# GOAL DIRECTED THERAPY IN SEVERE SEPSIS AND SEPTIC SHOCK

## Essay

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**In Critical Care Medicine**


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# التقييم الإكلينيكي للعلاج المبكر الهادف للتعفن الشديد والصدمة التعفنية


**دراسة مقدمة من**

**الطبيب/ ماجد رضا موسى موسى**

**بكالوريوس الطب والجراحة**


**توطئة للحصول على درجة الماجستير في طب الحالات الحرجة**

**تحت إشراف**


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# Summary

Sepsis is a clinical syndrome that complicates severe infection and is characterized by systemic inflammation and widespread tissue injury. In this syndrome, tissues remote from the original insult display the cardinal signs of inflammation, including vasodilatation, increased micro-vascular permeability, and leucocyte accumulation. Although inflammation is an essential host response, current believes regarding the onset and progression of sepsis center upon a "dysregulation of the normal response", with a massive and uncontrolled release of pro-inflammatory mediators creating a chain of events that leads to widespread tissue injury and frequently to death , Current pathophysiologic concepts of sepsis include Activation of coagulation, Impairment of anticoagulant mechanisms, so the coagulation system and anti-inflammatory cascade work in concert, with one potentiating the effects of the other.

A number of organ abnormalities may occur in septic shock. The lungs may develop low- pressure pulmonary oedema, or adult respiratory distress syndrome. Dissiminated intravascular coagulation may ocurr and carries a high mortality. Renal impairment & gastrointestinal dysfunction may occur secondary to regional ischemia; Central nervous system dysfunction is also common, cardiac muscle dysfunction causing myocardial depression, hepatic dysfunction, adrenal insufficiency, vasodilatation, disturbed oxygen consumption, delivery and disturbed peripheral metabolism.

***Summary***

Clinical signs of systemic inflammation such as changes in body temperature, leukocytosis, and tachycardia may therefore have an infectious or non-infectious etiology and are neither specific nor sensitive for sepsis. It is, thus, frequently difficult to distinguish patients with systemic infection from those who appear septic but have no evidence of infection. Bacteriologic evidence of infection also has drawbacks because it may not develop concurrently with clinical signs of sepsis, and a negative bacteriologic result does not exclude the presence of infection or sepsis. Since these common clinical and laboratory parameters lack sensitivity and specificity, others are needed to provide an early marker of the infectious etiology of a generalized inflammatory response and thus allow early diagnosis and the application of more specific therapeutic interventions.

A lot of markers help in diagnosis and prognosis of sepsis which include procalcitonin, polymorphnuclear elastase enzyme, cytokines, eosinophils, acute phase reactant proteins and Blood lactate level.

The basic treatment of sepsis involves control of infection by antibiotics and surgical intervention if required, fluid resuscitation by colloid and crystalloids, blood transfusion when required, vasopressor and inotropic therapy, administration of oxygen and ventilation and others.

# Aim of the work

The aim of this work is to evaluate the efficacy of early goal directed therapy in critically ill patient with severe sepsis or septic shock as regards:

Incidence of complication Outcome:

a. Morbidity

b. Mortality

c. Improvement

# Contents

# LIST OF ABBREVIATIONS

| | |
|---|---|
| < | Less than |
| > | More than |
| °C | Celsius degree |
| °F | Fahrenheit degree |
| ACCCM | American College of Critical Care Medicine |
| ADH | Antidiuretic hormone |
| ADP | Adenosine Di- Phosphate |
| AIDS | Acquired Immune Deficiency Syndrome |
| APC | Activated Protein C |
| ARDS | Acute Respiratory Distress Syndrome |
| ATP | Adenosine Tri-Phosphate |
| BBB | Blood-Brain Barrier |
| Bp | Blood pressure |
| Bpm | Beat per minute |
| Bw | Body weight |
| CaO2 | Arterial oxygen content |
| CI | Cardiac Index |
| Cl | Chloride |
| CNS | Central nervous system |
| CMV | Cyto megalo virus |
| CORTICUS | Corticosteroid Therapy of Septic Shock |
| CO | Carbon Monoxide |
| CQI | Quality improvement initiative |
| CRRT | Continuos renal replacement therapy |
| CRT | Capillary refill time |
| CVC | Central Venous Cannulation |
| DAD | Diffuse Alveolar Damage |
| CVP | Central Venous Pressure |
| DIC | Disseminated Intravascular Coagulopathy |
| $DO_2$ | Oxygen delivery |
| EBV | Epstein Barr virus |

| | |
|---|---|
| **ECA** | **Enterobacteriaceae common antigen** |
| **ECF** | **Extracellular fluid** |
| **ECLS** | **Extracorporeal life support** |
| **ECMO** | **ExtraCorporeal Membrane Oxygenation** |
| **ED** | **Emergency department** |
| **ESBL** | **Extended-spectrum beta-lactamase** |
| **EGDT** | **Early goal-directed therapy** |
| **ETT** | **Endotracheal tube** |
| **$Fe^{2+}$** | **Ferrous** |
| **$FiO_2$** | **Fraction of oxygen in inspired gas** |
| **GCS** | **Galascow coma scale** |
| **G-CSF** | **Granulocyte colony-stimulating factor** |
| **CSF** | **Colony-stimulating factor** |
| **GM-CSF** | **Granulocyte-macrophage colony stimulating factor** |
| **HA-1A** | **Human monoclonal anti endotoxin antibody** |
| **GFR** | **Glomerular filtration rate** |
| **$H_2O$** | **Water** |
| **HAART** | **Highly active antiretroviral therapy** |
| **HFV** | **High Frequency Ventiltion** |
| **HFIV** | **High Frequency Interrupted Ventiltion** |
| **HFJV** | **High Frequency Jet Ventiltion** |
| **HFOV** | **High Frequency Oscillatory Ventiltion** |
| **ICAMs** | **Intercellular adhesion molecules** |
| **ICG** | **Indo cyanine green** |
| **ICF** | **Intracellular fluid** |
| **ICU** | **Intensive care unit** |
| **IL** | **Interleukin** |
| **IMV** | **Intermittent mandatory ventilation** |
| **IOC** | **Intraosseous cannulation** |
| **IPP** | **Inspiratory plateau pressure** |
| **IV** | **Intravenous** |
| **IVIG** | **Polyclonal IV immunoglobulin** |
| **K** | **Potassium** |
| **kg** | **Kilogram** |

| | |
|---|---|
| **LBM** | **Lean body mass** |
| **LES** | **Lower esophageal sphincter** |
| **MAP** | **Mean arterial pressure** |
| **MRSA** | **Methicillin-Resistant *S aureus*** |
| **mcg** | **Microgram** |
| **mEq/dL** | **Mill equivalent per deciliter** |
| **mg** | **Milligram** |
| **MHC** | **Major histo-compatibility complex** |
| **ml** | **Milliliter** |
| **mm Hg** | **Millimeter mercurey** |
| **mmol** | **Milli mol** |
| **MODS** | **Multiorgan dysfunction syndrom** |
| **MOF** | **Multi organ failure** |
| **MyD88** | **Myeloid differentiation factor 88** |
| **Na** | **Sodium** |
| **$NAD^+$** | **Nicotinamide adenine dinucleotide** |
| **$NaHCO_3$** | **Sodium bicarbonate** |
| **NF-κB** | **Nuclear factor-κB** |
| **NO** | **Nitric Oxide** |
| **NPO** | **Nothing by mouth** |
| **$O_2$** | **Oxygen** |
| **$O_2$ sat** | **Oxygen saturation** |
| **OPS** | **Orthogonal polarization spectroscopy** |
| **$ONOO^-$** | **Peroxynitrite radicals** |
| **Pa $O_2$** | **Arterial oxygen tension** |
| **PAI-1** | **Plasminogen activator inhibitor-1** |
| **PALS** | **Pediatric Advanced Life Support** |
| **PARS** | **Poly ADP ribose synthetase** |
| **P (CV-a) CO2** | **Central venous-to-arterial carbon dioxide difference** |
| **PEEP** | **Positive end expirat/ry pressure** |
| **PICU** | **Pediatric intensive care unit** |
| **PIP** | **Peak inspiratory pressure** |
| **PMNs** | **Polymorpho.uclear neutrophils** |
| **PSV** | **Pressure support ventilation** |

| | |
|---|---|
| **PVR** | **Pulmonary vascular resistance** |
| **RBCs** | **Red blood cells** |
| **rh APC** | **Recombinant activated protein C** |
| **REE** | **Resting energy expenditure** |
| **SAg** | **Super-antigens** |
| **$SaO_2$** | **Arterial oxygen saturation** |
| **$ScvO_2$** | **Central venous oxygen saturation** |
| **SD** | **Standard deviation** |
| **SICU** | **surgical intensive care unit** |
| **SIRS** | **Systemic inflammatory response syndrome** |
| **SOFA** | **Sequential Organ failure Assessment** |
| **SV** | **Stroke volume** |
| **$SvO_2$** | **Mixed venous oxygen saturation** |
| **SVR** | **Systemic vascular resistance** |
| **$t_{1/2}$** | **Elimination half-life** |
| **T3** | **Tri-iodothyronin** |
| **TEE** | **Transesophageal echocardiography** |
| **TF** | **Tissue factor** |
| **TGF** | **Tissue growth factor** |
| **Ti** | **Inspiratory Time** |
| **TIRAP** | **Toll–IL-1-resistance adaptor-like proteins** |
| **TLR** | **Toll Like Receptors** |
| **TNF** | **Tumor necrosis factor** |
| **UGT** | **Glucuronosyl transferase** |
| **VASST** | **Vasopressin and Septic Shock Trial** |
| **$V\cdot CO_2$** | **Carbon dioxide production** |
| **$V\cdot O_2$** | **Oxygen consumption** |
| **VCAMs** | **Vascular adhesion molecules** |
| **Vd** | **Volume of distribution** |
| **vWF** | **Von Willebrand's factor** |
| **Wk** | **Week** |

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# Introduction

In 1914, Schottmueller define: "Septicemia is a state of microbial invasion from a portal of entry into the blood stream which causes sign of illness" the definition did not change much over the years because the terms sepsis and septicemia referred to several ill-defined clinical conditions present in a patient with bacteremia. ***(Sharma* and Mink, *2007)***

In practice, the terms often were used interchangeably; however, less than one half of the patients with signs and symptoms of sepsis have positive results on blood culture. Furthermore, not all patients with bacteremia have signs of sepsis; therefore, sepsis and septicemia are not identical. ***(Rangel-Frausto et al., 1995)***

In the last few decades, discovery of endogenous mediators of the host response have led to the recognition that the clinical syndrome of sepsis is the result of excessive activation of host defense mechanisms rather than the direct effect of micro-organisms. Sepsis and its sequelae represent a continuum of Clinical and Pathophysiologic severity. ***(Shapiro NI et al., 2009)***

Sever sepsis is one of the most significant challenges in critical care. Each year, more than 750,000 people in the U.S. will develop severe sepsis, and more than 215,000 will die from this condition. ***(Angus DC et al., 2001)***

Severe sepsis affects people of all age, whether they are healthy or chronically ill. But certain patients are predisposed to developing severe sepsis. Screening those at-risk patients is highly recommended to diagnose and treat the condition early. ***(Hotchkiss RS et al., 2007)***

Early and accurate diagnosis of sepsis is essential to provide adequate early therapy. An ideal marker of sepsis should be able to differentiate a patient with sepsis from one without sepsis, many such markers has been proposed, and as our understanding of sepsis improves, new mediators and potential markers will be identified.***(Póvoa P. et al., 1998)***

With continuing advances in proteomic, genomic, and microarray techniques we will be able to obtain an infectious or septic profile on each patient almost instantaneously from one small blood sample. ***(Jean-Louis Vincent and Marc Van Nuffelen, 2007)***

In a landmark study by Rivers et al, patients admitted to an emergency department with severe sepsis and septic shock were randomized to standard therapy (fluid loading targeted to central venous pressure [CVP] of 8–12 mmHg, mean arterial pressure [MAP] 65 mmHg, and urine output 0.5 ml/kg/h), or to early goal directed therapy in which, in addition to the previous parameters, a central venous oxygen saturation ($ScvO^2$) 70 % was targeted through algorithmic management ***(Rivers E. et al., 2011)***

# Pathophysiology 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. The current understanding of the pathophysiology of sepsis including mechanisms of multiple organ system dysfunctions. ***(Pinsky MR et al., 1989)***

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.

When tissue is injured or infected, there is simultaneous release of pro inflammatory and anti-inflammatory elements. The balance of these contrasting signals helps to facilitate tissue repair and healing. However, remote tissue injury may ensue when this equilibrium in the inflammatory process is lost, and these mediators exert systemic effects. ***(Bone RC et al., 1991)***