Surviving sepsis and multiple organ dysfunction in intensive care unit

Essay
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List of abbreviations

ACCP	American College of Clinical Pharmacy
ACTH	Adreno-Cortico-Trphic Hormone
AD	Anno Domini
ADM	Adrenomedullin
AIDS	Acquired Immuno-Deficiency Syndrome
ALI	Acute Lung Injury
ANP	Atrial Natriuretic Peptide
APACHE	Acute Physiology And Chronic Health Evaluation
APC	Activated Protein C
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Renal Failure
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
ATS	American Thoracic Society
AXR	Abdominal X Ray
BC	Before Christ
BRM	Beat Per Minute
BUN	Blood Urea Nitrogen
CARS	Compensatory Anti-inflammatory Reaction Syndrome
CBC	Complete Blood Count
CBS	Cystathionine Beta Synthase
CD	Cluster of Differentiation
CNS	Central Nervous System
CO_2	Carbon Dioxide
COPD	Chronic Obstuctive Pulmonary Disease
CRP	C-Reactive Protein
CSE	Cystathionine Gamma Lyse
CSF	Cerebro-Spinal Fluid
CT	Computed Tomography

CVC	Central Venous Catheter.
CVP	Central Venous Pressure.
CVVHDF	Continuous Veno-Veno Hemo Di-Filtration
CXR	Chest X Ray.
C5a	Complement factor 5a.
C5AR	C5a Receptor.
C5L2	C5a Like receptor 2.
DA	Dopamine.
DIC	Dissiminated Intravascular Coagulopathy.
DVT	Deep Venous Thrombosis.
ECG	Electro Cardio Gram.
ED	Emergency Department.
EGDT	Early Goal Directed Therapy.
eNOS	Endothelial Nitric Oxide Synthase.
EPCR	Endothelial Protein C Receptor.
ESICM	European Society of Intensive Care Medicine.
ESR	Erythrocyte Sedimentation Rate.
FB	Fluid Balance.
FiO_2	Inspired Oxygen fraction.
GCS	Graduated Compression Stocking.
GFR	Glomerular Filtration Rate.
GIT	Gastro Intestinal Tract.
HIV	Human Immuno-deficiency Virus.
HMGB1	High Mobility Group protein B1.
H_2 blocker	Histamine 2 receptor blocker.
H_2S	Hydrogen Sulfide.
IBW	Ideal Body Weight.
ICD	Intermittent Compression Devices.
ICU	Intensive Care Unit.
IgA	Immunoglobulin A.

IL	Interleukin
INF-γ	Inerferon gamma.
I NOS	Inducible Nitric Oxide Synthase.
INR	International Normalized Ratio.
IV	Intravenous.
LMWH	Low Molecular Weight Heparin.
LOC	Level Of Consciousness.
LPS	Lipopolysaccharide.
MAC	Membrane Attack Complex.
MBP	Mean Blood Pressure.
MIF	Migration Inhibitory Factor.
MODS	Multiple Organ Dysfunction Syndrome.
MODS	Multiple Organ Dysfunction Score.
MPM	Mortality Prediction Model.
MRI	Magnetic Resonance Imaging.
MRNA	Messenger Ribonucleic acid.
MRSA	Methicillin Resistant Staph. Aureus.
NE	Nor Epinephrine.
NMBAs	Neuro Muscular Blocker Agents.
NNOS	Neuronal Nitric Oxide Synthase.
NO	Nitric Oxide.
NOS	Nitric Oxide Synthase.
OSF	Organ System Failure.
PAC	Pulmonary Artery Catheter.
$PaCO_2$	Partial Carbon Dioxide Pressure in blood.
PAG	Propargylglycine.
PAI1	Plasminogen Activator Inhibitor 1.
PAOP	Pulmonary Artery Occlusion Pressure.
PaO_2	Partial Oxygen Pressure in BLOOD.
PCT	Procalcitonin.
PEEP	Positive End Expiratory Pressure.

PGs	Prostaglandins.
PRBCs	Packed RBCs.
PTT	Partial Thromboplastine Time.
RNS	Reactive Nitrogen Species.
ROS	Reactive Oxygen Species.
RRT	Renal Replacement Therapy.
SAPS	Simplified Acute Physiology Score.
SBP	Systolic Blood Pressure.
$SCVO_2$	Central Venous Oxygen Saturation.
SD	Standard Deviation.
SDD	Selective Digestive tract Decontamination.
SIRS	Systemic Inflammatory Response Syndrome.
SIS	Surgical Infection Society.
SOFA	Sequential Organ Failure Assessment.
SSC	Surviving Sepsis Campaign.
ST	Standard Treatment.
SUP	Stress Ulcer Prophylaxis.
TAFI	Thrombin Activitable Fibrinolysis Inhibitor.
TB	Total Bilirubin.
TFPI	Tissue Factor Pathway Inhibitor.
TH	T Helper cells.
TLR	Toll Like Receptors.
TNF-α	Tumor Necrosis Factor Alfa.
TREM-1	Triggering Receptor Expressed on Myloid cells.
TX	Thromboxane.
UFH	Unfractionated Heparin.
WBCs	White Blood Cells.

Introduction

Sepsis remains one of the leading causes of mortality in critically ill patients in the ICU. Over the last decade there has been a demonstrable significant reduction in mortality from severe sepsis and septic shock through the use of performance metrics and collaborative quality improvement efforts that facilitate the incorporation of the latest scientific and clinical advancements into bedside practice. As scientific knowledge and clinical expertise continue to grow as to the treatment of patients with sepsis, and new innovative technologies and approaches are developed, continued efforts must be made to translate this into improved patient care **(Levision et al., 2011)**.

During sepsis, a wide array of endogenous humoral and cellular mediator systems are activated, including complement, coagulation and fibrinolytic systems, with the release of cytokines and lipid mediators such as eicosanoids, platelet-activating factor, and endothelin-1. The inflammatory response involve the activation of endothelial cells, platelets, macrophages, monocytes and neutrophils generating oxygen and nitrogen radicals. Also, the activation of sympathoadrenal axis (with increased level of norepinephine), the activation of rennin-angiotensin-aldosterone system (with increased level of angiotensin II), and increase in the vasopressin levels are often part of host response. These mechanisms largely responsible for the clinical manifestations of sepsis, finally lead to tissue hypoxia, which represents the common pathway of organ dysfuncyion **(Kotch et al., 2001)**.

Multiple Organ Dysfunction Syndrome (MODS) has been described as a"disease of medical progress" or the unwanted outcome of successful shock resuscitation. MODS refers to the presence of altered organ

function in a severely ill patient, so that homeostasis can not be maintained without intervention. In the ICU, the incidence of single organ failure approaches 48%. The lung is the most common organ to develop obvious clinical failure, followed by the liver, kidney, gastrointestinal tract and cardiovascular system. The physiologic definition is severe acquired dysfunction of at least two organ systems lasting at least 24 to 48 hours in the setting of sepsis. Both the number of dysfunction organs and the duration of the dysfunction are critical to the condition. The mortality increases proportionally with number and duration of dysfunction **(Irwin and Rippe, 2010)**.

The diagnosis of sepsis and evaluation of its severity is complicated by the highly variable and non-specific nature of the signs and symptoms of sepsis. However, the early diagnosis and stratification of the severity of sepsis is very important, increasing the possibility of starting timely and specific treatment. Biomarkers can have an important place in this process because they can indicate the presence or 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 prognostication, guiding antibiotic therapy, evaluating the response to therapy and recovery from sepsis, differentiating Gram-positive from Gram-negative microorganisms as the cause of sepsis, predicting sepsis complications and the development of organ dysfunction (heart, kidneys, liver or multiple organ dysfunction) **(Pierrakos and Vincent, 2010)**.

The past two decades have seen a remarkable growth in our understanding of sepsis and the complex interconnection of multiple biological pathways involved in septic process. Despite initial enthusiasm with "disease modifying agents", the early administration of appropriate

antibiotics and early hemodynamic resuscitation remain the corner stone of the management of patients with sepsis. This resuscitation of patients with sepsis should be based on the best current scientific evidence and coordinated by intensivests with expertise in managing these complex patients **(Marik, 2011)**.

Aim of the essay

This work aims at discussing pathophysiology, diagnosis and management of sepsis, in addition to multiple organ failure resulting from sepsis in intensive care unit.

Pathophysiology of sepsis and MODS

Sepsis is a complex condition starting from an infective stimulus and resulting in an exaggerated immune response. The inflammatory response that was initiated to fight the infection ultimately lead to damage of various organs through out the body.

During the onset of sepsis, the inflammatory system becomes hyperactive, involving both cellular and humoral defense mechanisms. Endothelial and epithelial cells, as well as neutrophils, macrophages and lymphocytes produce powerful inflammatory mediators especially Tumor Necrosis Factor α (TNF-α), Interleukin-6 (IL-6), IL-1 and IL-8. Simultaneously, robust production of acute phase proteins such as C-reactive protein occurs, and humoral defence mechanisms such as the complement system are activated, resulting in production of pro-infalmmatory mediators, including C_{5a}, the complement split product. C5a ultimately enhances cytokine and chemokine production. Furthermore the coagulation system become activated through various mechanisms, often resulting in disseminated intravascular coagulopathy.

The hallmarks of sepsis are excessive inflammation, excessive coagulation and suppression of fibrinolysis. In addition endogenous Activated Protein C (APC), which modulate coagulation, control inflammation and support fibrinolysis is also decreased. There is considerable variability in response which is almost certainly to a large degree genetically determined. Those with a tendency to produce excessive cytokines and TNF will have a greater inflammatory response. Simultaneously, the initial vascular damage result in neutrophil activation, neutrophil-endothelial cell adhesion, and further elaboration of inflammatory cytokines. In tissues already prone to dysfunctional oxygen

uptake and metabolism, this vascular injury promotes further tissue hypoxia through regional hypoperfusion. This uncontrolled cascade of inflammation and coagulation fuels the progression of sepsis, resulting in tissue hypoxia and ischemia with resultant organ dysfunction and death. **(Qureshi and Rajah, 2008)**.

Pro-inflammatory mediators facilitate inflammation by promoting endothelial cell-leukocyte adhesion, inducing the release of arachidonic acid metabolites and complement activation. In addition, pro-inflammatory mediators also promote coagulation by increasing tissue factors and membrane coagulants, inhibit anticoagulant activity by decreasing thrombomodulin and inhibit fibrinolysis. In contrast, anti-inflammatory mediators inhibit inflammation by inhibiting TNF-α, augmenting acute-phase reactants and immunoglobulins and inhibiting T-lymphocyte and macrocyte functions. Anti-inflammatory mediators also inhibit activation of the coagulation system by cytokines. The anti-inflammatory response serves as a negative feedback mechanism to downregulate the synthesis of pro-inflammatory mediators and modulate their effects, thereby restoring homeostasis. SIRS is the result of an excessive pro-inflammatory response, whereas a Compensatory Anti-inflammatory Reaction (CARS) is the result of inappropriate immunosuppression. If an imbalance develops between SIRS and CARS, homeostasis is violated **(Ramnath et al., 2006)**.

Definition of sepsis:

Two major consensus conferences have defined sepsis. The first, in 1992, put forth the concept of the Systemic Inflammatory Response Syndrome (SIRS), recognizing that lethally altered pathophysiology could be present without positive blood cultures. The SIRS criteria are represented by two or more of the following:

1) Body temperature > 38°C.

2) Heart rate > 90 beats per minute.

3) Respiratory rate >20 breaths per minute or arterial CO_2 tension less than 32 mmHg or a need for mechanical ventilation.

4) White blood count > 12,000/ mm^3 or > 10% immature forms.

Sepsis represents SIRS that has been induced by an infection. Severe sepsis is sepsis with dysfunction of a least one organ or organ system, and septic shock is severe sepsis with hypotension.

The 2001 International Sepsis Definitions Conference modified the model of SIRS and developed an expanded view of sepsis after revisiting the literature. This conference developed the concept of a staging system for sepsis based on four separate characteristics designated by the acronym PIRO. ***P*** stands for the Predisposition, indicating pre-existing co-morbid conditions that would reduce survival. ***I*** is the Insult or infection, which reflects the clinical knowledge that some pathogenic organisms are more lethal than others. ***R*** represents the Response to the infectious challenge, including the development of SIRS. The last letter ***O*** stands for Organ dysfunction and includes organ failure as well as the failure of a system such as the coagulation system **(Remick, 2007)**.

Aetiology of sepsis:

Although gram-negative bacteremia is commonly found in patients with sepsis, gram-positive infection may affect 30-40% of patients. Fungal, viral and parasitic infections are usually encountered in immunocompromised patients. Sources of bacteremia leading to sepsis include the urinary, respiratory ,GI tracts, skin and soft tissues (including catheter sites). The source of bacteremia is unknown in 30% of patients. Escherichia coli is the most frequently encountered gram-negative organism, followed by Klebsiella pneumoniae, Enterobacter aerogenes or cloacae, Serratia marcescens, Pseudomonas aeruginosa, Proteus mirabilis, Providencia, and Bacteroides species. Up to 16% of sepsis cases are polymicrobic. Gram-positive organisms, including methicillin-sensitive and methicillin-resistant Staphylococcus aureus and Staphylococcus epidermidis, are associated with catheter or line-related infections **(Brenner, 2006)**.

Mechanism of sepsis:

Innate immunity and inflammation in early sepsis:

Host defenses can be categorized according to innate and adaptive immune system responses. The innate immune system responds rapidly by means of pattern-recognition receptors [e.g. Toll-Like Receptors (TLRs)] that interact with highly conserved molecules present in microorganisms. For example, TLR-2 recognizes a peptidoglycan of gram-positive bacteria, whereas TLR-4 recognizes a lipopolysaccharide of gram-negative bacteria. Binding of TLRs to epitopes on microorganisms stimulates intracellular signaling, increasing transcription of pro-inflammatory