RECENT CONCEPTS OF SEPTIC SHOCK IN INTENSIVE CARE UNIT

Essay
Submitted in Partial Fulfillment Master Degree M.Sc.
IN Critical care Medicine

BY
Mariam "Mohammed Salah Eldin" "Mohammed Alasify" Wahdan
M.B.B.Ch Benha Faculty of Medicine
Benha University

Under supervision of

Prof. Dr. Ehab Ahmed Abdel Rahman Hanafi

Professor of Anesthesia and Intensive Care
Faculty of Medicine
Benha University

Dr. Ahmed Hamdy Abdel Rahman Ali

Lecturer of Anesthesia and Intensive care
Faculty of Medicine
Benha University

Faculty of Medicine
Benha University
2015
قالوا:
نعلم أنك علمنا كيفية النجاة.
إلا ما علمتنا إلا أنك أنت العلي العليم الأكيم.
First of all, thanks to God who granted me the ability to finish this work.

Words can never express my deepest gratitude and sincere appreciation to Prof. Dr. Ehab Abdel Rahman Professor of Anesthesia and Intensive care Dept., Benha University for his continuous encouragement, powerful support, extreme patient and faithful advice.

My deepest thanks and appreciation and sincere gratitude to Dr. Ahmed Hamdy Lecturer of Anesthesia and Intensive care Dept., Benha University, who spared no time and effort to provide me with his valuable instructions and expert touches.

My truthful love to my family who were and will always be by my side, all my life.

Mariam Mohammed Salah Wahdan
## List of Contents

<table>
<thead>
<tr>
<th>Items</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of Abbreviation</td>
<td>I</td>
</tr>
<tr>
<td>List of Table</td>
<td>V</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Aim of the work</td>
<td>5</td>
</tr>
<tr>
<td>Chapter (I): Definitions and pathophysiology</td>
<td>6</td>
</tr>
<tr>
<td>Chapter (II) Microbiology of sepsis</td>
<td>22</td>
</tr>
<tr>
<td>Chapter (III) Diagnosis of sepsis and septic shock</td>
<td>30</td>
</tr>
<tr>
<td>Chapter (IV) Management of severe sepsis and septic shock</td>
<td>50</td>
</tr>
<tr>
<td>Summary</td>
<td>77</td>
</tr>
<tr>
<td>References</td>
<td>83</td>
</tr>
<tr>
<td>Arabic Summary</td>
<td>1</td>
</tr>
</tbody>
</table>
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPT</td>
<td>Activated Partial Thromboplastin Time</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute Kidney Injury.</td>
</tr>
<tr>
<td>ALI</td>
<td>Acute Lung Injury.</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine Tri Phosphate.</td>
</tr>
<tr>
<td>ACTH</td>
<td>AdrenoCorticotropic Hormone</td>
</tr>
<tr>
<td>ALB</td>
<td>Albumin</td>
</tr>
<tr>
<td>ALBIOS</td>
<td>Albumin Italian Outcome Sepsis Study.</td>
</tr>
<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>ARISE</td>
<td>Australasian Resuscitation In Sepsis Evaluation</td>
</tr>
<tr>
<td>ARISE</td>
<td>Australasian Resuscitation of Sepsis Evaluation.</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen.</td>
</tr>
<tr>
<td>CRP</td>
<td>C Reactive Protein.</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System.</td>
</tr>
<tr>
<td>CVC</td>
<td>Central Venous Catheters.</td>
</tr>
<tr>
<td>ScVO2</td>
<td>Central Venous Oxyhemoglobin Saturation.</td>
</tr>
<tr>
<td>CVP</td>
<td>Central Venous Pressure.</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid.</td>
</tr>
<tr>
<td>CAMRS</td>
<td>Community Acquired Methicillin Resistent Staphylococcus Aureus</td>
</tr>
<tr>
<td>COMRS</td>
<td>Community Onset Methicillin Resistent nStaphylococcus Aureus.</td>
</tr>
<tr>
<td>CAPs</td>
<td>Community-acquired pneumonias.</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CVVH</td>
<td>Continous venovenous hemofiltration</td>
</tr>
<tr>
<td>CORTIC</td>
<td>Corticosteroid Therapy of Septic Shock Study</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>DIC</td>
<td>Dissiminated Intravascular Coagulopathy.</td>
</tr>
<tr>
<td>EGDT</td>
<td>Early Goal Directed Therapy.</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram.</td>
</tr>
<tr>
<td>ERCP</td>
<td>Endoscopic Retrograde Cholangio Pancreatography</td>
</tr>
<tr>
<td>E.COLI:</td>
<td>Escherichia Coli.</td>
</tr>
<tr>
<td>ESICM</td>
<td>European Society of Intensive Care Medicine.</td>
</tr>
<tr>
<td>EVLW</td>
<td>Extravascular lung water</td>
</tr>
<tr>
<td>FEAST</td>
<td>Fluid Expansion as Supportive Therapy</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasco Coma Score.</td>
</tr>
<tr>
<td>GNBs</td>
<td>Gram Negative Bacillus</td>
</tr>
<tr>
<td>GM</td>
<td>Granulocyte-macrophage colony stimulating factor</td>
</tr>
<tr>
<td>HAP</td>
<td>Hospital Acquired Pneumonia.</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit.</td>
</tr>
<tr>
<td>IL6</td>
<td>Interleukin 6</td>
</tr>
<tr>
<td>IL8</td>
<td>Interleukin 8.</td>
</tr>
<tr>
<td>IV</td>
<td>Intra Venous</td>
</tr>
<tr>
<td>IVIG</td>
<td>Intravenous immunoglobulin</td>
</tr>
<tr>
<td>LPS</td>
<td>Lipopolysaccharides.</td>
</tr>
<tr>
<td>LFTs</td>
<td>Liver Function Tests.</td>
</tr>
<tr>
<td>LP</td>
<td>Lumber Puncture</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean Arterial Pressure</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin Resistant Staphylococcus Aureus</td>
</tr>
<tr>
<td>MIF</td>
<td>Migration Inhibition factor</td>
</tr>
<tr>
<td>MODS</td>
<td>Multi organ Dysfunction Syndrome.</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric Oxide.</td>
</tr>
<tr>
<td>NS</td>
<td>Normal Saline.</td>
</tr>
<tr>
<td>NP</td>
<td>Nosocomial Pneumonia.</td>
</tr>
<tr>
<td>PAF</td>
<td>Platelet Activating Factor.</td>
</tr>
<tr>
<td>PMNLs:</td>
<td>Polymorphnuclear leukocytes.</td>
</tr>
<tr>
<td>PBFC</td>
<td>Polymyxin B fiber column</td>
</tr>
<tr>
<td>PARs</td>
<td>Protease Activated Receptors.</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin Time</td>
</tr>
<tr>
<td>ProMISe</td>
<td>Protocolised Management In Sepsis.</td>
</tr>
<tr>
<td>ProCES</td>
<td>Protocolized Care for Early Septic Shock.</td>
</tr>
<tr>
<td>PCWP</td>
<td>Pulmonary Capillary Wedge Pressure.</td>
</tr>
<tr>
<td>PDH</td>
<td>Pyruvate dehydrogenase</td>
</tr>
<tr>
<td>RL</td>
<td>Ringer Lactate</td>
</tr>
<tr>
<td>SAFE</td>
<td>Saline vs Albumin Fluid Evaluation.</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment</td>
</tr>
<tr>
<td>SCCM</td>
<td>Society of Critical Care Medicine</td>
</tr>
<tr>
<td>SCCM</td>
<td>Society of Critical Care Medicine.</td>
</tr>
<tr>
<td>SIS</td>
<td>Surgical Infection Society.</td>
</tr>
<tr>
<td>SIRS</td>
<td>Systemic inflammatory response syndrome.</td>
</tr>
<tr>
<td>TH2</td>
<td>T Helper Cell Type 2</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ACCCM</td>
<td>The American College of Critical Care Medicine.</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll Like Receptors</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor.</td>
</tr>
<tr>
<td>USCOM</td>
<td>Ultrasonic Cardiac Output Monitor</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin Resistant Enterococci.</td>
</tr>
<tr>
<td>VSE</td>
<td>Vancomycin Sensitive Enterococci.</td>
</tr>
<tr>
<td>VASST</td>
<td>Vasopressin in Septic Shock Trial</td>
</tr>
<tr>
<td>VAP</td>
<td>Ventilator Associated Pneumonia.</td>
</tr>
<tr>
<td>WBCs</td>
<td>White Blood Cells.</td>
</tr>
</tbody>
</table>
# List of Tables

<table>
<thead>
<tr>
<th>Table No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table (1)</td>
<td>Diagnostic criteria of sepsis.</td>
<td>34</td>
</tr>
<tr>
<td>Table (2)</td>
<td>Severe sepsis.</td>
<td>35</td>
</tr>
<tr>
<td>Table (3)</td>
<td>Sequential Organ Failure Assessment Score.</td>
<td>48-49</td>
</tr>
<tr>
<td>Table (4)</td>
<td>Clinical features that should alert the physician to the diagnosis of severe sepsis.</td>
<td>52</td>
</tr>
</tbody>
</table>
Introduction

Sepsis refers to the systemic inflammatory response following microbial infection, sepsis may be best defined as the systemic response to infection with the presence of some degree of organ dysfunction.

(Vincet, et al., 2013)

Severe sepsis and septic shock is the leading cause of hospital death. An enormous economic burden is attributed to severe sepsis and the general consensus is that early identification and early appropriate evidence-based medical care will impact this burden. (Hall, et al., 2011)

As the concept of the host theory emerged, it was first assumed that the clinical features of sepsis were the result of inflammation , later on it was found that the initial inflammatory response give way to compensatory anti inflammatory response syndrome. (Bone, et al., 2008)

Knowledge of pathogen recognition has increased in the past decade. Pathogens activate immune cells through an interaction with pattern-recognition receptors, of which four main classes: toll-like receptors, C-type lectin receptors, retinoic acid inducible gene 1–like receptors, and nucleotide-binding oligomerization domain–like receptors — have been identified. (Takeuchi, et al., 2010)

Severe sepsis is almost invariably associated with altered coagulation, frequently leading to disseminated intravascular coagulation (DIC). (Levi, et al., 2010)

The immune system harbors humoral, cellular, and neural mechanisms that attenuate the potentially harmful effects of the proinflammatory response. (Opal, et al., 2008)
Although the mechanisms that underlie organ failure in sepsis have been only partially elucidated, impaired tissue oxygenation plays a key role. *(Goldenberg, et al., 2011)*

Physician need to have high index of suspicion for the presence of sepsis, clinical features that should alert the physician to diagnose severe sepsis and septic shock include: heart rate >100/min, systolic BP<90, respiratory rate >20/min, temperature >38.5 or <36 c, confusion, oliguria, chills, rigors, tachypnea. *(Westphal, et al., 2011)*

Acute lung injury (ALI)—mild Acute respiratory distress syndrome (ARDS), by the Berlin Definition-leading to moderate or severe ARDS is a major complication of severe sepsis and septic shock. The incidence of ARDS is approximately 18% in patients with septic shock, and mortality approaches 50%. *(Ranieri, et al., 2012)*

Sepsis is the most common cause of Acute kidney injury (AKI) which affects 40-70% of all critically ill patients. *(Hall, et al., 2011)*

The Sequential Organ Failure Assesment (SOFA) score was developed to quantify the severity of patient illness based on the degree of organ dysfunction. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems *(Vincent, et al., 1997)*

Workup and investigative studies include laboratory tests and imaging modalities to detect clinically suspected focal infection, they include blood chemistries, coagulation studies, complete blood with differential, blood cultures, plain radiography, ultrasonography, CT and MRI. *(Dellinger, et al., 2013)*
The management of patients with sepsis centers on the administration of antibiotics, IV fluids, and vasoactive agents, followed by source control. However, it is likely that the early detection of sepsis with the early administration of appropriate antibiotics is the single most important factor in sepsis. *(Barochia, et al., 2010)*

Empirical IV antibiotic therapy should be started as soon as possible and within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained. *(Kumar, et al., 2006)*

Current teaching suggests that aggressive fluid resuscitation is the best initial approach for the cardiovascular instability of sepsis. *(Hilton, et al., 2012)*

A low MAP is a reliable predictor for the development of organ dysfunction. *(Bellomo, et al., 2001)*

In patients with sepsis, norepinephrine increases BP as well as cardiac output and renal, splanchnic, cerebral, and microvascular blood flow, while minimally increasing heart rate. *(Silva, et al., 2012)*

A large number of hemodynamic, perfusion, oxygenation, and echocardiographic targets have been proposed as resuscitation goals in patients with severe sepsis and septic shock. *(Dellinger, et al., 2012)*

The 2012 Surviving Sepsis Campaign guidelines state that —during the first 6 hours of resuscitation, if Scvo2 is less than 70%, dobutamine infusion or transfusion packed red blood cells to achieve a hematocrit of greater than or equal to 30% in attempts to achieve the Scvo2 goal are options. *(Dellinger, et al., 2012)*
The use of low dose corticosteroids in patients with severe sepsis remains controversial. *(Marik, et al., 2011)*

It has been known for centuries that, unless the source of the infection is controlled, the patient cannot be cured of his/her infective process and death will eventually ensue. *(Dellinger, et al., 2012)*

Although considered an important body of knowledge for physician education and a reference source for optimal treatment, guidelines do not have high impact on bedside healthcare practitioner performance. Simply put, guidelines are not enough. In order to change bedside behavior, protocols and performance improvement programs with audit and feedback are needed. Early screening and hospital-based performance improvement programs are now recommended by the Campaign. *(Levi, et al., 2010)*
Aim Of The Work

The aim of this work is to discuss the causes and pathogenesis of sepsis and septic shock for early detection and initiation of recent trends of management and its impact on reducing morbidity and mortality.
Chapter (I)

Definitions and pathophysiology

Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were initially defined in 1991 by a consensus panel convened by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM), then they were reconsidered in 2001 during an International Sepsis Definitions Conference that included representatives from the ACCP, SCCM, American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), and Surgical Infection Society (SIS).

(Levi, et al., 2003)

A practical modification of the definitions has since been published, which provides exact hemodynamic definitions for septic shock. (Annane, et al., 2005)

The definitions presented in a way that highlights the notion that both SIRS and sepsis exist on a continuum of severity that ends with multiple organ dysfunction syndrome (MODS).

**SIRS** is defined as 2 or more of the following variables: Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F) , Heart rate of more than 90 beats per minute , Respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension (PaCO₂) of less than 32 mm Hg , Abnormal white blood cell count (>12,000/µL or < 4,000/µL or >10%immature [band] forms) , Increased C reactive protein, Increased cardiac output, low systemic vascular resistance, Increased oxygen consumption, Increased procalcitonine concentration, Increased interleukin 6 (IL6), IL8, Otherwise unexplained alternation in coagulation
parameter, alternation in mental status, hyperbilirubinemia, Increased insulin requirement. *(Fink, et al., 2004)*

**Infection** is defined as "a microbial phenomenon characterized by an inflammatory response to the microorganisms or the invasion of normally sterile tissue by those organisms."

**Bacteremia** is the presence of viable bacteria within the bloodstream, but this condition does not always lead to SIRS or sepsis. *(Bae, et al., 2012)*

**Sepsis** is the systemic response to infection and is defined as the presence of SIRS in addition to a documented or presumed infection.

**Sepsis-induced hypotension** is defined as the presence of a systolic blood pressure of less than 90 mm Hg or a reduction of more than 40 mm Hg from baseline in absence of any other cause of hypotension. *(Heffner, et al., 2010)*

**Severe sepsis** is defined as sepsis plus at least one of the following signs of hypoperfusion or organ dysfunction:

- Areas of mottled skin, Capillary refilling requires three seconds or longer, Urine output <0.5 mL/kg for at least one hour, or renal replacement therapy, Lactate >2 mmol/L, Abrupt change in mental status, Abnormal electroencephalographic (EEG) findings, Platelet count <100,000 platelets/mL, Disseminated intravascular coagulation, Acute lung injury or acute respiratory distress syndrome (ARDS), Cardiac dysfunction (i.e., left ventricular systolic dysfunction), as defined by echocardiography or direct measurement of the cardiac index. *(Fink, et al., 2003)*

**Septic shock** Septic shock exists if there is severe sepsis plus one or both of the following:
Systemic mean blood pressure is <60 mmHg (or <80 mmHg if the patient has baseline hypertension) despite adequate fluid resuscitation (Adequate fluid resuscitation is defined as infusion of 20 to 30 mL/kg of starch, infusion of 40 to 60 mL/kg of saline solution, or a measured pulmonary capillary wedge pressure (PCWP), also known as (the pulmonary artery occlusion pressure) of 12 to 20 mmHg. For patients who have a central venous catheter rather than a pulmonary arterial catheter, a central venous pressure (CVP) of 8 to 12 mmHg is a reasonable substitute).

Maintaining the systemic mean blood pressure >60 mmHg (or >80 mmHg if the patient has baseline hypertension) requires dopamine >5 mcg/kg per min, norepinephrine <0.25 mcg/kg per min, or epinephrine <0.25 mcg/kg per min despite adequate fluid resuscitation.

(Levi, et al., 2003)

**Refractory septic shock** Refractory septic shock exists if maintaining the systemic mean blood pressure >60 mmHg (or >80 mmHg if the patient has baseline hypertension) requires dopamine >15 mcg/kg per min, norepinephrine >0.25 mcg/kg per min, or epinephrine >0.25 mcg/kg per min despite adequate fluid resuscitation.

**Multiple organ dysfunction syndromes** multiple organ dysfunction syndromes refer to progressive organ dysfunction in an acutely ill patient, such that homeostasis cannot be maintained without intervention. It is at the severe end of the severity of illness spectrum of both SIRS and sepsis.
Chapter (I)    Definitions and Pathophysiology

MODS can be classified as primary or secondary:

- Primary MODS is the result of a well-defined insult in which organ
dysfunction occurs early and can be directly attributable to the insult
itself (e.g., renal failure due to rhabdomyolysis)
- Secondary MODS is organ failure that is not in direct response to
the insult itself, but is a consequence of the host’s response (e.g.,
acute respiratory distress syndrome in patients with pancreatitis).

(Martin, et al., 2006)

There are no universally accepted criteria for individual organ
dysfunction in MODS. However, progressive abnormalities of the
following organ-specific parameters are commonly used to diagnose
MODS and are correlated with increased ICU mortality:

PO2/FiO2 ratio, Serum creatinine, Platelet count, Glasgow coma score,
Serum bilirubin, Pressure-adjusted heart rate (defined by heart rate
multiplied by the ratio of central venous pressure and mean arterial
pressure). (Cook, et al., 2007)

Pathophysiology

Host response

As the concept of host theory emerged, it was first assumed that
the clinical features of sepsis were the result of inflammation, later on it
was found that the initial inflammatory response gave way to
compensatory anti inflammatory response syndrome. However, it has
become apparent that infection triggers a much more complex, variable,
and prolonged host response, in which both proinflammatory and
antiinflammatory mechanisms can contribute to clearance of infection
and tissue recovery on the one hand and organ injury and secondary
infections on the other (Van der poll, et al., 2010)
The specific response in any patient depends on the causative pathogen (load and virulence) and the host (genetic characteristics and coexisting illnesses), with differential responses at local, regional, and systemic levels. The composition and direction of the host response probably change over time in parallel with the clinical course. In general, proinflammatory reactions (directed at eliminating invading pathogens) are thought to be responsible for collateral tissue damage in severe sepsis, whereas antiinflammatory responses (important for limiting local and systemic tissue injury) are implicated in the enhanced susceptibility to secondary infections. (Opal, et al., 2008)

**Innate Immunity**

Knowledge of pathogen recognition has increased tremendously in the past decade. Pathogens activate immune cells through an interaction with pattern-recognition receptors, of which four main classes: toll-like receptors, C-type lectin receptors, retinoic acid inducible gene 1–like receptors, and nucleotide-binding oligomerization domain–like receptors — have been identified, with the last group partially acting in protein complexes called inflamasomes. (Takeuchi, et al., 2010)

These receptors recognize structures that are conserved among microbial species, so-called pathogen-associated molecular patterns, resulting in the up-regulation of inflammatory gene transcription and initiation of innate immunity. The same receptors also sense endogenous molecules released from injured cells, so-called damage-associated molecular patterns, or alarmins, such as high-mobility group protein B1, S100 proteins, and extracellular RNA, DNA, and histones.

(Chan, et al., 2012)
Alarmins are also released during sterile injury such as trauma, giving rise to the concept that the pathogenesis of multiple organ failure in sepsis is not fundamentally different from that in noninfectious critical illness. *(Roth, et al., 2012)*

**Coagulation Abnormalities**

Severe sepsis is almost invariably associated with altered coagulation, frequently leading to disseminated intravascular coagulation. Excess fibrin deposition is driven by coagulation through the action of tissue factor, a transmembrane glycoprotein expressed by various cell types; by impaired anticoagulant mechanisms, including the protein C system and antithrombin; and by compromised fibrin removal owing to depression of the fibrinolytic system *(Van der poll, et al., 2010)*.

Protease-activated receptors (PARs) form the molecular link between coagulation and inflammation. Among the four subtypes that have been identified, PAR1 in particular is implicated in sepsis. *(Levi, et al., 2010)*

PAR1 exerts cytoprotective effects when stimulated by activated protein C or low-dose thrombin but exerts disruptive effects on endothelial-cell barrier function when activated by high-dose thrombin. The protective effect of activated protein C in animal models of sepsis is dependent on its capacity to activate PAR1 and not on its anticoagulant properties *(Ruf, et al., 2010)*

**Antiinflammatory mechanisms and Immunosuppression**

The immune system harbors humoral, cellular, and neural mechanisms that attenuate the potentially harmful effects of the proinflammatory response *(Opal, et al., 2010).*
Phagocytes can switch to an anti-inflammatory phenotype that promotes tissue repair, and regulatory T cells and myeloid-derived suppressor cells further reduce inflammation. In addition, neural mechanisms can inhibit inflammation. \textit{(Andersson, et al., 2012)}.

In the so-called neuroinflammatory reflex, sensory input is relayed through the afferent vagus nerve to the brain stem, from which the efferent vagus nerve activates the splenic nerve in the celiac plexus, resulting in norepinephrine release in the spleen and acetylcholine secretion by a subset of CD4+ T cells. The acetylcholine release targets \( \alpha 7 \) cholinergic receptors on macrophages, suppressing the release of proinflammatory cytokines. \textit{(Rosas, et al., 2011)}

In animal models of sepsis, disruption of this neural-based system by vagotomy increases susceptibility to endotoxin shock, whereas stimulation of the efferent vagus nerve or \( \alpha 7 \) cholinergic receptors attenuates systemic inflammation. \textit{(Tracey, et al., 2012)}

Patients who survive early sepsis but remain dependent on intensive care have evidence of immunosuppression, in part reflected by reduced expression of HLA-DR on myeloid cells. \textit{(Boomer, et al., 2011)}

These patients frequently have ongoing infectious foci, despite antimicrobial therapy, or reactivation of latent viral infection. \textit{(Torgersen, et al., 2009)}

Multiple studies have documented responsiveness in blood leukocytes to pathogens in patients with sepsis. \textit{(Van Der Poll, et al., 2008)}

Findings that were recently corroborated by postmortem studies revealing strong functional impairments of splenocytes obtained from patients who had died of sepsis in the ICU. \textit{(Boomer, et al., 2011)}. 
Besides the spleen, the lungs also showed evidence of immunosuppression; both organs had enhanced expression of ligands for T-cell inhibitory receptors on parenchymal cells. *Boomer, et al., 2011*

Enhanced apoptosis, especially of B cells, CD4+ T cells, and follicular dendritic cells, has been implicated in sepsis-associated immunosuppression and death *Hotchkiss, et al., 2005*

Epigenetic regulation of gene expression may also contribute to sepsis-associated immunosuppression *Carson, et al., 2011*

**Organ Dysfunction**

Although the mechanisms that underlie organ failure in sepsis have been only partially elucidated, impaired tissue oxygenation plays a key role. Several factors: including hypotension, reduced red cell deformability, and microvascular thrombosis contribute to diminished oxygen delivery in septic shock. Inflammation can cause dysfunction of the vascular endothelium, accompanied by cell death and loss of barrier integrity, giving rise to subcutaneous and body cavity edema.

*Goldenber, et al., 2011*

In addition, mitochondrial damage caused by oxidative stress and other mechanisms impairs cellular oxygen use. *Galley, et al., 2011*

Moreover, injured mitochondria release alarmins into the extracellular environment, including mitochondrial DNA and formyl peptides, which can activate neutrophils and cause further tissue injury. *Zhang, et al., 2010*

**Systemic Effects of Sepsis**

Widespread cellular injury may occur when the immune response becomes generalized, cellular injury is the precursor to organ dysfunction. The precise mechanism of cellular injury is not understood,
but its occurrence is indisputable as autopsy studies have shown widespread endothelial and parenchymal cell injury. Mechanisms proposed to explain the cellular injury include: tissue ischemia (insufficient oxygen relative to oxygen need), cytopathic injury (direct cell injury by proinflammatory mediators and/or other products of inflammation), and an altered rate of apoptosis (programmed cell death).

(Brealey, et al., 2008)

**Tissue ischemia**

Significant derangement in metabolic autoregulation, the process that matches oxygen availability to changing tissue oxygen needs, is typical of sepsis. In addition, microcirculatory and endothelial lesions frequently develop during sepsis. These lesions reduce the cross-sectional area available for tissue oxygen exchange, disrupting tissue oxygenation and causing tissue ischemia and cellular injury:

- Microcirculatory lesions – The microcirculatory lesions may be the result of imbalances in the coagulation and fibrinolytic systems, both of which are activated during sepsis.

- Endothelial lesions – The endothelial lesions may be a consequence of interactions between endothelial cells and activated polymorphonuclear leukocytes (PMNs). The increase in receptor-mediated neutrophil-endothelial cell adherence induces the secretion of reactive oxygen species, lytic enzymes, and vasoactive substances (nitric oxide, endothelin, platelet-derived growth factor, and platelet activating factor) into the extracellular milieu, which may injure the endothelial cells.
Another factor contributing to tissue ischemia in sepsis is that erythrocytes lose their normal ability to deform within the systemic microcirculation. (*Boudjeltia, et al., 2003*)

**Cytopathic injury**

Proinflammatory mediators and/or other products of inflammation may cause sepsis-induced mitochondrial dysfunction (e.g., impaired mitochondrial electron transport) via a variety of mechanisms, including direct inhibition of respiratory enzyme complexes, oxidative stress damage, and mitochondrial DNA breakdown. Such mitochondrial injury leads to cytotoxicity. There are several lines of evidence that support this belief. (*Harrois, et al., 2009*)

The clinical relevance of mitochondrial dysfunction in septic shock was suggested by a study of 28 critically ill septic patients who underwent skeletal muscle biopsy within 24 hours of admission to the ICU. Skeletal muscle ATP concentrations, a marker of mitochondrial oxidative phosphorylation, were significantly lower in the 12 patients who died of sepsis than in 16 survivors. In addition, there was an association between nitric oxide overproduction, antioxidant depletion, and severity of clinical outcome. Thus, cell injury and death in sepsis may be explained by cytopathic (or histotoxic) anoxia, which is an inability to utilize oxygen even when present. (*Brand, et al., 2002*)

Mitochondria can be repaired or regenerated by a process called biogenesis. Mitochondrial biogenesis may prove to be an important therapeutic target, potentially accelerating organ dysfunction and recovery from sepsis. (*Carraway, et al., 2007*)
**Apoptosis**

Apoptosis (also called programmed cell death) describes a set of regulated physiologic and morphologic cellular changes leading to cell death. This is the principal mechanism by which dysfunctional cells are normally eliminated and the dominant process by which inflammation is terminated once an infection has subsided. *(Gray, et al., 2003)*

During sepsis, proinflammatory cytokines may delay apoptosis in activated macrophages and neutrophils, thereby prolonging or augmenting the inflammatory response and contributing to the development of multiple organ failure. Sepsis also induces extensive lymphocyte and dendritic cell apoptosis, which alters the immune response efficacy and results in decreased clearance of invading microorganisms. The extent of lymphocyte apoptosis correlates with and the severity of the septic syndrome and the level of immunosuppression. Apoptosis has been also observed in parenchymal cells, endothelial, and epithelial cells. Several experiments studies show that inhibiting apoptosis protect animal from organ dysfunction and lethality.

*(Sharshar, et al., 2003)*

**Immunosuppression**

Clinical observations and animal studies suggest that the excess inflammation of sepsis may be followed by immunosuppression. Among the evidence supporting this hypothesis, an observational study removed the spleens and lungs from 40 patients who died with active severe sepsis and then compared them with the spleens from 29 control patients and the lungs from 30 control patients. The median duration of sepsis was four days. The secretion of proinflammatory cytokines (i.e., tumor necrosis factor, interferon gamma, interleukin-6, and interleukin-10) from the splenocytes of patients with severe sepsis was generally less than 10
percent that of controls, following stimulation with either anti-CD3/anti-CD28 or lipopolysaccharide. Moreover, the cells from the lungs and spleens of patients with severe sepsis exhibited increased expression of inhibitory receptors and ligands, as well as expansion of suppressor cell populations, compared with cells from control patients. The inability to secrete proinflammatory cytokines combined with enhanced expression of inhibitory receptors and ligands suggests clinically relevant immunosuppression. *(Hasper, et al., 2008)*

**Organ-Specific Effects of Sepsis**

The cellular injury accompanied by the release of proinflammatory and anti-inflammatory mediators, often progresses to organ dysfunction. No organ system is protected.

**Circulation**

Hypotension due to diffuse vasodilatation is the most severe expression of circulatory dysfunction in sepsis. It is probably an unintended consequence of the release of vasoactive mediators, whose purpose is to improve metabolic auto regulation (the process that matches oxygen availability to changing tissue oxygen needs) by inducing appropriate vasodilatation. Mediators include the vasodilators prostacyclin and nitric oxide (NO), which are produced by endothelial cells. *(Vincet, et al., 2008)*

NO is believed to play a central role in the vasodilatation accompanying septic shock, since NO synthase can be induced by incubating vascular endothelium and smooth muscle with endotoxin . When NO reaches the systemic circulation, it depresses metabolic auto regulation at all of the central, regional, and microregional levels of the circulation. *(Gray, et al., 2003)*
Another factor that may contribute to the persistence of vasodilatation during sepsis is impaired compensatory secretion of antidiuretic hormone (vasopressin). This hypothesis is supported by a study that found that plasma vasopressin levels were lower in patients with septic shock than in patients with cardiogenic shock (3.1 versus 22.7 pg/mL), even though the groups had similar systemic blood pressures. It is also supported by numerous small studies that demonstrated that vasopressin improves hemodynamics and allows other pressors to be withdrawn. *(Carsin, et al., 2008)*

Vasodilatation is not the only cause of hypotension during sepsis. Hypotension may also be due to redistribution of intravascular fluid. This is a consequence of both increased endothelial permeability and reduced arterial vascular tone leading to increased capillary pressure.

In addition to these diffuse effects of sepsis on the circulation, there are also localized effects:

- In the central circulation (i.e., heart and large vessels), decreased systolic and diastolic ventricular performance due to the release of myocardial depressant substances is an early manifestation of sepsis. Despite this, ventricular function may still be able to use the Frank Starling mechanism to increase cardiac output, which is necessary to maintain the blood pressure in the presence of systemic vasodilatation. Patients with preexisting cardiac disease (e.g., elderly patients) are often unable to increase their cardiac output appropriately. *(Price, et al., 1999)*

- In the regional circulation (i.e., small vessels leading to and within the organs), vascular hyporesponsiveness leads to an inability to appropriately distribute systemic blood flow among organ systems. As an example, sepsis interferes with the redistribution of blood
flow from the splanchnic organs to the core organs (heart and brain) when oxygen delivery is depressed. *(Nevier, et al., 2008)*

- The microcirculation (i.e., capillaries) may be the most important target in sepsis. Sepsis is associated with a decrease in the number of functional capillaries, which causes an inability to extract oxygen maximally. This may be due to extrinsic compression of the capillaries by tissue edema, endothelial swelling, and/or plugging of the capillary lumen by leukocytes or red blood cells (which lose their normal deformability properties in sepsis).

  *(De Backer, et al., 2008)*

- At the level of the endothelium, sepsis induces phenotypic changes to endothelial cells. This occurs through direct and indirect interactions between the endothelial cells and components of the bacterial wall. These phenotypic changes may cause endothelial dysfunction, which is associated with coagulation abnormalities reduced leukocytes, decreased red blood cell deformability, upregulation of adhesion molecules, adherence of platelets and leukocytes, and degradation of the glycocalyx structure.

  *(Donadello, et al., 2009)*

- Microparticles from circulating and vascular cells also participate in the deleterious effects of sepsis-induced intravascular inflammation *(Favory, et al., 2009)*

**Lung**

Endothelial injury in the pulmonary vasculature during sepsis disturbs capillary blood flow and enhances microvascular permeability, resulting in interstitial and alveolar pulmonary edema. Neutrophil entrapment within the lung's microcirculation initiates and/or amplifies the injury in the alveolocapillary membrane. The result is pulmonary
edema, which creates ventilation-perfusion mismatch and leads to hypoxemia. Acute respiratory distress syndrome is a manifestation of these effects. *(Ghosh, et al., 2003)*

**Gastrointestinal tract**

The circulatory abnormalities typical of sepsis may depress the gut's normal barrier function, allowing translocation of bacteria and endotoxin into the systemic circulation (possibly via lymphatics, rather than the portal vein) and extending the septic response. *(Arid, et al., 2003)*

**Liver**

The reticuloendothelial system of the liver normally acts as the first line of defense in clearing bacteria and bacteria-derived products that have entered the portal system from the gut. Liver dysfunction can prevent the elimination of enteric-derived endotoxin and bacteria-derived products. *(Luce, et al., 2008)*

**Kidney**

Sepsis is often accompanied by acute renal failure. The mechanisms by which sepsis and endotoxemia lead to acute renal failure are incompletely understood. Acute tubular necrosis due to hypoperfusion and/or hypoxemia is one mechanism. However, systemic hypotension, direct renal vasoconstriction, release of cytokines (e.g., tumor necrosis factor), and activation of neutrophils by endotoxin may also contribute to renal injury. *(Auch, et al., 2003)*

The likelihood of death is increased in patients with sepsis who develop renal failure. It is not well understood why this occurs. One factor may be the release of proinflammatory mediators as a result of leukocyte-dialysis membrane interactions when hemodialysis is
necessary. Use of biocompatible membranes can prevent these interactions and may improve survival and the recovery of renal function.

(Hakim, et al., 2007)

**Nervous system**

Central nervous system (CNS) complications occur frequently in septic patients, often before the failure of other organs. The most common CNS complications are an altered sensorium (encephalopathy). The pathogenesis of the encephalopathy is poorly defined.

(Hecht, et al., 2007)

CNS dysfunction has been attributed to changes in metabolism and alterations in cell signaling due to inflammatory mediators. Dysfunction of the blood brain barrier probably contributes, allowing increased leukocyte infiltration, exposure to toxic mediators, and active transport of cytokines across the barrier . (Fleshner, et al., 1998)
Chapter (II)

Microbiology of sepsis

Until the beginning of the 20th century, reports describing infections other than those due to *Salmonella enterica* serovar Typhi (typhoid fever) and *Yersinia pestis* (plague) were rare. Sepsis and septic shock, caused by gram-negative and gram-positive bacteria, fungi, viruses, and parasites, have become increasingly important over the past decades (*Glauser, et al., 1991*)

In the United States, the septicemia rates more than doubled between 1979 and 1987 causing up to 250,000 deaths annually. In three distinct studies, the proportion of infections due to gram-negative bacteria varied between 30 and 80% and that of infections due to gram-positive bacteria varied between 6 and 24% of the total number of cases of sepsis, with the remainder being accounted for by other pathogenic organisms (*Opal, et al., 1999*)

However, the contribution of gram-positive bacteria to sepsis has increased, and in the early 1990s it accounted for more than 50% of all cases of septicemia, with *Staphylococcus aureus* and *S. epidermidis* being responsible for more than half of the cases of sepsis due to gram-positive bacteria (*Bates, et al., 1995*)

The increasing septicemia rates are probably caused by the increasing use of catheters and other invasive equipment, by chemotherapy, and by immunosuppression in patients with organ transplants or inflammatory diseases. Furthermore, improvements in medical care have resulted in longer life spans for the elderly and patients with metabolic, neoplastic, or immunodeficiency disorders. These groups remain at increased risk for infection (*Bone, et al., 1994*)
Due to differences in interpretation of the clinical condition “septic shock,” reported mortality rates in patients with septic shock vary from 20 to 80%. The mortality is related to both the severity of sepsis and the underlying disease that is nearly always present. In many cases of sepsis, the presence of microorganisms (bacteremia) or Lipopolysaccharide (Lps) in the blood (endotoxemia) cannot be established. 

(Bone, et al., 1994)

There are marked differences in the responses to gram-positive and gram-negative bacteria. Where as gram-negative bacteria all contain LPS as their major pathogenic determinant, gram-positive bacteria contain a number of immunogenic cell wall components besides the highly deleterious exotoxins. The immunological response to gram-negative bacteria mainly involves leukocytes and the production of cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6. The release of exotoxins, many of which are superantigens, by gram-positive bacteria activates T cells, resulting in a different cellular response and different cytokine profile, with relatively low levels of TNF-α, IL-1, and IL-6 and increased levels of IL-8 (Opal, et al., 1999)

Bacterial infections are the commonest aetiological agents of both community-acquired and hospital related sepsis, but a causative organism is confirmed in only 60% cases. Disease progression is similar regardless of organism. However, there has been a rise in multiply resistant bacteria such as Acinobacter species, Enterococci and methicillin resistant Staphylococcus aureus (MRSA). The microbiology and primary sources of infection have undergone a remarkable transition over the past 30 years. The predominant pathogen responsible for sepsis in the 1960s and 1970s were Gram-negative bacilli; however, over the past few decades there has been a progressive increase in the incidence of sepsis caused by
Gram-positive and opportunistic fungal pathogens. Although the abdomen was the major source of infection in sepsis from 1970 to 1990, in the past decade pulmonary infections have emerged as the most frequent site of infection (Eaton, et al., 2003)

The most common organisms identified in community acquired Infection requiring intensive care hospitalization are S. pneumoniae, Legionella, and Haemophilus influenzae, with S. aureus, Early-onset nosocomial Infection (< 4–7 days) in patients who have not received prior antibiotic therapy is typically caused by Enterobacteriaceae, Haemophilus species, S. aureus, and pneumococci E coli. Patients who develop late-onset Infection (> 4–7 days) and who have received prior antibiotic therapy are at risk for infection with P. aeruginosa, MRSA, Enterobacteriaceae, including Citrobacter, Klebsiella, Enterobacter, Serratia, Proteus, Morganella, and Providencia spp. Approximately 20–40% of nosocomial Infection are polymicrobial in etiology.

(Dillinger, et al., 2008)

Infection has been and remains a leading cause of death in patients with leukemia and lymphoma and a major cause of morbidity and mortality in patients with solid tumors or transplants. Rapid progression of fungal, bacterial, and mycobacterial infections occurs in patients given monoclonal antibodies to treat Crohn's disease and autoimmune diseases such as rheumatoid arthritis. (Robin, et al., 2005)

Although a great variety of microorganisms have been noted to cause severe, life-threatening infections in immunocompromised hosts, the clinician can formulate a diagnostic plan and decide on empiric therapy by giving careful consideration to the nature, duration, and severity of the immunosuppression that is causing the patient's predisposition to infection. Additionally, immunocompromised patients
and Elderly patients, uremic patients, and patients with end-stage liver disease or those receiving corticosteroids often will fail to mount a significant febrile response even to serious infection.

(Darmon, et al., 2005)

Overwhelming pneumococcal sepsis occurs in patients with asplenia or diminished splenic function. Such patients usually present with overwhelming pneumococcal sepsis rather than pneumococcal pneumonia even if the initial site of infection is the lungs or upper respiratory tract. Patients who have overwhelming pneumococcal sepsis, unlike those who have other pneumonias, present with a diffuse petechial or ecchymotic rash and shock. (Cunha, et al., 2006)

Polymicrobial diseases, caused by combinations of viruses, bacteria, fungi, and parasites, are being recognized with increasing frequency. In these infections, the presence of one micro-organism generates a niche for other pathogenic micro-organisms to colonize; one micro-organism predisposes the host to colonization by other microorganisms, or two or more non-pathogenic micro-organisms together cause disease. The medical community is recognizing the significance of Polymicrobial diseases and the major types of microbial community interactions associated with human health and disease. Many traditional therapies are just starting to take into account the polymicrobial cause of diseases and the repercussions of treatment and prevention. Polymicrobial episodes were significantly more likely to be hospital-acquired, to emanate from bowel or multiple foci, and to occur in immunocompromised patients, especially those with terminal malignancies, nonhematologic malignancies or multiple underlying diseases (Bakaletz, et al., 2004)
Deaths directly related to sepsis were two fold higher in polymicrobial versus unimicrobial bacteremia. Factors associated with increased mortality in polymicrobial sepsis included age greater than 40 years, absent or diminished febrile response to sepsis, absolute granulocytopenia, inadequate antimicrobial therapy for all microorganisms isolated and a primary focus of infection in the bowel, the respiratory tract, an abscess, or an occult site. (Brogden, et al., 2002)

Enterobacteriaceae, non group A streptococci, anaerobic bacteria, and pseudomonads were disproportionately common in polymicrobial bacteremia. The occurrence and type of polymicrobial bacteremia can suggest a source of sepsis as well as additional diagnostic and therapeutic maneuvers. Polymicrobial sepsis is associated with immunosuppression caused by the predominance of anti-inflammatory mediators and profound loss of lymphocytes through apoptosis. (Lipsky, et al., 2004)

**Common sources of sepsis**

**Gastrointestinal tract**

Very important source of sepsis is the distal gastrointestinal tract. The colon contains more bacteria than any other organ. The fecal flora is predominantly 75% Bacteroides fragilis. Most of the remaining anaerobic fecal flora are common coliforms 20% and less common aerobic gram negative bacilli(GNBs), excluding Pseudomonas aeruginosa. The remaining portion of fecal flora 5% is comprised of group D enterococci. Of this, about 95% are E faecalis and about 5% are Enterococcus faecium, which are virtually all vancomycin resistant (VRE). Because group D enterococci are "permissive" pathogens in the gastrointestinal tract (excluding the biliary tract), specific anti vancomycin sensitive enterococcus (VSE) coverage is unnecessary in intra-abdominal infections. The predominant organism in the colonic flora is B fragilis.
Making up the other component of the fecal flora are aerobic GNBs, which are the organisms that cause bacteremia and peritonitis.

(Cruz, et al., 2002)

B fragilis is the predominant pathogen in lower intra-abdominal and pelvic abscesses. When the integrity of the colon is breached and high numbers of GNBs are released into the peritoneum or bloodstream by infection (e.g., diverticulitis) or trauma (e.g., surgery or colitis), sepsis is predictably frequent. Biliary tract sepsis is usually due to Escherichia coli, Klebsiella pneumoniae, or VSE. Optimal empiric monotherapy is with meropenem, piperacillin- tazobactam, levofloxacin, or tigecycline

(Marshall, et al., 2002)

Central venous catheters

For CVC sepsis infection mainly caused by Staphylococcus aureus. If methicillin-sensitive Staph aureus (MSSA) strains predominate in an institution, anti-methicillin-resistant S aureus (anti-MRSA) is not necessary after catheter removal. CVC breaches the normal skin barrier to infection and bacteria may be directly introduced into the bloodstream and if present in sufficient numbers will result in clinical sepsis.

(Gill, et al., 1999)

Genitourinary tract

Urosepsis is sepsis originating from the urinary tract, where the organism cultured from the urine is the same as the organism cultured from the blood. The urinary tract, like other organ systems, is designed to prevent infection. Urosepsis occurs only in the setting of pre-existing renal disease, abnormal urinary tract anatomy, foreign bodies (stents), renal or bladder stones, or genitourinary instrumentation with infected urine. Uropathogens causing urosepsis originate from the gastrointestinal
tract and expectedly are aerobic GNBs or group D enterococci, usually Enterococcus faecalis (i.e., vancomycin-sensitive enterococci [VSE]

(Cunha, et al., 2007)

**Pulmonary**

Pneumonias may be classified in many ways by causative organism or by site of acquisition (i.e., community-acquired pneumonias [CAPs] or nosocomial pneumonia [NP]. A subset of hospital-acquired pneumonia (HAP) or NP is ventilator-associated pneumonia (VAP). From the infectious disease perspective, NP, HAP, and VAP are caused by the same pathogens. Occasionally, patients with HAP, NP, or VAP may be complicated by septic shock. There are three NP, HAP, and VAP pathogens that have the potential to cause sepsis and septic shock. These are Klebsiella pneumoniae, Staph aureus, and Pseudomonas aeruginosa. CAPs are not associated with sepsis or septic shock except in three circumstances. Firstly, K pneumoniae is seen virtually only in chronic alcoholics. (Cunha, et al., 2007)

K pneumoniae CAP is similar to K pneumoniae NP in terms of its clinical characteristics and radiograph appearance. Nosocomial K pneumoniae is more likely to present with sepsis and shock than its community-acquired counterpart. P aeruginosa is not a cause of CAP except in patients with cystic fibrosis or chronic bronchiectasis and even in these patients does not present with sepsis or septic shock. Patients who have febrile neutropenia who are predisposed to Pseudomonas bacteremia do not present with Pseudomonas pneumonia with sepsis or septic shock. CAP due to MSSA or MRSA, either community-onset MRSA (COMRSA) or community-acquired MRSA (CA-MRSA), may present with sepsis and shock in patients with viral influenza or an influenza like illness. (Routsi, et al., 2007)
Most staphylococcal pneumonias seen in the hospital are community acquired and superimposed upon viral influenza. In the absence of influenza, S aureus is rarely, if ever, a CAP pathogen. Viral influenza with associated tracheo-bronchial damage predispose to necrotizing hemorrhagic MSSA and MRSA CAP. Viral influenza alone is associated with a high mortality and morbidity even in young healthy adults. Certainly patients with viral influenza and superimposed MSSA or MRSA pneumonia are critically ill. However, it is difficult to factor out the relative contributions of the bacterial versus the viral component in terms of its virulence potential which, if not synergistic, is certainly additive. (*Lipsky, et al., 2007*)
Chapter (III)

Diagnosis of sepsis and septic shock

Sepsis is one of the oldest and most elusive syndromes in medicine. Hippocrates claimed that sepsis was the process by which flesh rots, swamps generate foul airs, and wounds fester.

(Majino, et al., 1991)

With the confirmation of germ theory by Semmelweis, Pasteur, and others, sepsis was recast as a systemic infection, often described as —blood poisoning,‖ and assumed to be the result of the host's invasion by pathogenic organisms that then spread in the bloodstream. However, with the advent of modern antibiotics, germ theory did not fully explain the pathogenesis of sepsis: many patients with sepsis died despite successful eradication of the inciting pathogen. Thus, researchers suggested that it was the host, not the germ, that drove the pathogenesis of sepsis.

(Cerra, et al., 1985)

In 1992, an international consensus panel defined sepsis as a systemic inflammatory response to infection, noting that sepsis could arise in response to multiple infectious causes and that septicemia was neither a necessary condition nor a helpful term. Instead, the panel proposed the term —severe sepsis‖ to describe instances in which sepsis is complicated by acute organ dysfunction, and they codified —septic shock‖ as sepsis complicated by either hypotension that is refractory to fluid resuscitation or by hyperlactatemia. (Bone, et al., 1992)
In 2003, a second consensus panel endorsed most of these concepts, with the caveat that signs of a systemic inflammatory response, such as tachycardia or an elevated white-cell count, occur in many infectious and noninfectious conditions and therefore are not helpful in distinguishing sepsis from other conditions. Thus, —severe sepsis∥ and —sepsisl are sometimes used interchangeably to describe the syndrome of infection complicated by acute organ dysfunction (Fink, et al., 2003)

**Incidence and Causes**

The incidence of severe sepsis depends on how acute organ dysfunction is defined and on whether that dysfunction is attributed to an underlying infection. Organ dysfunction is often defined by the provision of supportive therapy (e.g., mechanical ventilation), and epidemiologic studies thus count the —treated incidenecel rather than the actual incidence. In the United States, severe sepsis is recorded in 2% of patients admitted to the hospital. Of these patients, half are treated in the intensive care unit (ICU), representing 10% of all ICU admissions. (Lidicker, et al., 2001)

The number of cases in the United States exceeds 750,000 per year and was recently reported to be rising. (Lago, et al.,2012)

The true incidence is presumably far higher. Severe sepsis occurs as a result of both community-acquired and health care–associated infections. Pneumonia is the most common cause, accounting for about half of all cases, followed by intraabdominal and urinary tract infections. (Barie, et al., 2012)

Blood cultures are typically positive in only one third of cases, and in up to a third of cases, cultures from all sites are negative. Staphylococcus aureus and Streptococcus pneumoniae are the most common gram-positive isolates, whereas Escherichia coli, klebsiella
species, and Pseudomonas aeruginosa predominate among gram-negative isolates. An epidemiologic study of sepsis showed that during the period from 1979 to 2000, gram-positive infections overtook gram-negative infections. *(Thompson, et al., 2012)*

However, in another study involving 14,000 ICU patients in 75 countries, gram-negative bacteria were isolated in 62% of patients with severe sepsis who had positive cultures, gram-positive bacteria in 47%, and fungi in 19%. *(Marshall, et al., 2009)*

**Risk factors**

Risk factors for severe sepsis are related both to a patient's predisposition for infection and to the likelihood of acute organ dysfunction if infection develops. There are many well-known risk factors for the infections that most commonly precipitate severe sepsis and septic shock, including chronic diseases (e.g., the acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, and many cancers) and the use of immunosuppressive agents. *(Pinsky, et al., 2001)*

Among patients with such infections, however, the risk factors for organ dysfunction are less well studied but probably include the causative organism and the patient's genetic composition, underlying health status, and preexisting organ function, along with the timeliness of therapeutic intervention. Age, sex, and race or ethnic group all influence the incidence of severe sepsis, which is higher in infants and elderly persons than in other age groups, higher in males than in females, and higher in blacks than in whites. *(Mayr, et al., 2010)*

There is considerable interest in the contribution of host genetic characteristics to the incidence and outcome of sepsis, in part because of strong evidence of inherited risk factors. Many studies have focused on
polymorphisms in genes encoding proteins implicated in the pathogenesis of sepsis, including cytokines and other mediators involved in innate immunity, coagulation, and fibrinolysis. However, findings are often inconsistent, owing at least in part to the heterogeneity of the patient populations studies. *(Namath, et al., 2011)*

Although a recent genomewide association study explored drug responsiveness in sepsis, no such large-scale studies of susceptibility to or outcome of sepsis have been performed *(Man, et al., 2012)*

**Clinical Features**

The clinical manifestations of sepsis are highly variable, depending on the initial site of infection, the causative organism, the pattern of acute organ dysfunction, the underlying health status of the patient, and the interval before initiation of treatment. The signs of both infection and organ dysfunction may be subtle, and thus the most recent international consensus guidelines provide a long list of warning signs of incipient sepsis. *(Levi, et al., 2003)*
Table (1): Diagnostic criteria for sepsis:

<table>
<thead>
<tr>
<th>Infection, documented, or suspected, and some of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General variables</strong></td>
</tr>
<tr>
<td>Fever, &gt;38.3 °C</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt;36 °C)</td>
</tr>
<tr>
<td>Heart rate &gt;90/min⁻¹ or more than two SD above the normal value for age</td>
</tr>
<tr>
<td>Tachypnea</td>
</tr>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>Significant edema or positive fluid balance (&gt;20 mL/kg over 24 h)</td>
</tr>
<tr>
<td>Hyperglycemia (plasma glucose &gt;140 mg/dL or 7.7 mmol/L) in the absence of diabetes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytosis (WBC &gt;12 000 µL⁻¹)</td>
</tr>
<tr>
<td>Leukopenia (WBC count &lt;4000 µL⁻¹)</td>
</tr>
<tr>
<td>Normal WBC count with greater than 10% immature forms</td>
</tr>
<tr>
<td>Plasma C-reactive protein more than two SD above the normal value</td>
</tr>
<tr>
<td>Plasma procalcitonin more than 2 SD above the normal value</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypotension (SBP &lt;90 mmHg, MAP &lt;70 mmHg, or an SBP decrease &gt;40 mmHg in adults or less than 2 SD below normal for age )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ dysfunction variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypoxemia (PaO₂/FiO₂ &lt;300)</td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt;0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation)</td>
</tr>
<tr>
<td>Creatinine increase &gt;0.5 mg/dL or 44.2 µmol/L</td>
</tr>
<tr>
<td>Coagulation abnormalities (INR &gt;1.5 or aPTT &gt;60 s)</td>
</tr>
<tr>
<td>Ileus (absent bowel sound)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;100 000 µL⁻¹)</td>
</tr>
<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt;4 mg/dL or 70 µmol/L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue perfusion variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlactatemia (&gt;1 mmol/L)</td>
</tr>
<tr>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>

*(Sunderram, et al., 2007)*
Table (2): Severe sepsis:

<table>
<thead>
<tr>
<th>Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis-induced hypotension</td>
</tr>
<tr>
<td>Lactate above upper limits laboratory normal</td>
</tr>
<tr>
<td>Urine output &lt;0.5 mL/kg/h for more than 2 h despite adequate fluid resuscitation</td>
</tr>
<tr>
<td>Acute lung injury with PaO₂/FiO₂ &lt;250 in the absence of pneumonia as infection source</td>
</tr>
<tr>
<td>Acute lung injury with PaO₂/FiO₂ &lt;200 in the presence of pneumonia as infection source</td>
</tr>
<tr>
<td>Creatinine &gt;2.0 mg/dL (176.8 μmol/L)</td>
</tr>
<tr>
<td>Bilirubin &gt;2 mg/dL (34.2 μmol/L)</td>
</tr>
<tr>
<td>Platelet count &lt;100,000 μL</td>
</tr>
<tr>
<td>Coagulopathy (international normalized ratio &gt;1.5)</td>
</tr>
</tbody>
</table>

(Martin, et al., 2007)

Acute organ dysfunction most commonly affects the respiratory and cardiovascular systems. Respiratory compromise is classically manifested as the acute respiratory distress syndrome (ARDS), which is defined as hypoxemia with bilateral infiltrates of noncardiac origin. (Rubenfeld, et al., 2012)

Cardiovascular compromise is manifested primarily as hypotension or an elevated serum lactate level. After adequate volume expansion, hypotension frequently persists, requiring the use of vasopressors, and myocardial dysfunction may occur. (Dellinger, et al., 2013)
The brain and kidneys are also often affected. Central nervous system dysfunction is typically manifested as obtundation or delirium. Imaging studies generally show no focal lesions, and findings on electroencephalography are usually consistent with nonfocal encephalopathy. Critical illness polyneuropathy and myopathy are also common, especially in patients with a prolonged ICU stay.

(Sharshar, et al., 2002)

Acute kidney injury is manifested as decreasing urine output and an increasing serum creatinine level and frequently requires treatment with renal-replacement therapy. Paralytic ileus, elevated aminotransferase levels, altered glycemic control, thrombocytopenia and disseminated intravascular coagulation, adrenal dysfunction, and the euthyroid sick syndrome are all common in patients with severe sepsis.

(Fink, et al ., 2003)

Outcome

Before the introduction of modern intensive care with the ability to provide vital organ support, severe sepsis and septic shock were typically lethal. Even with intensive care, rates of in-hospital death from septic shock were often in excess of 80% as recently as 30 years ago.

(Silva, et al ., 1998)

However, with advances in training, better surveillance and monitoring, and prompt initiation of therapy to treat the underlying infection and support failing organs, mortality is now closer to 20 to 30% in many series. (Kumar, et al ., 2011)

With decreasing death rates, attention has focused on the trajectory of recovery among survivors. Numerous studies have suggested that patients who survive to hospital discharge after sepsis remain at increased risk for death in the following months and years. Those who survive often
have impaired physical or neurocognitive functioning, mood disorders, and a low quality of life. *(Carlet, et al., 2003)*

In most studies, determining the causal role of sepsis in such subsequent disorders has been difficult. However, a recent analysis of the Health and Retirement Study, involving a large, longitudinal cohort of aging Americans, suggested that severe sepsis significantly accelerated physical and neurocognitive decline. *(Balk, et al., 1997)*

**Complications**

End organ failure is a major contributor to mortality in sepsis and septic shock. The complications with the greatest adverse effect on survival are Acute respiratory distress syndrome (ARDS), DIC, and acute kidney injury (AKI) previously termed acute renal failure (ARF). Acute lung injury (ALI)—mild ARDS, by the Berlin Definition—leading to moderate or severe ARDS is a major complication of severe sepsis and septic shock. The incidence of ARDS is approximately 18% in patients with septic shock, and mortality approaches 50%. *(Ranieri, et al., 2012)*

ARDS also leads to prolonged intensive care unit (ICU) stays and an increased incidence of ventilator-associated pneumonia. ARDS secondary to severe sepsis demonstrates the manifestations of underlying sepsis and the associated multiple organ dysfunction. Pulmonary manifestations include acute respiratory distress and acute respiratory failure resulting from severe hypoxemia caused by intrapulmonary shunting. Fever and leukocytosis may be present secondary to the lung inflammation.

The severity of ARDS may range from mild lung injury to severe respiratory failure. The onset of ARDS usually is within 12-48 hours of the inciting event. The patients demonstrate severe dyspnea at rest,
tachypnea, and hypoxemia; anxiety and agitation are also present. The frequency of ARDS in sepsis has been reported to range from 18% to 38% (with gram-negative sepsis, 18-25%). Sepsis and multiorgan failure are the most common cause of death in ARDS patients. Approximately 16% of patients with ARDS die of irreversible respiratory failure. Most patients who show improvement achieve maximal recovery by 6 months, with lung function improving to 80-90% of predicted values.

(Thompson, et al., 2012)

**Acute kidney injury**

Sepsis is the most common cause of AKI (ARF), which affects 40-70% of all critically ill patients, depending on how AKI is defined (eg, according to the RIFLE [risk, injury, failure, loss, and end stage] or AKIN [Acute Kidney Injury Network] classifications). AKI complicates therapy and worsens the overall outcome. (Dennen, et al., 2010)

There is an increased risk of mortality when urosepsis is present with severe sepsis and septic shock; however, the global prognosis for patients with urosepsis is better than that for those with sepsis from other infectious sites. (Grabe, et al., 2011)

**Other complications**

Other complications of septic shock include the following:

DIC (also occurring in 40% of patients with septic shock), Chronic renal dysfunction, Mesenteric ischemia, Myocardial ischemia and dysfunction, Liver failure, Other complications related to prolonged hypotension and organ dysfunction.
Diagnostic Considerations

A clinical continuum of severity exists, from sepsis to severe sepsis to septic shock and multiple organ dysfunction syndrome (MODS). In a study that evaluated 2527 intensive care unit (ICU) patients with systemic inflammatory response syndrome (SIRS), 26% developed sepsis, 18% developed severe sepsis, and 4% developed septic shock. The incidence of positive results on blood culture was 17% in patients with sepsis and 69% in patients with septic shock. (Wenzel, et al., 1998)

The diagnosis of septic shock requires features of SIRS (eg, mental changes, hyperventilation, distributive hemodynamics, hyperthermia or hypothermia, or reduced, elevated, or left-shifted white blood cells [WBCs]) in addition to a potential source of infection.

Whenever a patient presents with shock, an early working diagnosis must be formulated, an approach to urgent resuscitation must be established, and steps must be taken to confirm the working diagnosis. The following points should be considered for early diagnosis of sepsis:

- Patients with sepsis may present in a myriad of ways, and high clinical suspicion is necessary to identify subtle presentations.

- Patients in a septic state should be screened for evidence of tissue hypoperfusion, such as cool or clammy skin, mottling, and elevated shock index (heart rate–to–systolic blood pressure >0.9)

- A lactic acid level higher than 4 mmol/dL has been used as an entry criterion for early goal-directed therapy (EGDT) and an indicator of severe tissue hypoperfusion. (Annané, et al., 2003)

Important to note, three large prospective multicenter randomized clinical trials of EGDT in the management of septic shock (ProCESS [Protocolized Care for Early Septic Shock] ARISE [Australasian
Resuscitation In Sepsis Evaluation], and ProMISE [Protocolised Management In Sepsis] have all yielded the same negative results, namely that the use of strict protocolized monitoring (central venous catheterization, lactate and ScvO2 measures) and management (targeting a hemoglobin >8 g/dL, ScvO2 >70%) were no better than usual care as long as patients were managed closely. (Yealy, et al., 2014)

Initial laboratory studies

**Complete blood count with differential**

The white blood cell (WBC) count and the WBC differential can be somewhat helpful in predicting bacterial infection, though an elevated WBC count is not specific to infection. In the setting of fever without localizing signs of infection, a WBC count higher than 15,000/μL or a neutrophil band count higher than 1500/μL has about a 50% correlation with bacterial infection. WBC counts higher than 50,000/μL or lower than 300/μL are associated with significantly decreased survival rates. Hemoglobin concentration dictates oxygen-carrying capacity in blood, which is crucial in shock to maintain adequate tissue perfusion. Although there is no specific hematocrit or hemoglobin target, keeping the hemoglobin concentration above 7 g/dL is usually practiced, and studies comparing this versus 9 g/dL have shown no increased survival benefit from either arm. Platelets, as acute-phase reactants, usually increase at the onset of any serious stress and are typically elevated in the setting of inflammation. However, the platelet count will fall with persistent sepsis, and disseminated intravascular coagulation (DIC) may develop.

(Levi, et al., 2009)
Coagulation studies

Coagulation status should be assessed by measuring the prothrombin time (PT) and the activated partial thromboplastin time (aPTT). Patients with clinical evidence of a coagulopathy require additional tests to detect the presence of DIC. The PT and the aPTT are elevated in DIC, fibrinogen levels are decreased, and fibrin split products are increased. *(Carlet, et al., 2008)*

Blood chemistries

At regular intervals, metabolic assessment should be carried out by measuring serum levels of electrolytes, including magnesium, calcium, phosphate, and glucose. Sodium and chloride levels are abnormal in severe dehydration. Decreased bicarbonate can point to acute acidosis, however sodium bicarbonate therapy is not recommended to improve hemodynamics or replace vasopressor requirements in patients with metabolic acidemia from hypoperfusion whose pH level is 7.15 or greater *(Levi, et al., 2005)*

Serum lactate is perhaps the best serum marker for tissue perfusion, in that it is elevated under conditions of anaerobic metabolism, which occurs when tissue oxygen demand exceeds supply. This can result from decreased arterial oxygen content (hypoxemia), decreased perfusion pressure (hypotension), maldistribution of flow, and decreased diffusion of oxygen across capillary membranes to target tissues, as well as decreased oxygen utilization on a cellular level. There is also evidence that lactate can be elevated in sepsis in the absence of tissue hypoxia, as a consequence of mitochondrial dysfunction and down regulation of pyruvate dehydrogenase, which is the first step in oxidative phosphorylation. *(Levy, et al., 2005)*
Lactate levels higher than 2.5 mmol/L are associated with an increase in mortality. The higher the serum lactate, the worse the degree of shock and the higher the mortality. Lactate levels higher than 4 mmol/L in patients with suspected infection have been shown to yield a 5-fold increase in the risk of death and are associated with a mortality approaching 30%. (Howell, et al., 2005)

It has been hypothesized that lactate clearance is a measure of tissue reperfusion and an indication of adequate therapy. (Jones, et al., 2010)

Liver function tests (LFTs) and levels of bilirubin, alkaline phosphatase, and lipase are important in evaluating multiorgan dysfunction or a potential causative source (eg, biliary disease, pancreatitis, or hepatitis). Increased BUN and creatinine levels can point to severe dehydration or renal failure. In severely ill patients suspected of having adrenal insufficiency, a delta cortisol level below 9 µg/dL (after administration of 250 µg of cosyntropin) or a random total cortisol level below 10 µg/dL is diagnostic. (Marik, et al., 2003)

It should be kept in mind that the adrenocorticotropic hormone (ACTH) stimulation test is not recommended for identifying the subset of patients with septic shock or acute respiratory distress syndrome (ARDS) who should receive corticosteroid therapy. (Pastores, et al., 2008)

The American College of Critical Care Medicine (ACCCM) does not recommend the routine use of free cortisol measurements in critically ill patients. There are no clear parameters for the normal range of free cortisol in such patients, and the free cortisol assay is not widely available, despite its advantages over the total serum cortisol level. (Arlt, et al., 2008)
Microbiology Studies

Blood cultures

Blood cultures should be obtained in patients with suspected sepsis to facilitate isolation of a specific organism and tailoring of antibiotic therapy. These cultures are the primary means of diagnosing intravascular infections (eg, endocarditis) and infections of indwelling intravascular devices. Individuals at high risk for endocarditis are intravenous (IV) drug abusers and patients with prosthetic heart valves.

(Wood, et al., 2006)

The Surviving Sepsis Campaign recommends obtaining at least 2 blood cultures before antibiotics are administered, with 1 percutaneously drawn and the other(s) obtained through each vascular access (unless the device was inserted < 48 hours beforehand). (Rhodes, et al., 2013)

Again, however, it must be remembered that blood cultures are positive in fewer than 50% of cases of sepsis. (Kumar, et al., 2006)

To optimize recovery of aerobic bacteria from patients with suspected intra-abdominal infection, 1-10 mL of fluid can be directly inoculated into an aerobic blood culture; an additional 0.5 mL of fluid should be sent for Gram staining and, if indicated, fungal cultures.

(Solomkin, et al., 2010)

For anaerobic bacteria, 1-10 mL of fluid can also be directly inoculated into an anaerobic blood culture bottle. Susceptibility testing for organisms that have a high risk for resistance (eg, Pseudomonas, Proteus, Acinetobacter, Staphylococcus aureus, and predominant [moderate to heavy growth] Enterobacteriaceae) should be performed.

(Bradley, et al., 2010)
Urine analysis and urine culture

Urine analysis and urine culture are indicated for every patient who is in a septic state. Urinary tract infection (UTI) is a common source for sepsis, especially in elderly individuals. Adults who are febrile without localizing symptoms or signs have a 10-15% incidence of occult UTI. Obtaining a culture is important for isolating a specified organism and tailoring antibiotic therapy. *(Mazuski, et al., 2010)*

Gram stain and culture of secretions and tissue

The Gram stain is the only immediately available test that can document the presence of bacterial infection and guide the choice of initial antibiotic therapy. Secretions or tissue for Gram stain and culture from the sites of potential infection (eg, cerebrospinal fluid [CSF], wounds, respiratory secretions, or other body fluids) may be are obtained as they are identified, preferably before administering antibiotic therapy. *(Opal, et al., 2012)*

At least 1 mL of fluid or tissue is needed for cultures. For aerobic or anaerobic cultures, 0.5 mL of fluid or 0.5 g of tissue should be transported to the laboratory in the appropriate aerobic or anaerobic transport medium. *(Goldstein, et al., 2010)*

If pneumonia is suspected, a sputum specimen should be obtained for Gram stain and culture, provided that the patient has a productive cough and that a good quality specimen can be obtained. *(Mandell, et al., 2007)*

Drainage

Any abscess should be drained promptly and purulent material sent to the microbiology laboratory for analysis. If meningitis is suspected, a CSF specimen should be obtained. *(Dean, et al., 2007)*
Routine culture and susceptibility studies should be obtained in the following cases:

- Perforated appendicitis and other community acquired intraabdominal infections in which there is significant resistance of a common community isolate to an antimicrobial regimen in widespread use locally. *(Solomkin, et al., 2010)*

- Higher risk patients who have a greater risk of harboring resistant pathogens, such as those with previous antibiotic exposure.

  *(Baron, et al., 2010)*

Although Gram staining may be helpful for identifying healthcare-related infections (eg, presence of yeast), it has not proved to be of clinical value in community-acquired intra-abdominal infections. Anaerobic cultures are not necessary for community-acquired intra-abdominal infections if empiric antimicrobial therapy against common anaerobic pathogens is administered *(Rodovold, et al., 2010)*

**Plain Radiography**

**Chest**

Because most patients who present with sepsis have pneumonia, and because the clinical examination is unreliable for the detection of pneumonia (especially in elderly patients), a chest radiograph is warranted. Chest radiography detects infiltrates in about 5% of febrile adults without localizing signs of infection; accordingly, it should be routine in adults who are febrile without localizing symptoms or signs and in patients who are febrile with neutropenia and without pulmonary symptoms *(Solomkin, et al., 2010)*

Chest radiography is useful in detecting radiographic evidence of ARDS which carries a high mortality. The discovery of such evidence on
a chest radiograph should prompt consideration of early intubation and mechanical ventilation, even if the patient has not yet shown signs of overt respiratory distress. (Thompson, et al., 2012)

**Abdomen**

Supine and upright or lateral decubitus abdominal radiographs should be obtained; these may be useful when an intra-abdominal source of sepsis is suspected. Abdominal plain films should be obtained if clinical evidence of bowel obstruction or perforation exists. However, if obvious signs of diffuse peritonitis are present and immediate surgical intervention is planned, further diagnostic imaging is not require.

(Mazuski, et al., 2010)

In adult patients with suspected intra-abdominal infection who are not undergoing immediate laparotomy, computed tomography (CT) of the abdomen is preferable to abdominal radiography. (Baron, et al., 2010)

**Ultrasonography**

Abdominal ultrasonography is indicated when patients have evidence of acute cholecystitis or ascending cholangitis exists (eg, right upper quadrant abdominal tenderness, fever, vomiting, elevated LFT results, elevated bilirubin level, or elevated alkaline phosphatase level).

(Goldstein, et al., 2010)

Surgery or endoscopic retrograde cholangiopancreatography (ERCP) may be urgently necessary in the setting of sepsis with acute cholecystitis or ascending cholangitis. (Baron, et al., 2010)

**Echocardiography**

Has a number of uses in assessing patients with septic shock and may be considered. This imaging modality can provide a comprehensive cardiac evaluation in patients with hemodynamic instability and can be
helpful for guiding fluid therapy and monitoring treatment effects. Other conditions that can be assessed include sepsis-induced myocardial dysfunction, right heart failure, dynamic left ventricular obstruction, and tamponade. *(Merkel, et al., 2010)*

**Lumbar Puncture**

An LP is indicated when there is clinical evidence or suspicion of meningitis or encephalitis. If the opening pressure is elevated, only as much CSF as is needed for culture should be obtained. Broad spectrum antibiotics to cover meningitis should be administered before the start of the procedure. In patients with an acute fulminant presentation, rapid onset of septic shock, and severely impaired mental status, this procedure is used to rule out bacterial meningitis. *(Janoo, et al., 2007)*

**The Sequential Organ Failure Assessment score**

The SOFA score is a scoring system to determine the extent of a person's organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological system Both the mean and highest SOFA scores being predictors of outcome. *(Ferreira, et al., 2001)*

An increase in SOFA score during the first 24 to 48 hours in the ICU predicts a mortality rate of at least 50% up to 95%. Scores less than 9 give predictive mortality at 33% while above 11 can be close to or above 50% *(Vincent JL, et al., 2000).*

The score tables below only describe points-giving conditions. In cases where the physiological parameters do not match any row, zero points are given. In cases where the physiological parameters match more than one row, the row with most points is picked.
1- Respiratory System  
2 - Nervous System  
3- Cardio Vascular System  
4 - Liver  
5 - Coagulation  
6- Renal System  

**Table (3): The Sequential Organ Failure Assessment score**

**Respiratory system**

<table>
<thead>
<tr>
<th>PaO2/FiO2 (mmHg)</th>
<th>SOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 400</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 300</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 200 and mechanically ventilated</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 100 and mechanically ventilated</td>
<td>4</td>
</tr>
</tbody>
</table>

**Nervous system**

<table>
<thead>
<tr>
<th>Glasgow coma scale</th>
<th>SOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>13–14</td>
<td>1</td>
</tr>
<tr>
<td>10–12</td>
<td>2</td>
</tr>
<tr>
<td>6–9</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>4</td>
</tr>
</tbody>
</table>

**Cardio Vascular system**

Mean Arterial Pressure OR administration of vasopressors required (doses are in µg/kg/min) | SOFA score |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP &lt; 70 mm/Hg</td>
<td>1</td>
</tr>
<tr>
<td>dopamine&lt;= 5 or dobutamine (any dose)</td>
<td>2</td>
</tr>
<tr>
<td>dopamine&gt; 5 OR epinephrine&lt;= 0.1 OR norepinephrine &lt;= 0.1</td>
<td>3</td>
</tr>
<tr>
<td>dopamine&gt; 15 OR epinephrine&gt; 0.1 OR norepinephrine&gt; 0.1</td>
<td>4</td>
</tr>
</tbody>
</table>

**Liver**

<table>
<thead>
<tr>
<th>Bilirubin (mg/dl) [µmol/L]</th>
<th>SOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2–1.9 [&gt; 20-32]</td>
<td>1</td>
</tr>
</tbody>
</table>
### Diagnosis of sepsis and septic shock

<table>
<thead>
<tr>
<th>Coagulation</th>
<th>SOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelets</strong>×103/µl</td>
<td></td>
</tr>
<tr>
<td>&lt; 150</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>2</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>4</td>
</tr>
</tbody>
</table>

### Renal System

<table>
<thead>
<tr>
<th>Creatinine (mg/dl) [µmol/L] (or urine output)</th>
<th>SOFA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2–1.9 [110-170]</td>
<td>1</td>
</tr>
<tr>
<td>2.0–3.4 [171-299]</td>
<td>2</td>
</tr>
<tr>
<td>3.5–4.9 [300-440] (or &lt; 500 ml/d)</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 5.0 [&gt; 440] (or &lt; 200 ml/d)</td>
<td>4</td>
</tr>
</tbody>
</table>

*(Vincent JL, et al., 2000).*
Chapter (IV)

Management of severe sepsis and septic shock

Sepsis refers to the systemic inflammatory response following microbial infection. Although the clinical criteria that defines sepsis remain controversial, sepsis may best be defined as the “systemic response to infection with the presence of some degree of organ dysfunction” (Angus, et al., 2013)

Sepsis is among the most common reasons for admission to ICUs throughout the world, and it is believed to be the third most common cause of death in the United States. Although the exact incidence of sepsis in the United States is unclear, the annualized incidence has been reported to have increased by 8.7% to 13% over the past 30 years.

(Edwards, et al., 2013)

The aging of the population in developed countries is believed to be largely responsible for the increasing incidence of sepsis.

(Martin, et al., 2006)

Sepsis is an exceedingly complex condition. Exposure of human macrophages to bacterial antigens has been demonstrated to result in a significant change in the expression of over 950 genes. These include genes for proinflammatory and antiinflammatory cytokines, chemokines, adhesion molecules, transcription factors, enzymes, clotting factors, stress proteins, and antiapoptotic molecules. These gene products alter the function of every cell and tissue in the body. Furthermore, these mediators interact in complex positive and negative feedback loops and result in epigenetic modifications that further alter the expression of this network of mediators. (Leentjens, et al., 2013)
Chapter (IV)  Management of severe sepsis and septic shock

The early phase of sepsis is generally believed to result from the uncontrolled production of proinflammatory mediators, the so-called “cytokine storm.” However, some data suggest that both a proinflammatory and an opposing antiinflammatory response occur concurrently in patients with sepsis. In general, following a variable time course, patients transition from a predominantly proinflammatory to an antiinflammatory immunosuppressive state. *(Boomer, et al., 2011)*

The pathogenetic mechanism and physiologic changes associated with sepsis are exceedingly complex. The major pathophysiologic changes in patients with severe sepsis and septic shock include vasoplegic shock (distributive shock), myocardial depression, altered microvascular flow, and a diffuse endothelial injury. *(Slutsky, et al., 2010)*

These pathophysiologic changes play a central role in the early management of patients with sepsis. The widespread endothelial injury results in a microvascular leak, with tissue and organ edema, hypotension, and shock. Increased endothelial permeability is caused by shedding of the endothelial glycocalyx and the development of gaps between endothelial cells (paracellular leak). *(Goldenberg, et al., 2011)*

Vasoplegic shock due to the failure of the vascular smooth muscle to constrict, results in arterial and venodilatation. Venodilatation decreases venous return and compounds the intravascular volume deficit caused by the vascular leak. *(Oliver, et al., 2001)*

**Management**

The early management of patients with severe sepsis and septic shock centers on the administration of antibiotics, IV fluids, and vasoactive agents, followed by source control. However, the specific approach to the resuscitation of patients with septic shock remains highly
controversial. However, it is likely that the early detection of sepsis with the timely administration of appropriate antibiotics is the single most important factor in reducing morbidity and mortality from sepsis. It has become increasingly apparent that in many patients there is a long delay in both the recognition of sepsis and the initiation of appropriate therapy. This has been demonstrated to translate into an increased incidence of progressive organ failure and a higher mortality. (Westphal, et al., 2011)

Physicians, therefore, need to have a high index of suspicion for the presence of sepsis. The clinical features that should heighten the index of suspicion for the diagnosis of sepsis are listed in table (4)

**Table (4) Clinical Features That Should Alert the Physician to the Diagnosis of Severe Sepsis**

<table>
<thead>
<tr>
<th>Clinical Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate &gt; 120/min</td>
</tr>
<tr>
<td>Systolic BP &lt; 90 mm Hg</td>
</tr>
<tr>
<td>Respiratory rate &gt; 20/min</td>
</tr>
<tr>
<td>Temperature &gt; 38.5° or &lt; 36° C</td>
</tr>
<tr>
<td>Confusion</td>
</tr>
<tr>
<td>Lactate &gt; 2 mmol/L</td>
</tr>
<tr>
<td>Procalcitonin &gt; 0.5 ng/mL</td>
</tr>
<tr>
<td>WBC count &gt; 12,000 or &lt; 4,000 cells/μL</td>
</tr>
<tr>
<td>Band count &gt; 5%</td>
</tr>
<tr>
<td>Lymphocytopenia &lt; 0.5 × 10³ μL</td>
</tr>
<tr>
<td>Thrombocytopenia &lt; 150 × 10³ μL</td>
</tr>
<tr>
<td>Oliguria</td>
</tr>
<tr>
<td>Chills and rigors</td>
</tr>
</tbody>
</table>

(Westphal, et al., 2011)

**Antibiotic Therapy**

Empirical IV antibiotic therapy should be started as soon as possible and within the first hour of recognition of severe sepsis, after
appropriate cultures have been obtained. In a retrospective analysis of 2,600 patients demonstrated that the risk of dying increased progressively with an increase in the time to receipt of the first dose of antibiotic from the onset of sepsis-induced hypotension.

(Kumar, et al., 2008)

Furthermore, there was a 5% to 15% decrease in survival with every hour of delay over the first 6 h. The choice of antibiotics is largely determined by the source or focus of infection, the patient’s immunologic status, whether the infection is nosocomial or community acquired, and knowledge of the local microbiology and sensitivity patterns.

(Dickinson, et al., 2011)

Initial empirical antiinfective therapy should include one or more drugs act against the likely pathogens and that penetrate into the presumed source of sepsis. Because the identity of the infecting pathogen(s) and its sensitivity pattern(s) are unknown at the time of initiation of antibiotics, the initial regimen in patients with severe sepsis and septic shock should include two or more antibiotics or an extended spectrum β-lactam antibiotic with the aim of treating all realistically possible microbial causes. A number of studies have demonstrated that appropriate initial antimicrobial therapy, defined as the use of at least one antibiotic active in vitro against the causative bacteria, reduced mortality when compared with the inappropriate therapy other patients received.

(Kollef, et al., 2011)

Once a pathogen is isolated, monotherapy is adequate for most infections; this strategy of initiating broad-spectrum cover with two or more antibiotics, and then narrowing the spectrum to a single agent when a pathogen is identified, is known as “antimicrobial de-escalation.

(Joung, et al., 2011)
Chapter (IV) Management of severe sepsis and septic shock

The indications for continuation of double-antimicrobial therapy include enterococcal infections and severe intraabdominal infections. In addition, double antimicrobial therapy (third-generation cephalosporin and macrolide) is recommended for patients with severe community-acquired pneumonia and those with pneumococcal bacteremia.

(Asadi, et al., 2014)

To rapidly achieve adequate blood and tissue concentrations, antibiotics should be given via IV, at least initially. Dosing regimens should take into account whether the antibiotic “kills” by time-dependent kinetics (eg, β-lactam antibiotics, vancomycin) or by concentration-dependent kinetics (eg, aminoglycoside). The clinical effectiveness of β-lactam antibiotics and vancomycin is optimal when the concentration of the antimicrobial agent in the serum exceeds the minimum inhibitory concentration of the infecting organism for at least 40% of the dosing interval. In addition, antibiotic dosing should take into account the patient’s hepatic and renal function. (Dickinson, et al., 2011)

Fluid Therapy

Beyond the early administration of antibiotics, aggressive “supportive measures” may be harmful and the “less is more” paradigm appears applicable for the management of patients with severe sepsis. In these highly vulnerable patients, more intensive treatment may promote the chance of unwanted adverse effects and, hence, iatrogenic injury.

(Kox, et al., 2013).

Current teaching suggests that aggressive fluid resuscitation is the best initial approach for the cardiovascular instability of sepsis. Consequently, large volumes of fluid (5-10 L) are often infused in the early stages of sepsis. There is, however, no human data that substantial
 (> 30 mL/kg) fluid resuscitation reliably improves BP or end-organ perfusion. \textit{(Hilton, et al., 2013)}

From a pathophysiologic point of view, large-volume fluid resuscitation in patients with sepsis is illogical and may worsen the hemodynamic derangements of sepsis. In patients with septic shock who are fluid responders (an increase in cardiac output with fluid boluses), vasodilatation with a fall in systematic vascular resistance has been observed. \textit{(Pierrakos, et al., 2012)}

A similar finding has been noted in an experimental sepsis model. \textit{(Rehberg, et al., 2012)}

Hence, although the cardiac output increases, vasodilatation occurs and the BP may remain unchanged. Increased shear stress increases the expression of nitric oxide synthetase with increased release of nitric oxide. In addition, increased cardiac filling pressures increase the release of natriuretic peptides, which act synergistically with nitric oxide, causing cyclic guanosine monophosphate-mediated vasodilatation. Endotoxin enhances this vasodilatory response. As cardiac filling pressures increase, extravascular lung water (EVLW) and tissue edema increase. \textit{(Marik, et al., 2012)}

Furthermore, increased cardiac filling pressures consequent to large volume resuscitation increase the release of natriuretic peptides. Natriuretic peptides cleave membrane-bound proteoglycans and glycoproteins (most notably syndecan-1 and hyaluronic acid) off the endothelial glycocalyx. The endothelial glycocalyx plays a major role in regulating endothelial permeability, and damage to the glycocalyx plays a major role in increasing tissue edema. Because of the endothelial injury, capillary leak, and increased hydrostatic pressures, < 5% of infused
crystalloid remains intravascular within 3 h after infusion, resulting in an increase in EVLW and further tissue edema. Increased EVLW has been demonstrated to be a strong independent predictor of death.

(Slva, et al., 2013)

In patients with pneumonia, large-volume fluid resuscitation may result in severe pulmonary edema. Myocardial edema due to excess fluid administration compounds the myocardial dysfunction. Evidence of the harmful effects of aggressive fluid resuscitation on the outcome of sepsis is supported by experimental studies as well as by data accumulated from clinical trials. (Sousse, et al., 2012)

Multiple clinical studies have demonstrated an independent association between an increasingly positive fluid balance and increased mortality in patient with sepsis. (Murphy, et al., 2010)

In a secondary analysis of the Vasopressin in Septic Shock Trial (VASST) demonstrated that a greater positive fluid balance and a higher central venous pressure (CVP) at both 12 h and 4 days were independent predictors of death. (Boyd, et al., 2011)

In a recent study, demonstrated that a positive fluid balance at 8 days was the strongest independent predictor of hospital mortality. In this study, the 24-h fluid balance was 37.5 mL/kg (about 2.5 L) in the survivors compared with 55.3 mL/kg (3.9 L) in those who died. (Hampton, et al., 2013)

In a recent study demonstrated a strong correlation among the net fluid balance, the increase in brain natriuretic peptide, and death in patients with sepsis. The most compelling data that fluid loading in sepsis is harmful come from the Fluid Expansion as Supportive Therapy (FEAST) study performed in 3,141 children with severe sepsis. In this study, aggressive fluid loading was associated with a significantly
increased risk of death. Furthermore, there was no subgroup of patients that benefited from aggressive fluid resuscitation. *(Boyd, et al., 2011)*

In the Australasian Resuscitation of Sepsis Evaluation (ARISE) study, which used the same entry criteria as the EGDT study, $2.2 \pm 1.9$ L of fluid were given in the first 6 h. The hospital mortality was 23% in the ARISE study compared with 30% in the intervention arm of the EGDT study. In the VASST, optimal survival occurred with a positive fluid balance of approximately 3 L at 12 h. *(Bellomo, et al., 2009)*

In some patients, hypotension and tachycardia do resolve with limited fluid resuscitation. However, fluids alone will not reverse the hemodynamic instability of patients with more severe sepsis; in these patients, fluids alone are likely to exacerbate the vasodilatory shock and increase the capillary leak and tissue edema. Based on these data, its better limiting the initial fluid resuscitation to approximately 20 to 30 mL/kg. It is important to emphasize that this conservative approach to fluid management in patients with sepsis is based on indirect evidence and not on a randomized controlled trial specifically designed to answer this question. Furthermore, this recommendation differs somewhat from that of the most recent Surviving Sepsis Campaign guidelines, which suggest “a minimum fluid challenge of 30ml/kg” and that “greater amounts of fluid may be needed in some patients *(Levi, et al., 2013)*

The optimal time to start a vasopressor agent in patients with sepsis has not been well studied. However, after receiving 20 to 30 mL/kg of crystalloidal, it seems unlikely that additional fluid boluses will increase the mean arterial pressure (MAP) in patients who remain hypotensive. *(Hilton, et al., 2012)*

Therefore, its recommended the initiation of a vasopressor agent (norepinephrine) in patients who remain hypotensive (MAP < 65 mm Hg)
after receiving 20 to 30 mL/kg of crystalloid solution. Additional fluid boluses (500 mL) may be given once the “target” norepinephrine dose is achieved (about 0.1-0.2 μg/kg/min), and this should be based on a dynamic assessment of volume responsiveness and ventricular function. Its suggested using the passive leg-raising maneuver coupled with minimally invasive cardiac output monitoring to assess volume responsiveness. Calibrated pulse contour analysis, bioreactance, the ultrasonic cardiac output monitor (USCOM), carotid Doppler flow, Doppler echocardiography, or esophageal Doppler techniques can be used to dynamically follow the cardiac output in real time.  

*(Funk, et al., 2013)*

Bioreactance, USCOM, and carotid Doppler flow are truly noninvasive and are suitable for guiding fluid resuscitation in the Emergency Department (ED). In cases of life-threatening hypotension (diastolic BP < 40 mm Hg), treatment with vasopressors should be started concurrently with fluid administration. *(Marik, et al., 2013)*

Recent data suggest that the choice of resuscitation fluid may have an effect on outcome. Balanced salt solutions (Lactated Ringers solution, Hartmann’s solution, Plasmalyte 148) are the preferred resuscitation fluids. Normal saline (0.9% NaCl) is associated with an increased risk of renal dysfunction, a hyperchloremic metabolic acidosis, and an increased risk of death. *(Shaw, et al., 2013)*

Similarly, hydroxyethyl starch solutions are associated with an increased risk of renal failure and death and are considered contraindicated in patients with sepsis. *(Perner, et al., 2012)*

Albumin has a number of theoretical benefits in patients with sepsis, including its antioxidant and antiinflammatory effects as well as
its ability to stabilize the endothelial glycocalyx. However, the use of albumin in patients with sepsis is controversial. (Kozar, et al., 2011)

The multicenter randomized Albumin Italian Outcome Sepsis Study (ALBIOS) demonstrated that a 25% albumin infusion decreased the mortality of patients with septic shock (and a serum albumin of < 3g/dL) once hemodynamic stability had been achieved. The use of albumin is patients with sepsis is supported by the Saline vs Albumin Fluid Evaluation (SAFE) study, as well as by a metaanalysis on this topic. Because a 25% albumin infusion may restore the damaged endothelial glycocalyx, this would appear to be a reasonable intervention in patients with severe septic shock. (Dan, et al., 2011)

**Vaspressors and Inotropic Agents**

A low MAP is a reliable predictor for the development of organ dysfunction. When the MAP falls below an organ’s autoregulatory threshold, organ blood flow decreases in an almost linear fashion. Because the autoregulatory ranges of the heart, brain, and kidney are > 60 mm Hg, a MAP below this level will likely result in organ ischemia. (Bellomo, et al., 2001)

An analysis of a large ICU database demonstrated that the risk of kidney injury and death increased sharply as the MAP fell below 60 mm Hg. Varpula and colleagues studied the hemodynamic variables associated with mortality in patients with septic shock. These researchers calculated the area under the curve (AUC) of various MAP thresholds over a 48-h time period. The highest AUC values were found for a MAP < 65 mm Hg. Because of the shift in the autoregulatory range (to the right) in patients with chronic hypertension, a higher MAP may be required in these patients. (Bailey, et al., 2009)
The Assessment Of Two Levels Of Arterial Pressure On Survival In Patients With Septic Shock (SEPSISPAM) is a multicenter, randomized controlled trial completed in France. In this study, patients with septic shock were randomized to achieve a target MAP of 65 to 70 or 80 to 85 mm Hg. The primary outcome was 28-day mortality. Secondary outcomes included 90-day mortality and organ failures. A priori, a secondary analysis was planned in patients with and without a history of hypertension. Overall, there was no difference in either primary or secondary end point between the two treatment groups. However the incidence of organ failures (particularly renal dysfunction) was higher in the subgroup of patients with chronic hypertension in the lower MAP group.

Based on these data, an initial MAP of 65 mm Hg in patients with septic shock is a target and in patients with a history of chronic hypertension, targeting a slightly higher MAP (75-80 mm Hg). (Panwar, et al., 2013)

In patients with sepsis, norepinephrine increases BP as well as cardiac output and renal, splanchnic, cerebral, and microvascular blood flow, while minimally increasing heart rate. Although not widely appreciated, norepinephrine causes α1 adrenergic receptor-mediated vasoconstriction; this increases the mean systemic pressure with a significant increase in venous return and cardiac preload. (Silva, et al., 2012)

The early use of norepinephrine restores BP and organ blood flow with a significant fluid sparing effect. The early administration of norepinephrine largely reverses the hemodynamic abnormalities of severe vasodilatory shock. Abid and colleagues demonstrated the early use of norepinephrine in patients with septic shock was a strong predictor of
survival. In situations in which norepinephrine is not available, epinephrine is a suitable alternative agent. In patients with septic shock, dopamine is associated with an increased mortality when compared with norepinephrine, and is best avoided. (Vasu, et al., 2012)

Similarly, phenylephrine is not recommended, because in experimental models it decreases cardiac output as well as renal and splanchnic blood flow. Furthermore, phenylephrine has not been well studied in patients with sepsis. (Malay, et al., 2004)

In patients who remain hypotensive or have evidence of inadequate organ perfusion despite fluid optimization and an adequate dose of norepinephrine (approximately 0.1-0.2 µg/kg/min), further hemodynamic assessment to exclude ventricular dysfunction is recommended. Global biventricular dysfunction has been reported in up to 60% of patients with septic shock. (Page, et al., 2008)

Dobutamine at a starting dose of 2.5 µg/kg/min is recommended in patients with significant ventricular dysfunction (milrinone is an alternative agent). The dose of dobutamine should be titrated to the hemodynamic response as determined by minimally invasive cardiac output monitoring. (Chimot, et al., 2011)

This recommendation is in keeping with the updated Surviving Sepsis Campaign guidelines, which suggest “a trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP. (Levi, et al., 2012)

These recommendations, however, differ from the EGDT study protocol, which suggests the use of an inotropic agent based on the CVP
(> 8-12 mm Hg) and a central venous oxygen saturation (Scvo$_2$) of < 70% (without an evaluation of ventricular function or cardiac output).

*(Chimot, et al., 2011)*

The Surviving Sepsis Campaign guidelines suggest that “vasopressin 0.03 units/min can be added to norepinephrine with the intent of either raising MAP or decreasing norepinephrine dosage (ungraded).” Vasopressin reverses the “relative vasopressin deficiency” seen in patients with septic shock and increases adrenergic sensitivity.

*(Oliver, et al., 2001)*

Terlipressin is an alternative agent should vasopressin not be available (terlipressin is not Food and Drug Administration-approved in the United States). *(Ertmer, et al., 2009)*

Vasopressin may be effective in raising BP in patients with refractory hypotension; however, the optimal time to initiate this drug is not clear. The VASST randomized patients with septic shock to norepinephrine alone or norepinephrine plus vasopressin at 0.03 units/min. By intention-to-treat analysis there was no difference in outcome between the groups. However, an a priori-defined subgroup analysis demonstrated that survival among patients receiving < 0.2 μg/kg/min norepinephrine at the time of randomization was better with the addition of vasopressin than that of those receiving norepinephrine at a dose > 0.2 μg/kg/min. , therefore, the addition of vasopressin at a dose of norepinephrine between 0.1 and 0.2 μg/kg/min is preferred.

*(Singer, et al., 2008)*

Thereafter the dose of norepinephrine should be titrated to achieve a MAP of at least 65 mm Hg. It is important to emphasize that vasopressin is administered as a fixed dose of 0.03 units/min and should not be uptitrated. *(Paul, et al., 2014)*
Resuscitation End Points

A large number of hemodynamic, perfusion, oxygenation, and echocardiographic targets have been proposed as resuscitation goals in patients with severe sepsis and septic shock. (Avwzedo, et al., 2010)

Most of these targets, however, are controversial and are not supported by outcome data. The Surviving Sepsis Campaign guidelines recommend a CVP of 8 to 12 mm Hg (12-15 mm Hg if mechanically ventilated), an Scvo2 > 70%, and a urine output > 0.5 mL/kg/h as targets for resuscitation. (Rhodes, et al., 2012)

It has been well established that there is no relationship between the CVP and intravascular volume and no relationship between the CVP and fluid responsiveness. Consequently, the CVP should not be used to guide fluid therapy. (Marik, et al., 2013)

The use of Scvo2 to guide the resuscitation of patients who are septic is equally problematic. Patients who are septic usually have a normal or increased Scvo2 caused by reduced oxygen extraction. Indeed, recently , a Scvo2 > 70% was considered a diagnostic criterion for severe sepsis. In a large, multicenter, goal-directed study, a high (> 90%) but not a low (< 70%) initial Scvo2 was an independent predictor of death. (Pope, et al., 2010)

Furthermore, Nee and colleagues conclude that the “attainment of a CVP of > 8 mm Hg and Scvo2 of > 70% did not influence survival in patients with septic shock.” (Nee, et al., 2011)

The Surviving Sepsis Campaign guidelines recommend “targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.” This recommendation is based on the notion that an elevated lactate is a consequence of tissue hypoxia and
inadequate oxygen delivery, and is “supported” by two studies that used lactate clearance as the target of resuscitation. *(Jones, et al., 2010)*

Multiple studies have demonstrated that the increased blood lactate concentration in sepsis is not caused by tissue hypoxia but is rather produced aerobically as part of the metabolic stress response. Increasing oxygen delivery in these patients does not increase oxygen consumption. *(Bellomo, et al., 2013)*

Previous studies have demonstrated that targeting supramaximal oxygen delivery does not improve outcome and may be harmful.

In the setting of septic shock, an infusion of a short-acting β-blocker reduced cardiac output and oxygen delivery; paradoxically, this intervention reduced blood lactate levels and improved patient survival as compared with the control group. *(Westphal, et al., 2013)*

These data would suggest that achieving a MAP of at least 65 mm Hg should be the primary target in the resuscitation of patients with septic shock. Furthermore, although attempts to achieve a supranormal cardiac index may be potentially harmful, normal cardiac index (> 2.5 L/min/m²) is a target. Although a falling arterial lactate concentration is a sign that the patient is responding to therapy (attenuation of the stress response), titrating therapy to a lactate concentration is devoid of scientific evidence. *(Garcia, et al., 2014)*

**Blood Transfusion**

The 2012 Surviving Sepsis Campaign guidelines state that “during the first 6 hours of resuscitation, if ScvO₂ is less than 70%...then dobutamine infusion…or transfusion of packed red blood cells to achieve a hematocrit of greater than or equal to 30% in attempts to achieve the ScvO₂ goal are options.” *(Rhodes, et al., 2013)*
In patients who are septic, RBC transfusions do not acutely increase tissue oxygen uptake; paradoxically, they have been demonstrated to impair microcapillary flow and tissue oxygenation. In addition, the release of cell-free hemoglobin from banked blood may be particularly deleterious in patients who are septic. (Janz, et al., 2013)

One study demonstrated that "transfusion of PRBCs was associated with worsened clinical outcomes in patients with septic shock treated with EGDT". (Fuller, et al., 2010)

Blood transfusions are associated with an increased risk of secondary infections, multiorgan dysfunction syndrome, and death and should be considered only in patients with a hemoglobin < 7 g/dL. (Fink, et al., 2011)

Corticosteroids

The use of low-dose corticosteroids in patients with severe sepsis remains controversial. (Marik, et al., 2011)

It has been proposed that inadequate cellular glucocorticoid activity (critical illness-related corticosteroid insufficiency) due to either adrenal suppression or glucocorticoid tissue resistance results in an exaggerated and protracted proinflammatory response. In addition to down-regulating the proinflammatory response, corticosteroids may have additional beneficial effects, including increasing adrenergic responsiveness and preserving the endothelial glycocalyx. (Chappell, et al., 2007)

It was found that corticosteroids were only of benefit if given within 6 h after the onset of septic shock-related hypotension. (Park, et al., 2012)
In the Corticosteroid Therapy of Septic Shock Study (CORTICUS), the initial time frame for the initiation of corticosteroids was 24 h, which was then increased to 72 h. (Flemmer, et al., 2012)

It is also important to recognize that in the CORTICUS, > 60% of the patients were surgical patients. It has now been well established that surgery induces an immunosuppressive state and that this occurs within hours of surgery. It would, therefore, appear counterproductive to give postsurgical patients who are septic corticosteroids because this is only likely to compound the immunosuppressive state and increase the risk of secondary infections (as was demonstrated in the CORTICUS).

(Marik, et al., 2012)

Although the mortality benefit of corticosteroids in septic shock is controversial, low-dose hydrocortisone has been demonstrated to significantly reduce vasopressor dependency, with a favorable side effect profile. (Annane, et al., 2009)

Furthermore, the combination of low dose corticosteroids and vasopressin has been associated with decreased mortality and organ dysfunction in patients with septic shock. (Luckner, et al., 2011)

Based on these data, treatment with hydrocortisone concomitant with the initiation of vasopressin for the management of severe vasodilatory septic shock is preferred, however, this approach has not been tested prospectively. Two large randomized controlled trials are currently underway, and it is hoped that they will resolve this ongoing controversy about the use of corticosteroids in septic shock.

(Oyen, et al., 2012)

**Source Control**

It has been known for centuries that, unless the source of the infection is controlled, the patient cannot be cured of his/her infective
process and death will eventually ensue. It is important that specific diagnoses of infection that require emergent source control be made in a timely manner (e.g., necrotizing soft tissue infection, peritonitis, cholangitis, intestinal infarction) and surgical consultation be obtained immediately. (Boyer, et al., 2009)

When source control in a patient who is severely septic is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess). If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established. (Mermel, et al., 2001)

**Therapies Being Investigated:**

A number of potential therapies for sepsis appear promising in animal models, but have not yet been adequately studied in humans. Other potential therapies have been studied in humans, but have given conflicting results and require additional investigations to clarify their effects.

**Inhibition of innate immunity**

Infecting microbes display highly conserved macromolecules (e.g., lipopolysaccharides, peptidoglycans) on their surface. When these macromolecules are recognized by pattern-recognition receptors (called Toll-like receptors [TLRs]) on the surface of immune cells, the host’s immune response is initiated. This may contribute to the excess systemic inflammatory response that characterizes sepsis. Inhibition of several TLRs is being evaluated as a potential therapy for sepsis:

Inhibition of TLR-4 with the antagonist, E5564 (Eritoran), is currently being tested in humans. The ACCESS (ACtivated
Comparison of Eritoran Tetrasodium and Placebo in Patients with Severe Sepsis) trial has finished enrolling patients, but its results have not been reported. An earlier clinical trial that evaluated the inhibition of TLR-4 with another antagonist, TAK 242 (Resatorvid), found a non-statistically significant reduction in 28-day mortality.

- Inhibition of TLR-2 with a neutralizing antibody (anti-TLR-2) successfully prevented lethal septic shock in an experimental mouse model, even if the antibody was given three hours after the initiation of systemic inflammation. Anti-TLR-2 has not been tested in humans.

(Delaney, et al., 2007)

**Restoration of the gastrointestinal barrier**

Talactoferrin is a glycoprotein that has anti-infective and anti-inflammatory properties, possibly by restoring the barrier properties of the gastrointestinal mucosa. In unpublished studies conducted using animal models, talactoferrin reduced mortality when given enterally up to 12 hours following the onset of sepsis. A randomized trial has been completed in humans with severe sepsis and another randomized trial in humans with severe sepsis is planned.

**Intravenous immunoglobulin**

It has been hypothesized that polyclonal intravenous immunoglobulin (IVIG) may benefit patients with sepsis by binding endotoxin. However, the data are conflicting:

- Suggesting that polyclonal IVIG has no benefit, a randomized trial of 653 patients with sepsis found that IVIG did not reduce 28-day mortality compared to placebo.

- Suggesting that polyclonal IVIG has a benefit, meta-analyses of randomized trials found that polyclonal IVIG decreased
mortality compared to either placebo or no IVIG. The mortality benefit was greatest when IgA- or IgM-enriched IVIG was used. *(Delaney, et al., 2007)*

Taken together, the evidence is insufficient to recommend the administration of polyclonal IVIG to patients with sepsis. However, well-designed randomized trials are warranted to evaluate the impact of IgA- and IgM-enriched IVIG. *(Laupland, et al., 2007)*

**Endotoxin inactivation or removal**

Strategies to improve sepsis by either inactivating or removing endotoxin have been investigated and some of the preliminary data appear promising:

- Hemoperfusion through an endotoxin-avid column-Polymyxin B is an antibiotic with a high affinity for endotoxin. Several studies have found that hemoperfusion through a column that contains polymyxin B may be beneficial to patients with sepsis. The largest was a multicenter trial that randomly assigned 64 patients with severe sepsis or septic shock to receive conventional therapy alone or conventional therapy plus hemoperfusion through a polymyxin B fiber column (PBFC). All of the patients had undergone emergency surgery for intraabdominal infection. The group that received hemoperfusion through a PBFC had lower 28-day mortality than the group that received conventional therapy alone (32 versus 53 percent). In addition, only the group that received hemoperfusion through a PBFC had increased mean arterial pressure, decreased vasopressor requirement, and decreased severity of illness at 72 hours. *(Vincent, et al., 2005)*
Chapter (IV) Management of severe sepsis and septic shock

- Plasma or whole blood exchange Case series and observational studies with historical controls reported favorable outcomes when endotoxin was removed by plasma or whole blood exchange, including lower plasma endotoxin concentrations and, possibly, lower mortality. (Reeves, et al., 2002)

Interferon-gamma

A decrease in monocyte function has been observed late in the course of sepsis, which may predispose patients to life-threatening secondary infections. This observation prompted a study in which patients with sepsis were administered interferon-gamma. The study found that interferon-gamma restored monocyct cell function. Controlled clinical trials measuring patient-important outcomes in patients with sepsis have not been reported, although a trial evaluating the impact of interferon-gamma in candidemia is underway. (Randow, et al., 1997)

Granulocyte-macrophage colony stimulating factor

Granulocyte-macrophage colony stimulating factor (GM-CSF, sargramostim, molgramostim) is a cytokine that promotes maturation of the progenitor cells of granulocytes, erythrocytes, megakaryocytes, and macrophages, as well as mature neutrophils, monocytes, macrophages, dendritic cells, T-lymphocytes, and plasma cells. Its use in sepsis has been studied in several controlled clinical trials. (Meisel, et al., 2009)

Augmentation of immunomodulation

Antibodies directed against macrophage migration inhibition factor (MIF) prevented death in a study that used a cecal puncture animal model of sepsis, even when administered up to eight hours after the onset of peritonitis. The mechanism of action is uncertain, but MIF inhibition might restore or augment the immunomodulatory actions of endogenous
glucocorticoids. While it is known that elevated MIF levels correlate with poor outcomes in humans with sepsis, the impact of MIF inhibition has not been studied in humans. *(Sehefold, et al., 2009)*

**Hemofiltration**

It has been proposed that hemofiltration may remove proinflammatory molecules that induce hemodynamic collapse in septic shock, improving outcomes. However, the data in humans are inconsistent. *(Mateo, et al., 2009)*

- Case series suggest that high-volume hemofiltration may benefit patients with sepsis.

- In a representative series, 20 patients with refractory hyperdynamic septic shock underwent a single, 12 hour session of high-volume hemofiltration. Eleven patients improved following hemofiltration (i.e., improved perfusion and decreased vasopressor requirement) and nine patients did not. ICU mortality was only 18 percent among those who improved, compared to 67 percent among those who did not.

- In contrast, a randomized trial that evaluated continuous venovenous hemofiltration (CVVH) in patients with sepsis did not demonstrate any improvement in the clearance of inflammatory mediators or clinical outcomes, while another trial was discontinued after an interim analysis showed more frequent and more severe organ failure in the hemofiltration group. *(Payen, et al., 2009)*

**Heparin**

Heparin has anti-thrombotic and immunomodulating effects, both of which have the potential to be beneficial in sepsis. In a retrospective cohort study of patients with septic shock, intravenous
therapeutic heparin was associated with decreased mortality, discontinuation of vasoactive drug infusions, and liberation from mechanical ventilation. The risk of major hemorrhage or the need for transfusion was not increased. *(Morales, et al., 2009)*

**Naloxone**

A meta-analysis of three randomized trials (61 patients) comparing naloxone to either placebo or no naloxone found that naloxone therapy led to hemodynamic improvement, but did not improve the case-fatality rate. Adverse effects that have been associated with naloxone therapy include pulmonary edema, hypertension, and seizures. Given the limitations of the meta-analysis that found a physiological benefit, the absence of patient-important benefits, and the potential for adverse effects, we believe that naloxone therapy is not warranted for patients with septic shock. *(Gauvin, et al., 2000)*

**Pentoxifylline**

Sepsis results in decreased red cell deformability and increased erythrocyte aggregation, effects that may be mitigated by pentoxifylline. Pentoxifylline also inhibits neutrophil adhesion and activation, and modulates endotoxin-induced expression of proinflammatory cytokines. In a trial of 51 surgical patients with severe sepsis who were randomly assigned to receive pentoxifylline or placebo, pentoxifylline improved the multiple organ dysfunction score and the arterial oxygen tension to fraction of inspired oxygen (PaO2/FIO2), but there was no improvement in the 28-day mortality. *(Rock, et al., 2011)*

**Statins**

HMG CoA reductase inhibitors (statins) are in wide clinical use and have an established role in the management of hyperlipidemia and
cardiovascular disease. Statins also appear to have beneficial anti-inflammatory properties, such as suppression of endotoxin-induced up-regulation of TLR-4 and TLR-2. Several observational studies have suggested that statins are beneficial in patients with sepsis.

(Plump, et al., 2011)

**Recombinant human activated protein C**

Activated protein C, a component of the natural anticoagulant system, is a potent antithrombotic serine protease with substantial antiinflammatory properties. What has the efficacy of this treatment taught us about the pathogenesis of sepsis, and what are the strengths and limitations of this important clinical trial. (Bernard, et al., 2001)

In the initial response to a localized infection, as in pneumonia or an intraabdominal abscess, the release of endotoxins or exotoxins by a bacterial infection induces tissue macrophages to generate inflammatory cytokines, including tumor necrosis factor α, interleukin-1β, and interleukin-8 Although these early-response cytokines play an important part in host defense by attracting activated neutrophils to the site of infection, the entry of these cytokines and bacterial products into the systemic circulation can bring about widespread microvascular injury, leading to multiorgan failure. Most prior clinical trials evaluated pharmacologic agents designed to attenuate these early inflammatory events in sepsis, including glucocorticoids and drugs designed to neutralize endotoxin, tumor necrosis factor α, or interleukin-1β. None of these treatments were effective, perhaps in part because the importance of the coagulation cascade in sepsis was not recognized.

(Daniei, et al., 2011)

There are a number of compelling reasons why activated protein C might be an effective therapy in patients with sepsis. First, most patients
with severe sepsis have diminished levels of activated protein C, in part because the inflammatory cytokines generated in sepsis down-regulate thrombomodulin and the endothelial-cell protein C receptor, components of the coagulation system that are necessary for the conversion of inactive protein C to activated protein C. Second, activated protein C inhibits activated factors V and VIII, thereby decreasing the formation of thrombin. Third, activated protein C stimulates fibrinolysis by reducing the concentration of plasminogen-activator inhibitor type 1. Fourth, the administration of activated protein C to baboons with gram-negative sepsis reverses the procoagulant and inflammatory effects of sepsis and increases survival. Finally, there is recent evidence that treatment with protein C may improve clinical outcomes in patients with severe meningococcemia. (Grubers, et al., 2012)

Activated protein C should be given to patients who meet all the inclusion criteria, including evidence of end-organ dysfunction with shock, acidosis, oliguria, or hypoxemia. The drug should not be given to patients with clinical signs of mild-to-moderate sepsis who do not have evidence of end-organ injury, unless a future trial shows a clear benefit in these patients. Furthermore, the risks and benefits of the agent must be studied in patients at a higher risk of bleeding, in children, and in immunosuppressed patients, especially those with thrombocytopenia or neutropenia. Because the cost of this new therapy will be substantial, ways to make this drug affordable throughout the world should be identified. (Bernard, et al., 2001)

Recombinant human activated protein C, an anticoagulant is the first anti-inflammatory agent that has proved effective in the treatment of sepsis. In patients with sepsis, the administration of activated protein C in
a dose of 24Mic/kg/hr resulted in a 19.4 percent reduction in the relative risk of death and an absolute risk reduction of 6.1 percent.

(Bernard, et al., 2001)

**Dosing:** (Adult)

Severe sepsis: I.V.: 24 mcg/kg/hour for a total of 96 hours; stop infusion immediately if clinically-important bleeding is identified. Note: Use actual body weight for dosing. There is no specific adjustment recomended in patients with renal impairment. (Bernard, et al., 2001)

**Administration**

Infuse separately from all other medications. Only dextrose, normal saline, dextrose/saline combinations, and lactated Ringer's solution may be infused through the same line. May administer via infusion pump. Administration of prepared solution must be completed within 12 hours of preparation. Suspend administration for 2 hours prior to invasive procedures or other procedure with significant bleeding risk; may continue treatment immediately following uncomplicated, minimally-invasive procedures, but delay for 12 hours after major invasive procedures/surgery. (Levy, et al., 2005)

**Compatibility**

Stable in NS(normal saline); only NS, dextrose, LR(lactate Ringer), or dextrose/saline mixtures may Activated protein C inactivates factors Va and VIIIa, thereby preventing the generation of thrombin.


The efficacy of an anticoagulant agent in patients with sepsis has been attributed to feedback between the coagulation system and the inflammatory cascade. Inhibition of thrombin generation by activated protein C decreases inflammation by inhibiting platelet activation, neutrophil recruitment, and mast-cell degranulation. Activated protein C
has direct anti-inflammatory properties, including blocking of the production of cytokines by monocytes and blocking cell adhesion. Also, activated protein C has antiapoptotic actions that may contribute to its efficacy.  

*(Joyce, et al., 2001)*

The debate regarding the appropriate use of activated protein C, as well as its potential adverse effects, particularly bleeding, has been discussed in many articles. A major risk associated with activated protein C is hemorrhage; in a study of activated protein C, 3.5 percent of patients had serious bleeding (intracranial hemorrhage, a life-threatening bleeding episode, or a requirement for 3 or more units of blood), as compared with 2 percent of patients who received placebo (P < 0.06).

*(Warren, et al., 2002)*

Activated protein C is compatible with Cisatracurium, fluconazole, nitroglycerin, potassium chloride, vasopressin. Incompatible with Amiodarone, ciprofloxacin, cyclosporine, gentamicin, imipenem/cilastatin sodium, insulin (regular), levofloxacin, magnesium sulfate, metronidazole, midazolam, nitroprusside, norepinephrine, piperacillin/tazobactam, ticarcillin/ clavulanate, tobramycin, vancomycin. Variable compatible with Albumin, ampicillin/sulbactam sodium, ceftazidime, ceftriaxone, clindamycin, dobutamine, dopamine, epinephrine, fosphenytoin, furosemide, heparin, potassium phosphate, ranitidine.

*(Sweeny, et al., 2009)*

**Contraindications**

Hypersensitivity to activated protein C or any component of the formulation., active internal bleeding., recent hemorrhagic stroke (within 3 months), severe head trauma (within 2 months)., recent intracranial or intraspinal surgery (within 2 months). intracranial neoplasm or mass lesion., evidence of cerebral herniation., presence of an epidural catheter., trauma with an increased risk of life-threatening bleeding.

*(Sweeny, et al., 2009)*
Summary

Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock were initially defined in 1991 by a consensus panel convened by the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM), then they were reconsidered in 2001 during an International Sepsis Definitions Conference that included representatives from the ACCP, SCCM, American Thoracic Society (ATS), European Society of Intensive Care Medicine (ESICM), and Surgical Infection Society (SIS).

(Levi, et al., 2003)

A practical modification of the definitions has since been published, which provides exact hemodynamic definitions for septic shock. (Annane, et al., 2005)

The definitions presented in a way that highlights the notion that both SIRS and sepsis exist on a continuum of severity that ends with multiple organ dysfunction syndrome (MODS).

SIRS is defined as 2 or more of the following variables: Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F) , Heart rate of more than 90 beats per minute , Respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension (PaCO₂) of less than 32 mm Hg , Abnormal white blood cell count (>12,000/μL or < 4,000/μL or >10%immature [band] forms) , Increased C reactive protein, Increased cardiac output, low systemic vascular resistance , Increased oxygen consumption, Increased procalcitonine concentration, Increased interleukin 6 (IL6), IL8 , Otherwise unexplained alternation in coagulation parameter, alternation in mental status, hyperbilirubinemia , Increased insulin requirement. (Fink, et al., 2004)
There are no universally accepted criteria for individual organ dysfunction in MODS. However, progressive abnormalities of the following organ-specific parameters are commonly used to diagnose MODS and are correlated with increased ICU mortality: PO2/FiO2 ratio, Serum creatinine, Platelet count, Glasgow coma score, Serum bilirubin, Pressure-adjusted heart rate (defined by heart rate multiplied by the ratio of central venous pressure and mean arterial pressure). (Cook, et al., 2007)

Bacterial infections are the commonest aetiological agents of both community-acquired and hospital related sepsis, but a causative organism is confirmed in only 60% cases. Disease progression is similar regardless of organism. However, there has been a rise in multiply resistant bacteria such as Acinobacter species, Enterococci and methicillin resistant Staphylococcus aureus (MRSA). The microbiology and primary sources of infection have undergone a remarkable transition over the past 30 years. The predominant pathogen responsible for sepsis in the 1960s and 1970s were Gram-negative bacilli; however, over the past few decades there has been a progressive increase in the incidence of sepsis caused by Gram-positive and opportunistic fungal pathogens. Although the abdomen was the major source of infection in sepsis from 1970 to 1990, in the past decade pulmonary infections have emerged as the most frequent site of infection. (Eaton, et al., 2003)

Polymicrobial diseases, caused by combinations of viruses, bacteria, fungi, and parasites, are being recognized with increasing frequency. In these infections, the presence of one micro-organism generates a niche for other pathogenic micro-organisms to colonize; one micro-organism predisposes the host to colonization by other microorganisms, or two or more non-pathogenic micro-organisms
together cause disease. The medical community is recognizing the significance of Polymicrobial diseases and the major types of microbial community interactions associated with human health and disease. Many traditional therapies are just starting to take into account the polymicrobial cause of diseases and the repercussions of treatment and prevention. Polymicrobial episodes were significantly more likely to be hospital-acquired, to emanate from bowel or multiple foci, and to occur in immunocompromised patients, especially those with terminal malignancies, nonhematologic malignancies or multiple underlying diseases (Bakaletz, et al., 2004)

Sepsis is one of the oldest and most elusive syndromes in medicine. Hippocrates claimed that sepsis was the process by which flesh rots, swamps generate foul airs, and wounds fester.

(Majino, et al., 1991)

Galen later considered sepsis a laudable event, necessary for wound healing (Funk, et al., 2009)

With the confirmation of germ theory by Semmelweis, Pasteur, and others, sepsis was recast as a systemic infection, often described as “blood poisoning,” and assumed to be the result of the host's invasion by pathogenic organisms that then spread in the bloodstream. However, with the advent of modern antibiotics, germ theory did not fully explain the pathogenesis of sepsis: many patients with sepsis died despite successful eradication of the inciting pathogen. Thus, researchers suggested that it was the host, not the germ, that drove the pathogenesis of sepsis.

(Cerra, et al., 1985)

In 1992, an international consensus panel defined sepsis as a systemic inflammatory response to infection, noting that sepsis could
arise in response to multiple infectious causes and that septicemia was neither a necessary condition nor a helpful term. *(Bone, et al., 1992)*

The incidence of severe sepsis depends on how acute organ dysfunction is defined and on whether that dysfunction is attributed to an underlying infection. Organ dysfunction is often defined by the provision of supportive therapy (e.g., mechanical ventilation), and epidemiologic studies thus count the “treated incidence” rather than the actual incidence. In the United States, severe sepsis is recorded in 2% of patients admitted to the hospital. Of these patients, half are treated in the intensive care unit (ICU), representing 10% of all ICU admissions. *(Lidicker, et al., 2001)*

Risk factors for severe sepsis are related both to a patient's predisposition for infection and to the likelihood of acute organ dysfunction if infection develops. There are many well-known risk factors for the infections that most commonly precipitate severe sepsis and septic shock, including chronic diseases (e.g., the acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, and many cancers) and the use of immunosuppressive agents. *(Pinsky, et al., 2001)*

The clinical manifestations of sepsis are highly variable, depending on the initial site of infection, the causative organism, the pattern of acute organ dysfunction, the underlying health status of the patient, and the interval before initiation of treatment. The signs of both infection and organ dysfunction may be subtle, and thus the most recent international consensus guidelines provide a long list of warning signs of incipient sepsis. *(Levi, et al., 2003)*

Acute organ dysfunction most commonly affects the respiratory and cardiovascular systems. Respiratory compromise is classically
manifested as the acute respiratory distress syndrome (ARDS), which is
defined as hypoxemia with bilateral infiltrates of noncardiac origin.

(Rubenfeld, et al., 2012)

Cardiovascular compromise is manifested primarily as hypotension or an elevated serum lactate level. After adequate volume expansion, hypotension frequently persists, requiring the use of vasopressors, and myocardial dysfunction may occur.

(Dellinger, et al., 2013)

Before the introduction of modern intensive care with the ability to provide vital organ support, severe sepsis and septic shock were typically lethal. Even with intensive care, rates of in-hospital death from septic shock were often in excess of 80% as recently as 30 years ago.

(Silva, et al., 1998)

The early management of patients with severe sepsis and septic shock centers on the administration of antibiotics, IV fluids, and vasoactive agents, followed by source control. However, the specific approach to the resuscitation of patients with septic shock remains highly controversial. However, it is likely that the early detection of sepsis with the timely administration of appropriate antibiotics is the single most important factor in reducing morbidity and mortality from sepsis. It has become increasingly apparent that in many patients there is a long delay in both the recognition of sepsis and the initiation of appropriate therapy. This has been demonstrated to translate into an increased incidence of progressive organ failure and a higher mortality. (Westphal, et al., 2011)

Empirical IV antibiotic therapy should be started as soon as possible and within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained. In a retrospective analysis of 2,600 patients demonstrated that the risk of dying increased progressively
with an increase in the time to receipt of the first dose of antibiotic from the onset of sepsis-induced hypotension. (Kumar, et al., 2008)

Beyond the early administration of antibiotics, aggressive “supportive measures” may be harmful and the “less is more” paradigm appears applicable for the management of patients with severe sepsis. In these highly vulnerable patients, more intensive treatment may promote the chance of unwanted adverse effects and, hence, iatrogenic injury. (Kox, et al., 2013).

In some patients, hypotension and tachycardia do resolve with limited fluid resuscitation. However, fluids alone will not reverse the hemodynamic instability of patients with more severe sepsis; in these patients, fluids alone are likely to exacerbate the vasodilatory shock and increase the capillary leak and tissue edema. Based on these data, its better limiting the initial fluid resuscitation to approximately 20 to 30 mL/kg. It is important to emphasize that this conservative approach to fluid management in patients with sepsis is based on indirect evidence and not on a randomized controlled trial specifically designed to answer this question. Furthermore, this recommendation differs somewhat from that of the most recent Surviving Sepsis Campaign guidelines, which suggest “a minimum fluid challenge of 30ml/kg” and that “greater amounts of fluid may be needed in some patients. (Levi, et al., 2013)

A large number of hemodynamic, perfusion, oxygenation, and echocardiographic targets have been proposed as resuscitation goals in patients with severe sepsis and septic shock. (Avwzedo, et al., 2010)

Most of these targets, however, are controversial and are not supported by outcome data. The Surviving Sepsis Campaign guidelines recommend a CVP of 8 to 12 mm Hg (12-15 mm Hg if mechanically ventilated), an Scvo2 > 70%, and a urine output > 0.5 mL/kg/h as targets for resuscitation. (Rhodes, et al., 2012)
References

A Controlled Comparison of Eritoran Tetrasodium and Placebo in Patients with Severe Sepsis.


Bark BP, Persson J, Grände PO, et al. Importance of the infusion rate for the plasma expanding effect of 5% albumin, 6% HES 130/0.4, 4% gelatin, and 0.9% NaCl in the septic rat. Crit Care Med. 2013;41(3):857-866.


**Boomer JS, To K, Chang KC, et al.** Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA 2011;306:2594-2605


**Diagn Microbiol Infect Dis.** 1986; 5(3):185-96 (ISSN: 0732-8893)


Gaykema RP, Dijkstra I, Tilders FJ, et al. Subdiaphragmatic vagotomy suppresses endotoxin-induced activation of hypothalamic


**References**


**Limaye AP, Kirby KA, Rubenfeld GD, et al.** Cytomegalovirus reactivation in critically ill immunocompetent patients. JAMA 2008;300:413-422.


Simvastatin in Patients with Septic Shock.


يعرف تسمم الدم أنه استجابة الجسم لوجود عدوى ميكروبية مع وجود دلء معين من التأثير على جهاز الجسم، ويعتبر تسمم الدم الشديد والصدمة التسميمية من الأسباب الرئيسية للوفاة في العناية.

وبعد ظهور نظرية المضيف (الجسم) وجد أن التسمم يحدث نتيجة للالتهاب. هذا الالتهاب يسبب في رد فعل في الجسم لمقاومة هذا الالتهاب بطرق مختلفة.

وقد وجد أن مسببات الأمراض تقوم بتشييغ خلايا مناعية من خلال التفاعل مع مستقبلات معينة.

يسبب تسمم الدم الشديد حدوث تغيرات في تجلط الدم مما يؤدي إلى حدوث تهيج الدم، ويوفر الجهاز المناعي بآليات مختلفة لمقاومة العدوى والالتهاب، ويغلب نقص الأكسجين دوراً مهماً في التسمم الشديد والصدمة التسميمية.

وجود هذه العلامات يزيد من احتمالية وجود تسمم في الدم: زيادة ضربات القلب أكثر من 110 في الدقيقة، انخفاض ضغط الدم أقل من 60، ارتفاع درجة الحرارة أكثر من 38 درجة، زيادة معدل التنفس أكثر من 20 في الدقيقة، نقص كمية البول، اضطراب في درجة الوعي.

ويتسبب التسمم الشديد والصدمة التسميمية في حدوث فشل كلوي حاد وفشل في التنفس (متلازمة الضائقة التنفسية الحادة).

وقد وضع نظام لتحديد شدة المرض يعتمد على مدى تأثيره على الأجهزة المختلفة. ويستند هذا النظام على ستة نقاط واحده لكل من الجهاز التنفسي، القلب والأوعية الدموية، تجلط الدم، الكلى، الجهاز العصبي، والكبد.

وتوجد عدة تحاليل وأشعات للتاكيد من وجود تسمم بالدم مثل: وظائف الكلى والكبد صورة دم كاملة، مزاحة دم، أشعه عادية، أشعه تلفيزيونية، أشعه مقطعية، وأشعة رنين مغناطيسي وذلك لمعرفة مكان العدوى.

علاج التسمم والتسمم الشديد والصدمة التسميمية يبدأ بالمضادات الحيوية والمحاليل والأدوية القابلضة.
ويعد سرعة بدء المضادات الحيوية في العلاج هي أهم عامل في العلاج، ولكن يجب سحب مزجار الدم قبلها.

ويعد دواء النورأدرينالين من أهم الأدوية في علاج الصدمة التسممية حيث يقوم بزيادة ضغط الدم في الجسم.

ولابد من استخدام الكورتيزون في علاج الصدمة التسممية محلي جداً.

ويعتبر نقل كرات دم مكدسة أو استخدام دواء الدوبيومين طريقة لتحسين نسبة الأكسجين في الدم.

ويعد اهم هدف في علاج تسمم الدم الشديد والصدمة التسممية هو علاج مصدر العدوى ولو لم يتم التحكم فيه سيؤدي ذلك إلى حدوث الوفاة.

وهدف هذا العمل لمعرفة أسباب وكيفية حدوث تسمم الدم والصدمة التسممية والتعرف على الطرق الحديثة للعلاج وتأثير ذلك على تقليل معدل الوفاة.
الجديد في الصدمة التسممية في وحدة العناية المركزية

رسالة
للحصول على درجة الماجستير في طب ورعاية الحالات الحرجة

مقدمة من الطبيبة / مريم "محمد صلاح الدين" "محمد العفيفي" وهدان بكالوريوس الطب والجراحه - جامعة بنها

تغطّى إشراف

أستاذ دكتور / إيهاب أحمد عبد الرحمن حالفي
أستاذ التخدير والعناية المركزية
كلية الطب - جامعة بنها

دكتور / أحمد حمدي عبد الرحمن علي
مدرس التخدير والعناية المركزية
كلية الطب - جامعة بنها

كلية الطب
جامعة بنها
2015