PREDICTION OF HOSPITAL OUTCOME

IN SEPTIC SHOCK

An ESSAY

Submitted for partial fulfillment of Master degree in General Intensive Care

By

MOHAMMED FATHY ALY SABIT

(M.B., B.CH.)(AIN SHAMS University)

Under supervision of

PROF. SHERIF FAROUK IBRAHEM

Professor of anesthesia and intensive care

Faculty of Medicine - Ain Shams University

PROF. AYMAN AHMAD ELSAYED ABD ELLATEF

Assistant Professor of anesthesia and intensive care
Faculty of Medicine -Ain Shams University

DR. DALIA MAHMOUD AHMAD ELFAWY

Assistant professor of anesthesia and intensive care
Faculty of Medicine - Ain Shams University

Faculty of Medicine

Ain Shams University

2016

List of figures

List of Tables

Contents

ABSTRACT

Septic shock is a medical condition as a result of severe infection and sepsis, though the microbe may be systemic or localized to a particular site. It can cause multiple organ dysfunction syndrome and death.
Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion is defined as either septic shock, an elevated lactate or oliguria
The pathophysiology of sepsis & septic shock include three stages: First, the host-pathogen interaction. Secondly, the different mechanisms leading to organ dysfunction. Last, the involvement of numerous systems of the body [MODS].

The clinical presentation of shock is variable, but several features are common. These include tachycardia and signs of compromised organ perfusion (skin, brain, and kidneys)
The diagnosis of septic shock requires features of SIRS (eg, mental changes, hyperventilation, distributive hemodynamics, hyperthermia , or reduced, elevated, or left-shifted white blood cells) in addition to a potential source of infection.

Effective treatment of septic shock requires resuscitation, proper assessment of the degree of septic shock, supportive care, monitoring, and broad spectrum initial antimicrobial therapy

Acute-phase proteins are the clinically most widely used biomarkers. High levels of the acute-phase proteins – C-reactive protein (CRP) and procalcitonin (PCT) – at onset of sepsis have been described to be associated with a fatal outcome
KEYWORDS :sepsis,septic shock,prognosis.

Introduction

Septic shock is a medical condition as a result of severe infection and sepsis, though the microbe may be systemic or localized to a particular site. It can cause multiple organ dysfunction syndrome and death. Its most common victims are children, immunocompromized individuals, and the elderly, as their immune systems can not deal with the infection as effectively as those of healthy adults. Frequently, patients suffering from septic shock are cared for in intensive care units. The mortality rate from septic shock is approximately 25-50% **(Kumar et al., 2007)**. Most cases of septic shock are caused by gram-positive bacteria followed by endotoxin-producing gram-negative bacteria **(Dellinger et al., 2013)**.

Angus et al. (2003) 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. **Iwashyna et al. (2010)** suggested that severe sepsis significantly accelerated physical and neurocognitive decline.

Several biomarkers are already available for clinical use in sepsis; however, their effectiveness in many instances is limited by the lack of specificity and sensitivity. Other factors include limitation to characterize the presence of an infection and the complexity of the inflammatory and immune processes to stratify patients into homogenous groups for specific treatments **(Samraj et al., 2013)**.

Procalcitonin (PCT) and C-Reactive Protein (CRP) have been most widely used, but even these have limited abilities to distinguish sepsis from other inflammatory conditions or to predict outcome. In view of the

complexity of the sepsis response, it is unlikely that a single ideal biomarker will ever be found **(Pierrakos and Vincent, 2010)**.

Treatment primarily consists of the following: volume resuscitation, early antibiotic administration, early goal-directed therapy, rapid source identification and control, and support of major organ dysfunction **(Levinson et al., 2011)**. Among the choices for vasopressors, norepinephrine is superior to dopamine in septic shock; however, both are still listed as first line in guidelines **(Vasu et al., 2011)**.

Aim of the Essay

The aim of the essay is to discuss the pathophysiology, early diagnosis, management and hospital outcome of septic shock.

Pathophysiology of septic shock

Sepsis is a complex syndrome caused by an uncontrolled systemic inflammatory response, of infectious origin, characterized by multiple manifestations which can bring about brokenness or disappointment of one or more organs and even demise **(Annane, 2005)**.

Definitions:

Infection is a pathologic process caused by the intrusion of ordinarily sterile tissue or liquid or body cavity by pathogenic or potentially pathogenic micro-organisms **(Cooper and Stewart, 2003)**.

Sepsis is defined as infection plus systemic manifestations of infection. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion.

Sepsis-induced hypotension is defined as a systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 70 mm Hg or a SBP decrease > 40 mm Hg in the absence of other causes of hypotension.

Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion is defined as either septic shock, an elevated lactate or oliguria **(Cooper and Stewart, 2003)**.

Epidemiology and Incidence:

Extreme sepsis and septic shock are regular, accounting for about 2.9% of hospital admissions and 10% of admissions into the intensive care unit (ICU).

In the U.S. there are approximately 750,000 new sepsis cases each year, with at least 210,000 fatalities and this is reported to be same throughout Europe. As medication turns out to be more exceptional, with invasive procedures and immunosuppression, the incidence of sepsis is likely to increase even more **(Jacobi, 2006)**.

Mortality associated with severe sepsis remains high at 20-50%. When shock is present, mortality is reported to be even higher at around 24-41%. Approximately 1400 people die from sepsis each day throughout the world **(Jacobi, 2006)**.

Patients admitted and treated for sepsis in the ICU are often transferred from general medical/surgical practice units, operating rooms, Emergency Departments, long- term care facilities and other hospitals. The diagnosis and treatment of these patients may be sub-optimal, even among those who were admitted to general medical or surgical practice units or the ICU **(Marik and Zaloga, 2002)**.

Delays in the identification, transfer and management of critically ill patients during the first 6 hours after ICU admission have been associated with higher mortality rates and increased utilization of hospital resources. Within the last 5 years, advances in the treatment of severe sepsis and septic shock have provided new therapies to treat this disease (**Levy** e**t a**l., 2003).

Although these studies were ICU-based, The timelines of treatment became a more important issue when **Rivers et al. (2001)** were able to show a significant mortality benefit when hemodynamic optimization was provided within the first few hours of disease presentation. This "golden hour" and "silver day" perspective of early resuscitation, which

traditionally has been applied to trauma, can now be applied to severe sepsis and septic shock.

Etiology:

The organism involved in severe sepsis and septic shock are most often bacterial, although in the past gram-negative organisms were most commonly implicated, increasingly gram- positive organisms are isolated, such that roughly similar numbers of gram-negative and gram-positive organisms are now involved (Table 1) (**Friedman et al., 1998)**.

(Methicillin Resistant Staphylococus Aureus) (MRSA) is now responsible for 60% of staphylococcal infections in the ICU intensive care unit, and now vancomycin-resistant S. aureus is beginning to emerge, leaving few antibiotic treatment options **(Angus et al., 2001)**.

Indwelling bladder catheters, intravenous central catheters and mechanical ventilation are ubiquitous throughout the modern day intensive care unit, compromising two of the body's key defenses against microbes - the skin and non instrumented orifices. S. aureus is the single most common causative organism of nosocomial pneumonia and is now responsible for approximately 40% of ventilator-associated pneumonia episodes, with an increasing prevalence of MRSA **(Bollaert et al., 1998)**.

Septic shock can also be caused by a fungal or parasitic infection, and in one third of the patients no infectious agent is identified. About one half of the infections are nosocomial, although the infection can arise anywhere, the lung is the most common cause of infection (40%),

followed by abdomen (20%), catheters and primary bacteremia (15%), and the urinary tract (10%) **(Natanson et al., 1998)**.

Table (1): Epidemiology of pathogenic organisms in sepsis.

Estimated frequency	
Gram positive bacteria	**30-50 %**
• Methicillin-sensitve S.aureus	14-24 %
• Methicillin-resistant S.aureus	5-11 %
• Other Staphylococcus species	1-3 %
• Streptococcus pneumonia	9-12 %
• Other Streptococcus species	6-11 %
• Enterococcus species	3-13 %
• Anaerobic organisms	1-2 %
• Other gram positive bacteria	1-5 %
Gram negative bacteria	**25-30 %**
• Escherichia coli	9-27 %
• Pseudomonas aeruginosa	8-15 %
• Klebsiella pneumoniae	2-7 %
• Other Enterobacter species	6-16 %
• Haemophilis influenza	2-10 %
• Anaerobic organisms	3-7 %
• Other gram negative bacteria	3-12 %
Others (virus, fungi, parasites)	**6-12 %**

(**Briegel et al., 1994)**

Risk Factors For Sepsis:

1. Age:

Aging patients account for 40–50% of all cases of bacteremia, and the overall case fatality rate for older patients with bacteremia ranges from 40% - 60%, or higher when Gram-negative organisms are involved **(Martin et al., 2003)**.

Incidence of septic shock is high among children < 1 year old, it decreases and then slowly rises again with age reaching its maximum value around 60 years. Incidence of severe sepsis is directly correlated to the number of pre-existing co-morbidities. **(Martin et al., 2003)**.

Older patients are often nutritionally or immunologically impaired, making them an easy target for infection and its associated complications. They are frequently affected by co-morbidities that require treatment with foreign devices that make patients vulnerable to infections or complications. The natural barriers of innate immunity are broken, providing increased access for pathogens, there is also evidence of abnormal T and B cell function in older patients (**Vincent et al., 2006)**.

2. Gender:

Sex steroids play an important modulatory role in the regulation of immune function. Numerous reports show that female sex hormones are immune-enhancing, whereas male sex hormones are immunosuppressive. However, when the plasma female sex hormone levels are substantially reduced by ovariectomy, mortality increased dramatically **(Sands et al., 1997)**.

3. Alcohol:

Mechanisms by which infections in alcoholics can lead to sepsis include an increased risk of aspiration, malnutrition, and alterations in the gut/ liver / lung & inflammatory axis. More importantly, alcohol is a potent immunosuppressive drug that impairs immunity, independent of a patient's nutritional status. The abnormalities seen in the immune function of alcoholics include suppression of neutrophil chemotaxis, spleen cell mitogenesis, and serum immunoglobulin production **(Reinhart et al., 2005)**.

4. Other risk factors include:

- Acquired immunodeficiency syndrome.
- Use of cytotoxic and immunosuppressant agents.
- Diabetes mellitus.
- Surgical / invasive procedures.
- Malnutrition.
- Broad-spectrum antibiotic use.
- Malignancy.

Pathophysiology:

The pathophysiology of sepsis & septic shock include three stages: First, the host-pathogen interaction, or how an infectious agent sets off a cascade of cellular events leading to a systemic inflammatory reaction. Secondly, the different mechanisms leading to organ dysfunction. Last, the involvement of numerous systems of the body [MODS].

I) Host-pathogen relation:

Recognition of the pathogen

Two new protein families involved in the detection of the pathogens have been recently discovered, they belong to the group of pattern recognition receptors (PRR): the Toll-like Receptors (TLR) and the nucleotide-binding oligomerisation domain (NOD) molecules, Nod1 and Nod2. These molecules are involved in the recognition of the pathogen and induce an inflammatory response through an enzymatic cascade leading to the activation of the nuclear transcription factor kappa β (NF-kβ).

A) Toll-like receptors (TLR)

TLR are surface membrane-bound proteins with an extracellular domain consisting of leucine-rich repeats (LRR) and a cytoplasmic domain called the Toll/IL-1 receptor or TIR domain **(Cohen, 2002)**.

10 TLRs have been identified in humans, each molecule is able to recognize numerous ligands. For instance, TLR4 recognizes LPS, TRL5 detects bacterial flagella, TLR3 recognizes viral double-strand RNA.

Lipopolysaccharide (LPS) liberated in the organism binds with LPS binding protein (LBP) forming a complex recognized by a surface membrane receptor then start a cascade of protein activation results in the activation of 2 Ikβ kinases, which after phosphorylation can inactivate Ikβ (Interleukin kappa β).

Ikβ is a protein which maintains the nuclear transcription factor (NF-kβ) in an inactive form in the cytoplasm. After its phosphorylation, Ikβ is degraded by proteasomes and the free NF-kβ can enter the nucleus and activate the expression of the genes involved in the inflammatory response **(Hotchkiss and karl, 2003).**