Sepsis Induced Nephropathy and Relation Between Acute Renal failure and Incidence Of Sepsis

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LIST OF ABBREVIATIONS

AKI	Acute kidney injury
ARF	Acute renal failure
ARDS	Acute respiratory disress syndrome
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CO_2	Carbon dioxide
CO	Cardiac output
CVP	Central venous pressure
CKD	Chronic kidney disease
DO-RE-MI	Dose Response Multicentre International collaborative Initiative
EGDT	Early goal directed therapy
MEDS	Emergency Department Sepsis
HVHF	High-volume hemofiltration
ICU	Intensive care unit
IHD	Intermittent hemodialysis
IVIG	Intravenous immunoglobulin
MAP	Mean arterial pressure
PAMPs	Pathogen-associated molecular patterns
RBF	Renal blood flow
RRT	Renal Replacement Therapy
$ScvO_2$	Saturation of central venous oxygen
SCCM	Society of Critical Care Medicine
SSC	Surviving Sepsis Campaign
SLEDD	Sustained low efficiency (daily) dialysis diafiltration
SIRS	Systemic inflammatory response syndrome
RENAL	The Randomized Evaluation of Normal versus Augmented Level
ATN	Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network
WBCs	White blood cells

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Abstract

Sepsis is a life-threatening condition that arises when the body's response to infection injures its own tissues and organs. Sepsis is caused by an immune response triggered by an infection.

The clinical diagnosis of sepsis requires finding a focus of infection as well as at least two signs of systemic inflammatory-response syndrome that comprise abnormal body temperature (higher than 38°C or less than 36°C), heart rate >90 beats/min, respiration >20 breaths/min or arterial partial pressure of CO_2 <32 mmHg, and deranged white blood cell counts (greater than 12 x $10^3/mm^3$, less than 4 x $10^3/mm^3$, or greater than 10% bands).

Sepsis has severe consequences, including multiple organ failure. It is well established that the kidney is a commonly affected organ during sepsis, and its involvement carries a high risk of mortality**.**

Acute renal failure, is a rapidly progressive loss of renal function, generally characterized by oliguria (decreased urine production, quantified as less than 400 mL per day in adults and fluid and electrolyte imbalance. It is characterized by the sudden loss of the kidney capacity to excrete waste products, concentrate urine, preserve electrolytes and keep the water balance. It is particularly common in the intensive care unit (ICU), where it is associated to 50-80% mortality.

Historically, acute renal failure during sepsis has been considered to be a consequence of diminished renal blood flow. Indeed, in early stages of sepsis or in sepsis associated to cardiogenic shock, RBF may decrease.

Despite several advances in treatment and in understanding of the pathogenesis of ARF, many aspects in this field remain subject to controversy.

Keywords: AKI : Acute kidney injury; **ARF:** Acute renal failure; **CKD:** Chronic kidney disease**; ICU:** Intensive care unit; **IHD:** Intermittent Hemodialysis

Introduction

Sepsis is a life-threatening condition that arises when the body's response to infection injures its own tissues and organs. Sepsis is caused by an immune response triggered by an infection (**Deutschman and Tracey, 2014**).

The clinical diagnosis of sepsis requires finding a focus of infection as well as at least two signs of systemic inflammatory-response syndrome that comprise abnormal body temperature (higher than 38°C or less than 36°C), heart rate >90 beats/min, respiration >20 breaths/min or arterial partial pressure of CO_2 <32 mmHg, and deranged white blood cell counts (greater than 12 x $10^3/mm^3$, less than 4 x $10^3/mm^3$, or greater than 10% bands) (**Vincent, 2008**).

Sepsis has severe consequences, including multiple organ failure. It is well established that the kidney is a commonly affected organ during sepsis, and its involvement carries a high risk of mortality **(Bagshaw et al., 2009).**

Acute renal failure, is a rapidly progressive loss of renal function, generally characterized by oliguria (decreased urine production, quantified as less than 400 mL per day in adults and fluid and electrolyte imbalance (**Moore et al., 2012**). It is characterized by the sudden loss of the kidney capacity to excrete waste products, concentrate urine, preserve electrolytes and keep the water balance. It is particularly common in the intensive care unit (ICU), where it is associated to 50-80% mortality (**Ricci and Ronco, 2012**).

Historically, acute renal failure during sepsis has been considered to be a consequence of diminished renal blood flow. Indeed, in early stages of sepsis or in sepsis associated to cardiogenic shock, RBF may decrease. However, recent studies have shown that in resuscitated sepsis, in which cardiac output is characteristically normal or even elevated and there is systemic vasodilatation, RBF is normal or even increased, with no associated histological evidence of significant tubular necrosis. Thus, other factors may participate in the genesis of ARF in sepsis. These include apoptosis, glomerular and medullary microcirculatory disorders, cell changes in response to the pro-inflammatory cascade characteristic of sepsis, oxidative stress, mitochondrial dysfunction and damage induced by mechanical ventilation, among others (**Regueiraa et al., 2011**).

Despite several advances in treatment and in understanding of the pathogenesis of ARF, many aspects in this field remain subject to controversy (**Bellomo et al., 2001**).

Aim of the work

To highlight the mechanisms underlying sepsis induced nephropathy and relation between acute renal failure and incidence of sepsis.

Sepsis; An overview

Sepsis is a life-threatening condition that arises when the body's response to infection injures its own tissues and organs. Common signs and symptoms include fever, increased heart rate, increased breathing rate, and confusion (**Jui, 2011**).

Definition

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This new definition emphasizes the primacy of the nonhomeostatic host response to infection, the potential lethality that is considerably in excess of a straightforward infection, and the need for urgent recognition. A modest degree of organ dysfunction when infection is first suspected is associated with in-hospital mortality in excess of 10%. Recognition of this condition thus merits a prompt and appropriate response (**Singer et al., 2016**).

Severe sepsis is sepsis causing poor organ function or insufficient blood flow. Insufficient blood flow may be evident by low blood pressure, high blood lactate, or low urine output. *Septic shock* is low blood pressure due to sepsis that does not improve after reasonable amounts of intravenous fluids are given (**Dellinger et al., 2012**).

In the early 1990s, a consensus statement was developed by the American College of Chest Physicians and the Society of Critical Care Medicine (SCCM) that defined systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock in terms of both clinical and laboratory abnormalities (**American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, 1992**), emphasizing a continuum of acute inflammation and organ

dysfunction. Revised modestly in 2001 (**Levy et al., 2003**), these definitions have formed the basis of the past quarter century of research into sepsis and catalyzed the evolution of its clinical recognition and management, and the design of clinical trials. However, the sensitivity and specificity of SIRS criteria have been questioned (**Churpek et al., 2015**), as has the contention that SIRS, sepsis, severe sepsis, and septic shock occur along a continuum rather than as discrete clinical entities (**Ulloa and Tracey, 2005**).

In February 2016, the European Society of Intensive Care Medicine and the SCCM published new consensus definitions of sepsis and related clinical criteria. The most important changes were:

- The terms SIRS and severe sepsis were eliminated
- Sepsis is now defined as life threatening organ dysfunction caused by dysregulated host response to infection
- Organ dysfunction is newly defined in terms of a change in baseline SOFA (sequential organ failure assessment) score
- Septic shock is defined as the subset of sepsis in which underlying circulatory and cellular or metabolic abnormalities are profound enough to increase mortality substantially (**Gotts and Matthay, 2016**).

Etiology

Sepsis is caused by an immune response triggered by an infection (**Deutschman and Tracey, 2014**). The most common primary sources of infection resulting in sepsis are the lungs, the abdomen, and the urinary tract. Typically, 50% of all sepsis cases start as an infection in the lungs.

No definitive source is found in one third to one half of cases (**Dellinger et al., 2013**).Infections leading to sepsis are usually bacterial but can also be fungal or viral (**Munford and Suffredini, 2014**). While gram-negative bacteria were previously the most common cause of sepsis, in the last decade gram-positive bacteria, most commonly staphylococci, are thought to cause more than 50% of cases of sepsis (**Bloch, 2010**). Other commonly implicated bacteria include Streptococcus pyogenes, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella species (**Ramachandran, 2014**). Fungal sepsis accounts for approximately 5% of severe sepsis and septic shock cases; the most common cause of fungal sepsis is infection by Candida species of yeast (**Delaloye and Calandra, 2014**).

Epidemiology

Sepsis causes millions of deaths globally each year and is the most common cause of death in people who have been hospitalized (**Deutschman and Tracey, 2014**). The worldwide incidence of sepsis is estimated to be 18 million cases per year (**Lyle et al., 2014**). In the United States sepsis affects approximately 3 in 1,000 people (**Soong and Soni, 2012**), and severe sepsis contributes to more than 200,000 deaths per year (**Munford, 2011**).

The total number of cases worldwide is unknown as there is little data from the developing world (**Jawad et al., 2012)**. Estimates suggest sepsis affects millions of people a year (**Dellinger et al., 2013**). In the developed world about 0.2 to 3 per 1000 people get sepsis yearly or about a million cases per year in the United States (**Martin, 2012**). Rates of disease have been increasing (**Dellinger et al., 2013**). Sepsis is more common among males than females (**Jui, 2011**). The terms septicemia and blood poisoning referred to the microorganisms or their toxins in the

blood and are no longer commonly used. The condition has been described at least since the time of Hippocrates (**Angus and van der Poll, 2013**).

Sepsis occurs in 1-2% of all hospitalizations and accounts for as much as 25% of ICU bed utilization. Due to it rarely being reported as a primary diagnosis (often being a complication of cancer or other illness), the incidence, mortality, and morbidity rates of sepsis are likely underestimated (**Ely and Goyette, 2005**). It is the second-leading cause of death in non-coronary intensive care unit (ICU) patients, and the tenth-most-common cause of death overall (the first being heart disease) (**Martin et al., 2003**).

Several medical conditions increase a person's susceptibility to infection and developing sepsis. Common sepsis risk factors include age (especially the very young and old); conditions that weaken the immune system such as cancer, diabetes, or the absence of a spleen; and major trauma and burns (**Rubin and Schaffner, 2014**).

Pathophysiology

Sepsis is caused by a combination of factors related to the particular invading pathogen(s) and to the status of the host's immune system. The early phase of sepsis characterized by excessive inflammation (which can sometimes result in a cytokine storm) can be followed by a prolonged period of decreased functioning of the immune system (**Shukla et al., 2014**). Either of these phases can prove fatal.

- ***Microbial factors***

  Bacterial virulence factors such as glycocalyx and various adhesins allow colonization, immune evasion, and establishment of

disease in the host. Sepsis caused by gram-negative bacteria is thought to be largely due to the host's response to the lipid A component of lipopolysaccharide, also called endotoxin (**Park and Lee, 2013**).

Sepsis caused by gram-positive bacteria can result from an immunological response to cell wall lipoteichoic acid. Bacterial exotoxins that act as super-antigens can also cause sepsis. Super-antigens simultaneously bind major histocompatibility complex and T-cell receptors in the absence of antigen presentation. This forced receptor interaction induces the production of pro-inflammatory chemical signals (cytokines) by T-cells (**Ely et al., 2005**).

There are a number of microbial factors which can cause the typical septic inflammatory cascade. An invading pathogen is recognized by its pathogen-associated molecular patterns (PAMPs). Examples of PAMPs include lipopolysaccharides and flagellin in gram-negative bacteria, muramyl dipeptide in the peptidoglycan of the gram-positive bacterial cell wall, and CpG bacterial DNA. These PAMPs are recognized by the innate immune system's pattern recognition receptors (PRRs), which can be membrane-bound or cytosolic (**Leentjens et al., 2013**).

There are four families of PRRs: the toll-like receptors, the C-type lectin receptors, the NOD-like receptors and the RIG-I-like receptors. The association of a PAMP and a PRR will invariably cause a series of intracellular signalling cascades. Consequentially, transcription factors like nuclear factor-kappa B and activator protein-1 will up-regulate the expression of pro-inflammatory and anti-inflammatory cytokines **(Antonopoulou and Giamarellos-Bourboulis, 2011**).

- ***Host factors***

Cytokines such as tumor necrosis factor, interleukin 1, and interleukin 6 can activate procoagulation factors in the cells lining blood vessels, leading to endothelial damage. The damaged endothelial surface inhibits anticoagulant properties as well as increases antifibrinolysis, which can lead to intravascular clotting, the formation of blood clots in small blood vessels, and multiple organ failure (**Nimah and Brilli, 2003**).

A systemic inflammatory response syndrome can also occur in patients without the presence of infection, for example in those with burns, polytrauma, or the initial state in pancreatitis and chemical pneumonitis. The low blood pressure seen in those with sepsis is the result of various processes including excessive production of chemicals that dilate blood vessels such as nitric oxide, a deficiency of chemicals that constrict blood vessels such as vasopressin, and activation of ATP-sensitive potassium channels. In those with severe sepsis and septic shock, this sequence of events leads to a type of circulatory shock known as distributive shock (**Marik, 2014**).

Diagnosis

Early diagnosis is necessary to properly manage sepsis, as initiation of early goal directed therapy is a key to reducing mortality from severe sepsis. Within the first three hours of suspected sepsis, diagnostic studies should include WBCs, measuring serum lactate and obtaining appropriate cultures before starting antibiotics, so long as this does not delay their use by more than 45 minutes (**Dellinger et al., 2013**).