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بسم الله الرحمن الرحيم

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

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تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

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بعض الوثائق الأصلية تالفة

بالرسالة صفحات لم ترد بالأصل

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CORTISOL THERAPY IN SEPTIC SHOCK

THESIS

Submitted For Partial Fulfillment Of M.D Degree In Anaesthesiology

BY

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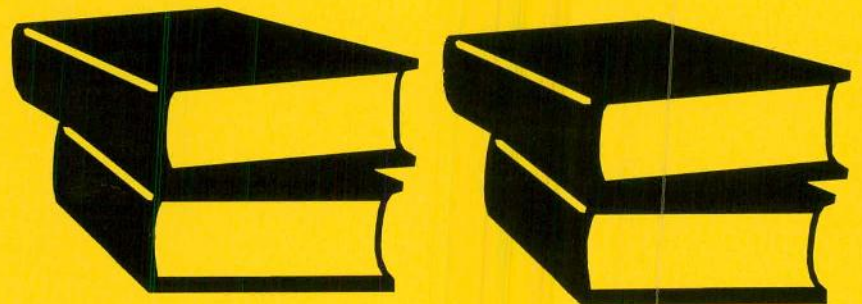
Review of literature



Introduction

Definition of sepsis :

The systemic response to infection has been termed sepsis [1,2] . Sepsis is an increasingly common cause of morbidity and mortality, particularly in elderly,immunocompromised ,and critically ill patients[1,3-5] ,sepsis has been reported[4,6] to be the most common cause of death in the non-coronary ICU. Its increasing occurrence ,new etiologies and appearance in new populations of patients have been related to changing demographics and the increased use of more potent and broader spectrum antibiotics, immunosuppressive agents, and invasive technology in the treatment of inflammatory, infectious and neoplastic diseases[3,4].

Recent clinical trials[7,8] have been undertaken to evaluate both conventional and innovative therapies in the treatment of sepsis . However, interpretations of these results have been obscured by the use of varying definitions for the following terms infection, bacteremia, sepsis, septicemia, septic syndrome and septic shock[7-10]

An additional source of confusion has been the application of termes "sepsis" and "septic syndrome" to noninfectious inflammatory states[11]

Several editorials and position papers recently attempted to provide a framework for the standardization and simplification of this terminology [12,13]. Newer categories and more precise definitions have evolved from discussions at a recent consensus conference [14] .
These definitions should be used as general guidelines in the design of future investigations into potential new diagnostic and treatment modalities

Recommendation I [14]

The term "sepsis" in popular usage, implies a clinical response arising from infection . It is apparent that a similar, or even identical response can arise in the absence of infection .We therefore propose the phrase "systemic inflammatory response syndrome" to describe this inflammatory process, independent of its cause(Fig.1)

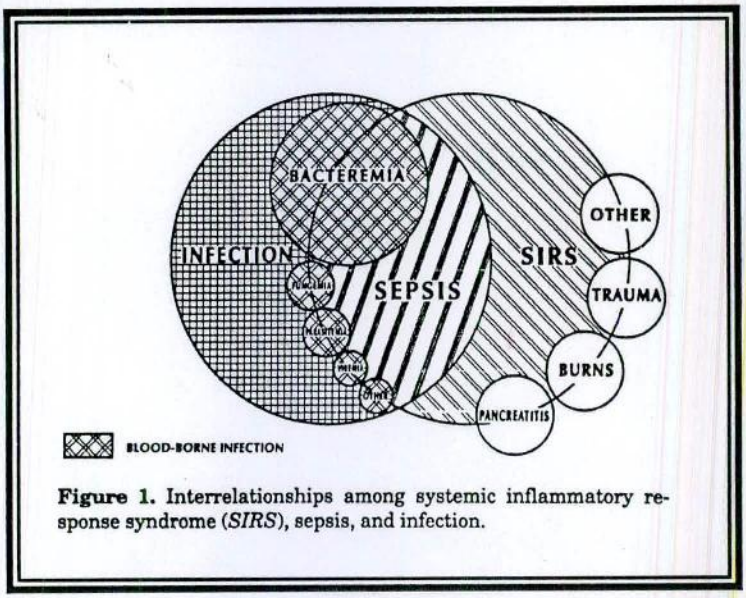


Figure 1. Interrelationships among systemic inflammatory response syndrome (*SIRS*), sepsis, and infection.

This systemic inflammatory response can be seen after a wide variety of insults and includes, but is not limited to, more than one of the following clinical manifestations:

- A body temperature of >38ċ or <36ċ.
- A heart rate (HR) of >90 beats/min.
- Tachypnea, as manifested by a respiratory rate of >20 breaths/min. or hyperventilation, as indicated by $PaCO_2$ of <32 torr.
- An alteration of WBC count of >12000 cells/mm^3 ,<4000 cells/mm^3, or the presence of >10% immature neutrophils "bands"

The systemic inflammatory response is seen in association with a large number of clinical conditions .Besides the infectious that may produce systemic inflammatory response syndrome, noninfectious pathologic causes

may include pancreatitis, ischemia, multitrauma and tissue injury, hemorrhagic shock, immune mediated organ injury, and the exogenous administration of such putative mediators of the inflammatory process as tumor necrosis factor or other cytokines[14] .

Recommendation II

When the systemic inflammatory response syndrome is the result of a confirmed infectious process, it is termed "sepsis" In this clinical circumstance, the term "sepsis" represents the systemic inflammatory response to the presence of infection [14].

RecommendationIII[14]

***Infection*:** is a microbial phenomenon characterized by an inflammatory response to the presence of micro-organisms or the invasion of normally sterile host tissue by those organisms.

***Bacteremia*:** is the presence of viable bacteria in the blood . The presence of viruses, fungi, parasites and other pathogens in the blood should be described in a similar manner (i.e, viremia, fungemia, parasitemia,etc.)

Septicemia: has been defined in the past as the presence of microorganisms or their toxins in the blood. However, this term has been used clinically and in the medical literature in a variety of ways which have added to confusion and difficulties in data interpretation. Septicemia also does not adequetely describe the entire spectrum of pathogenic organisms that may infect the blood. We therefore suggest that this term be eliminated from current usage

Recommendation IV[14]

Sepsis and its sequelae represent a continuum of clinical and pathophysiologic severity . The degree of severity may independently affect

prognosis .Some clinically recognizable stages along this continuum that can adversely affect prognosis include the following:

***Severe sepsis*:** is defined as sepsis associated with organ dysfunction, hypoperfusion abnormalities, or sepsis induced hypotension. Hypoperfusion abnormalities include lactic acidosis, oligouria, or an acute alteration of the mental status .

Sepsis-induced hypotension : is defined by the presence of a systolic BP of <90mmHg or its reduction by ≥40mmHg from the baseline, in the absence of other causes for hypotension (e.g, cardiogenic shock).

***Septic shock*:** is a subset of sepsis and is defined as sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction. Patients receiving inotropic or vasopressor agents might no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they would still be considered to have septic shock.

Multiple Organ Dysfunction Syndrome : presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention .

Sepsis And Cytokines

Architecture of the inflammatory response .

A vast array of mediators and cell types are involved in inflammation . The interaction between an inflammatory mediator (termed a ligand) and its cellular receptor provide a different cellular response to varying ligand concentrations, which results in exquisitely sensitive intercellular communication . Ligand – receptor interaction provide multiple levels of regulation of the inflammatory response such as production of inflammatory mediators, regulation of their receptors, and production of receptor agonists and antagonists . Ultimately these mediators affect cell activities . Multiple levels of mediators, receptors, and activation states at both cellular and molecular levels afford precise regulation of a response that is primarily intended to flood a site of microbial contamination or tissue injury with highly efficient effector cells . Inflammation is " tailored " to deal with a range of tissue injury states, from single cell death to extensive infection such as peritonitis; however, this highly potent system can overwhelm the host and can result in death from multisystem organ failure [(15)].

Cytokines :

Cytokines are intercellular messenger polypeptides that modulate many biologic responses . They are small, with molecular mass between 8 and 30 kilodaltons (KD) , and are biologically active at low concentrations (picomolar or less) [(16)]. Cytokines differ from classic endocrine hormones in that they :

1. are produced by many cell types rather than by discrete organs.
2. are primarily produced de novo in response to stimuli.
3. have little documented significant role in normal homeostasis .
4. are often induced in response to exogenous(not endogenous)stimuli.
5. commonly have autocrine and paracrine effects.

Functions are mediated through receptors already present in low density on the surfaces or through upregulation of new receptors [16,17]

It is probable that the cytokine system arose, at least partially, through gene duplication . The idea of gene duplication is based on structural and receptor similarities between cytokines .for example, the interleukins IL-2, IL-3, IL-4, IL-5, IL-6, IL-7 and IL-13 and granulocyte macrophage-colony stimulating factor(GM-CSF) cytokines share significant structural homology and belong to the short- chain significant structural homology and belong to the short-chain 4-α helix subfamily[18]

Numerous other cytokines are not uniquely proinflammatory or anti-inflammatory . At a given time they, can have stimulatory effects on certain mediators and inhibitory effects on other mediators . In some cases, the cytokine regulation of mediators can be very different between cell populations, depending on the dose and the presence of other stimuli .Cytokines also have the ability to regulate themselves [15] Cytokines are the major mediators of the inflammatory response .

There are four overlapping categories of cytokines:

1. Proximal mediators.
2. Proinflammatory cytokines induced by the proximal mediators.
3. Anti- inflammatory cytokines.
4. Growth factors for immune and nonimmune cells .

I Proximal Mediators :

Tumor Necrosis Factor- α

TNF has global effects on the body and the immune system . There are two subtypes of TNF, TNF-α and TNF-β . They share about 30% amino acid homology, bind to the same receptors, and elicit similar responses. [19]