

## Diagnostic Criteria for Sepsis in Burns Patients

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### Rezumat

#### *Criterii de diagnosticare a sepsisului la pacientul cu arsuri*

Sepsisul cu disfuncțiile multiple de organ secundare reprezintă cauza majoră de mortalitate la pacientul cu arsuri. Un tratament rapid și adecvat presupune un diagnostic prompt și corect. Au fost propuse criterii specifice de diagnostic al sepsisului iar introducerea în practica clinică curentă a campaniei Surviving Sepsis a condus la o îmbunătățire semnificativă a managementului pacienților cu sepsis, în paralel cu scăderea mortalității la pacientul cu arsuri. Sunt discutate criteriile specifice de diagnosticare a sepsisului, adaptate pentru pacienții cu arsuri.

**Cuvinte cheie:** arsuri, sepsis, ghiduri de practică

### Abstract

Sepsis with multiple-organ dysfunction represents the major cause of death in severe burns patients. Adequate and rapid treatments presume an accurate and prompt diagnosis. Specific criteria for sepsis diagnosis were proposed and introduction in clinical practice of the Surviving Sepsis Campaign has been associated with an improvement in sepsis management and decreased mortality. Hereby, the specific criteria for sepsis diagnosis adapted for burns patients are discussed.

**Key words:** burns, sepsis, guidelines

### Introduction

Mortality in severe burned patients has rapidly decreased in the last years (1). The overall death rates vary from 5% to 15% (2). Unfortunately, the survival rates did not equally improve for all ages. Thus, in children the survival rate is high even if more than 90% of the total body surface area is affected by burns (3). Conversely, in elderly patients the survival rate is significantly impaired because of age-associated immune dysfunction and age-related co-morbidities (such as diabetes, cardiovascular or pulmonary insufficiencies) (4). Several factors such as ventilation management, resuscitation, sepsis management contributed to the improvement of the survival rates in burned patients. All these methods are parts of the critical care management, developed in the last years. Moreover, the wound management has been significantly improved, including new methods of treatment and new antibiotics (5,6).

Sepsis with multi-organ failure remains the major cause of death and an important cause for morbidity after burns injuries (7). Severe sepsis and septic shock are major healthcare problems, affecting millions of individuals around the world each year (8). In-hospital mortality related to severe sepsis and septic shock is still high both in Europe and USA (32.3% vs. 31.3%)(9). As it is the case for polytrauma, acute myocardial infarction or stroke, the speed and appropriateness of the therapy administered in the initial hours after severe sepsis have a major impact on the outcome (8). Adequate and rapid treatments presume an accurate and prompt diagnosis. Evaluation of the burn patient in an emergency setting in

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order to assess the signs of sepsis requires well known and precise criteria. Thus, in 2004, an international group of experts in the diagnosis and management of infection and sepsis published the first widely accepted guidelines for severe sepsis and septic shock (10). In 2006 and 2007 these guidelines were updated (8,11). Introduction in clinical practice of the Surviving Sepsis Campaign has led to an improvement in sepsis management and was associated with a decreased mortality (12).

### Criteria for sepsis diagnosis

The diagnostic criteria for sepsis defined in 2008 by the Society of Critical Care Medicine includes infection (identified or suspected) and the following criteria (8):

#### General variables:

- 1) Fever ( $> 38,3^{\circ}\text{C}$ );
- 2) Hypothermia (core temperature  $< 36^{\circ}\text{C}$ );
- 3) Heart rate  $> 90$  min or 2 standard deviations above the normal value for age;
- 4) Tachypnea;
- 5) Altered mental status;
- 6) Significant edema or positive fluid balance ( $> 20$  mL/kg over 24 hrs);
- 7) Hyperglycemia (plasma glucose  $> 140$  mg/dL) in the absence of diabetes.

#### Inflammatory variables:

- 1) Leukocytosis (WBC count  $> 12,000$ );
- 2) Leukopenia (WBC count  $< 4000$ );
- 3) Normal WBC count with  $> 10\%$  immature forms;
- 4) Plasma C-reactive protein  $> 2$  standard deviations above the normal value;
- 5) Plasma procalcitonin  $> 2$  standard deviations above the normal value.

#### Hemodynamic variables:

- arterial hypotension (systolic blood pressure  $< 90$  mm Hg);
- mean arterial blood pressure  $< 70$  mm Hg;
- or a systolic blood pressure decrease  $> 40$  mm Hg in adults).

#### Organ dysfunction variables:

- 1) Arterial hypoxemia ( $\text{PaO}_2/\text{FIO}_2 < 300$ );
- 2) Acute oliguria (urine output  $< 0.5$  mL/Kg hr or  $45$  mmol/L for at least 2 hrs, despite adequate fluid resuscitation);
- 3) Creatinine increase  $> 0.5$  mg/dL;
- 4) Coagulation abnormalities (INR  $> 1.5$  or a PTT  $> 60$  s);
- 5) Ileus;
- 6) Thrombocytopenia (platelet count  $< 100,000$ );
- 7) Hyperbilirubinemia (plasma total bilirubin  $> 4$  mg/dL).

#### Tissue perfusion variables:

- 1) Hyperlactatemia ( $>$  upper limit of lab normal);
- 2) Decreased capillary refill or mottling.

Sepsis is defined as infection with systemic manifestations; severe sepsis is sepsis with organ dysfunctions generated by sepsis or tissue hypoperfusion (8,13). The threshold criteria for identification and diagnosis of severe sepsis can be found among the general criteria for sepsis, with increased severity, which is a marker for organ dysfunction or organ lesion generated by sepsis (8). Septic shock is defined as hypotension induced by sepsis, persisting despite constant fluid administration (8).

One of the major limitations in post-burn sepsis research is the absence of an adequate definition of sepsis induced by burn injury. Although sepsis definitions have been developed for critically ill patients (trauma, intensive care - acute pancreatitis or peritonitis) (14,15), their applicability in burn patients is limited because of the innate differences in the physiology of burn patients. For example, a burn patient is persistently hypermetabolic, resulting in tachycardia, tachypnea, and elevated body temperature. These physiological alterations would result in a sepsis definition in the vast majority of patients who have burn injury, many of whom would not have an ongoing infection. Recently, it was suggested that microRNA might play a role in differentiation of systemic inflammatory response to sepsis (16). To answer these issues, a conference consisting of burn experts from the United States and Canada defined in 2007 sepsis and infection for patients with burn injury (11). Thus, according to the American Burn Association, the diagnosis of sepsis in burns patients is made after establishing the existence of an infection (documented by clinical response to antibiotics, pathological analysis of tissues from the wound or positive cultures) and at least three of the following criteria (11):

1. Fever  $> 39^{\circ}\text{C}$ ;
2. Hypothermia ( $< 36.5^{\circ}\text{C}$ );
3. Progressive tachycardia ( $> 110$  beats per min);
4. Progressive tachypnea ( $> 25$  breaths per minute not ventilated or minute ventilation  $> 12$  L/min ventilated);
5. Thrombocytopenia ( $< 100,000/\mu\text{l}$ );
6. Hyperglycemia, in the absence of preexisting diabetes mellitus (untreated plasma glucose  $> 200$  mg/dl or  $> 7$  units of insulin/h intravenous drip or significant resistance to insulin,  $> 25\%$  increase in insulin requirement over 24 h);
7. Inability to continue enteral feedings  $> 24$  h (abdominal distension or high gastric residuals, residuals two times feeding rate or uncontrollable diarrhea,  $> 2500$  ml/day).

Recently, a retrospective study showed no strong correlation of the American Burns Association trigger for sepsis with bacteremia in severe burn patients (17).

Sepsis in burn patients is commonly due to bronchopneumonia, pyelonephritis, thrombophlebitis or wound infection and most of the septic episodes occur in the first two weeks after the burn (18,19). The burn wound remains

the main source of sepsis (19). Sepsis related mortality in burn patients was reported to be higher than in trauma and critical care patients (20).

The burn wound is the ideal substrate for bacterial development and provides a wide access for microbial invasion. Microbial colonization of the open burn wounds occurs primarily from an endogenous source. Infection is promoted by loss of the epithelial barrier, malnutrition induced by the hypermetabolic response to burn injury, and a generalized post-burn immunosuppression due to release of immunoreactive agents from the burn wound. *Pseudomonas aeruginosa*, *Acinetobacter* and *Klebsiella* are the most common Gram-negative organisms while *Staphylococcus aureus* is the most common Gram-positive organism in burn patients (21). Nevertheless, burn wound infection is an important source of nosocomial infection (22).

Burn injury leads to suppression of almost all the components of immune response. Serum levels of immunoglobulin, fibronectin, and complement are reduced. Granulocytopenia is a common characteristic in burned patients. Burn injury results in reductions of interleukin-2 production, T-cell and NK cell cytotoxicity. Chemotaxis, phagocytosis and killing function of neutrophils, monocytes, and macrophages are impaired (18). The dynamic profile of inflammatory markers in burns injuries has been extensively investigated (23,24).

The diagnosis of sepsis in burn patients can be difficult to distinguish from the usual hyperdynamic, hyperthermic, hypermetabolic post-burn state. Dynamic measurements of procalcitonin serum level may potentially differentiate between an inflammatory response and sepsis and may help in antibiotics therapy. (25) Moreover, blood cultures are commonly negative and fever spikes are not proportional to the degree of infection. This is the reason for the American Burn Association to affirm that all patients with extensive burn wounds have a systemic inflammatory response syndrome. As a consequence, terms such as systemic inflammatory response syndrome and severe sepsis are not applicable in burns patients (11). Nevertheless, when taking into consideration the pathogenesis of sepsis in burn patients, the systemic inflammatory response syndrome remains a valuable concept (26).

Although care of the burn wound is not the initial priority, subsequent survival depends upon it (18). Thus, early excision of the devitalized tissue appears to play an important role in decreasing the local and systemic effects of the mediators released from burn injuries (18,27). Wound infection, considered one of the major causes for complications after burn injuries (28), can be prevented by early excision of the dead tissue and temporary/ permanent wound closure (18). The avascular burn pressure ulcer is rapidly colonized at 5 days after injury, despite the use of antimicrobial agents. If the bacterial density exceeds the immune response of the host, then invasive burn sepsis appear. When bacterial wound counts are  $> 10^5$  microorganisms per gram of tissue, the risk of wound infection is great, skin graft survival is poor, and wound closure is delayed. The burn wound is initially colonized with Gram-

positive microorganisms; within one week they are replaced with Gram-negative microorganisms (28).

Wound infection in a burn patient should be differentiated from wound colonization. Thus, local signs for an inflammatory response such as pain, edema and redness, combined with the presence of pus in the wound area and systemic signs such as fever or increased leucocyte number should raise the suspicion of infection. Conversely, in colonization, although the bacterial cultures from wounds are positive, no clinical signs of infection are present and there is no evidence for microscopic infection (18).

The antimicrobial therapy is directed by bacterial surveillance through routine tri-weekly sputum, urine, and wound cultures. Quantitative wound biopsy is a better determinant of significant pathogens than qualitative surface swabs. Wound infection is confirmed by histological evidence of tissue invasion or clinical sepsis. Burn wounds invasive infections are life threatening and need urgent treatment (18).

## Conclusion

Sepsis-related complications remain a major cause for morbidity and a common cause for mortality in severe burns patients. An adequate and early treatment implies an immediate diagnosis, based on specific criteria. The wound management, although it is not a priority, has a significant impact on long-term outcome and patient survival.

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