell adhesion molecule
VISP	Volume substitution and insulin therapy in severe sepsis
VTE	Venous thrombo embolism
VWF	Von will brad factor
VWF CP	Von will brad factor cleaving protein
WBCS	White blood cell

Introduction And Aim Of Work



Introduction

Sepsis is a common cause for admission to the intensive care unit and associated with increased morbidity and mortality. Systemic inflammatory response syndrome is defined as a complex activation of immune system and characterized by altered body temperature < 36^{o}C or > 38^{o}C, hyperventilation (tachypnea > 20 breaths/min. or PaCO2 < 30 mm Hg) and altered leukocyte count (< 4, 000 or > 12, 000 cells per mm3), while sepsis is defined as systemic inflammatory response syndrome in conjunction with documented infection and if sepsis associated with organ dysfunction is called as severe sepsis. Septic shock is defined as sepsis associated with hypotension, despite adequate fluid resuscitation **(Dellinger et al., 2008)**.

Pathogenesis of sepsis involves an interaction between multiple microbial and hosts factors, the outcome of the process depend on the capability of the immune system, endothelium and haemostatic mechanisms to contain and eliminate the process. The survival depends on the ability to recognize invading pathogens and to respond to them rapidly. Many defenses against microbes are innate rather than adaptive to the particular pathogen. The innate immune system includes macrophages and natural killer cells, which may act directly on the pathogen or by releasing cytokines and expressing certain other stimulatory molecules triggers of the adaptive immune responses by activating T and B cells which have precise specificity in recognizing antigens **(Eliezer et al., 2007).**

Pathogenesis of sepsis also results from an exaggerated systemic inflammatory response induced by infectious microorganisms which release inflammatory mediators that cause injury to capillary endothelium leading to vasodilatation together with capillary leak resulting in loss of intravascular

fluid into interstitial space causing hypovolemia and tissue hypoxia **(Zeni et al., 2002).**

The progressive dysfunction of organ systems that characterize multiorgan dysfunction syndromes (MODS) usually occurs in a predictable manner. During the first 72 hours of the original insult, respiratory failure commonly occurs. This is followed by hepatic failure (5 to 7 days), gastrointestinal bleeding (10 to 15 days), and finally renal failure (11 to 17 days). The pathophysiologic processes leading to MODS have not been well defined. However, there are several hypotheses of the mechanisms that initiate and perpetuate multiorgan dysfunction syndrome **(Abraham et al., 2007).**

The Early Goals -Directed Therapy within first 6 hours are: Central Venous Pressure 8-12 mm Hg (12-15 in ventilator pts), mean arterial pressure > 65 mm Hg, urine output > 0.5 ml/kg/hr, ScvO2orSvO2≥70%; If not achieved with fluid resuscitation during first 6 hours: Transfuse packed red blood cells to hematocrit > 30% and/or Administer dobutamine (max 20 mcg/kg/min) to goal **(Otero et al., 2006).**

There are several biomarkers, which have roles in sepsis they are cytokines/chemokines biomarkers, cell membrane biomarkers, receptor biomarkers, , coagulation biomarkers, biomarkers of organ dysfunction, biomarkers related to vasodilatation, biomarkers related to vascular endothelial damage and others like Beta-thrombo globulin, Eicosanoid and Elastase **(Winters et al., 2010).**

Cytokines/chemokines biomarkers such as IL-8, IL-12 has a role in prediction of lethal outcome, cell membrane biomarkers as CD80, has a role in prediction of septic shock, receptor biomarkers as C512, IL-2 receptors, has a role in prediction of septic shock, coagulation biomarkers as PF-4 has a role in prediction of response to therapy, biomarkers of organ

dysfunction such as Gc-globulin, hepatocyte and growth factors, biomarkers related to vascular endothelial damage as Angiopoietin has a role in predication development of sepsis and other bio markers like Bet- thrombo globulin, Eicosanoid and Elastase, which have role in prediction of response to therapy **(Marshall et al., 2009).**

Aim of The Work

To review many recent biomarkers in diagnosis and management of sepsis.