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MODERN LABORATORY BIOMARKERS OF BURN SEPSIS (LITERATURE REVIEW)

Akhmedov Rakhmatillo Furkatovich,
Nurillayev Khasan Jamshid ugli
Samarkand State Medical University
Republic of Uzbekistan, Samarkand
e-mail: rahmatjon6868@mail.ru

Abstract. *Etiopathogenesis and diagnosis of sepsis is one of the controversial sections of combustiology, due to the difficult diagnosis and the possibility of developing severe complications such as multiple organ failure. Currently, there is no common view on the etiology, pathogenesis and diagnosis of burn sepsis.*

In this article, the authors have undertaken to summarize the experience in the diagnosis of burn sepsis. The opinions of various authors on the etiopathogenesis and diagnosis of this pathology are presented.

Key worfs: *etiopathogenesis, diagnosis, burn sepsis.*

Sepsis (putrefaction, pus - Greek) is a syndrome of systemic inflammatory response to invasion of microorganisms, combined with organ dysfunction, hypotension, impaired tissue perfusion, increased lactate concentration, oliguria and acute impairment of consciousness.

The problem of diagnosis, prevention and treatment of surgical sepsis remains one of the most pressing (Bochorishvili V.G. et al., 1998; Grinev M.V. et al., 1999; Savelyev B.C., Gelfand B.R., 2006). In combustiology, it is especially acute, since infectious complications are the main cause of fatal outcomes in burned patients (Vazina I.R. et al. 2002, Sheridan R.L .. 2000). Fundamental research Alekseeva A.A. (1993), Krutikova M.G. (2005), Spiridonova T.G. (2007). Ushakova T.A. (2008), Shlyk I.V. (2009), Alekseev A.A. et al. (2010), devoted to the study of infectious complications in burned patients, improved the overall results of treatment, but at the same time raised new questions regarding the pathogenesis, diagnosis and principles of intensive care of sepsis in patients with severe thermal injury (R.F. Akhmedov et al. 2020).

It should be noted that there are certain difficulties in making this diagnosis in a timely manner in burned patients. They are primarily due to the fact that the concept of "burn sepsis" has not yet been clearly defined. There is no generally accepted classification of this complication, which makes it difficult to generalize numerous clinical observations and develop unified approaches to its prevention and treatment.

The problematic nature of the situation is especially noticeable against the background of the active promotion of V.S. Bone (1992) to the diagnosis of sepsis in general surgical practice. Today, among the majority of general surgeons and anesthesiologists-resuscitators, the expediency of isolating the systemic inflammatory response syndrome, sepsis, severe sepsis, taking into account the severity of clinical signs reflecting the body's response to the formation of an infectious focus, is beyond doubt. At the same time, this approach has not yet been established in relation to sepsis in burns. Moreover, there is evidence that the systemic inflammatory response syndrome (SIRS), which is the basis of the modern concept of sepsis, is often observed in patients with extensive skin lesions already in the early periods of burn disease when there are no clinical signs of an infectious process (Krutikov M.G., 2005; Spiridonova T.G., 2007). This circumstance largely determines the difficulty of diagnosing burn sepsis. Often it is late, which inevitably affects the results of treatment. All this determines the interest in further study of the role of systemic inflammation in the pathogenesis of burn sepsis and the possibility of using criteria for early diagnosis of generalization of infection in severely burned patients (Shlyk I.V. et al. 2009; R.F. Akhmedov et al. 2018, 2019).

To date, there is no single view of the diagnosis of burn sepsis. In European countries and Canada, a diagnostic model of sepsis is followed. proposed at the Chicago Conciliation Conference (1991), based on the assessment of the clinical manifestations of the systemic inflammatory response syndrome caused by the development of the infectious process (Gumming J. et al., 2001; Bargues L. et al., 2007; Bloemsma G.C et al., 2008). The scale of organ failure associated with sepsis (SOFA), adopted by the European Society of Intensive Care (Paris, 1994), is used to assess the severity of multiple organ failure.

However, at the 2007 American Burn Association Consensus Conference on Sepsis and Infection in Burned Individuals, it was noted that extensive burn wounds support "chronic" production of inflammatory mediators, which is a physiological response of severely burned patients to stress and is not always caused by infection. In this regard, it was stated that the generally accepted criteria for sepsis, proposed at the consensus conference in 1991 in Chicago (temperature, tachycardia, tachypnea, leukocytosis), are not specific for patients with severe thermal injury.

The American Burns Association has proposed the following signs of sepsis in burn patients (Greenhalyh D.G. et al., 2007):

Body temperature - more than 39 ° or less than 36.5 ° C.

Tachycardia: in adults - 110 beats per minute; in children - twice the normal age.

Tachypnoe: in adults - more than 25 per minute (without mechanical ventilation), with mechanical ventilation - minute ventilation of the lungs - 12 l/min, in children, the age norm is doubled.

Thrombocytopenia (3 days after anti-shock infusion therapy): in adults less than 100,000 / μl, in children 2 times less than the age norm.

Hyperglycemia (without diabetes mellitus): uncorrected plasma glucose more than 200 mg / dL or the equivalent value in mmol / L. insulin resistance (in adults - more than 7 units of insulin per hour), signs of insulin resistance (an increase in insulin dose by 25% every hour during the day).

Enteric failure: intestinal paresis, uncontrolled diarrhea (2500 ml / day in adults or more than 400 ml a day in children). Additional criteria (documenting infection: positive blood culture or identification of the pathogen in altered tissues, clinical effect of antibiotic therapy.

Severe sepsis. Sepsis and multiple organ failure, assessed on the MODS scale.

Septic shock. Increased blood lactate levels of more than 4 mmol / L (36 mg / dL):

mean arterial pressure less than 65 mm Hg;

a decrease in the rate of urine output less than 0.5 ml / kg per hour in adults and less than 1 ml / kg per hour in children;

the saturation of mixed venous blood is less than 70%.

The Chicago diagnostic criteria and classification of sepsis were supported by the Russian Association of Specialists in Surgical Infections at a conference in Kaluga in 2004, however, among specialists in the treatment of burns, other criteria are used to diagnose sepsis:

1. decrease in the concentration of hemoglobin;
2. decrease in the number of lymphocytes;
3. bacteremia;
4. a clinically significant degree of contamination of burn wounds;
5. SIRS symptoms: 3-4 symptoms in the period of septicotoxemia and 4 in the period of burn shock and acute burn toxemia can serve as diagnostic criteria for sepsis in burned patients (Krutikov M., 2005).

The data of modern statistics on patients with generalized inflammatory complications indicate their significant number and, in addition, highlight a tendency for their constant growth to 78-80% (Tolstov A.V. et al., 2004; Krylov K.M. et al., 2006).

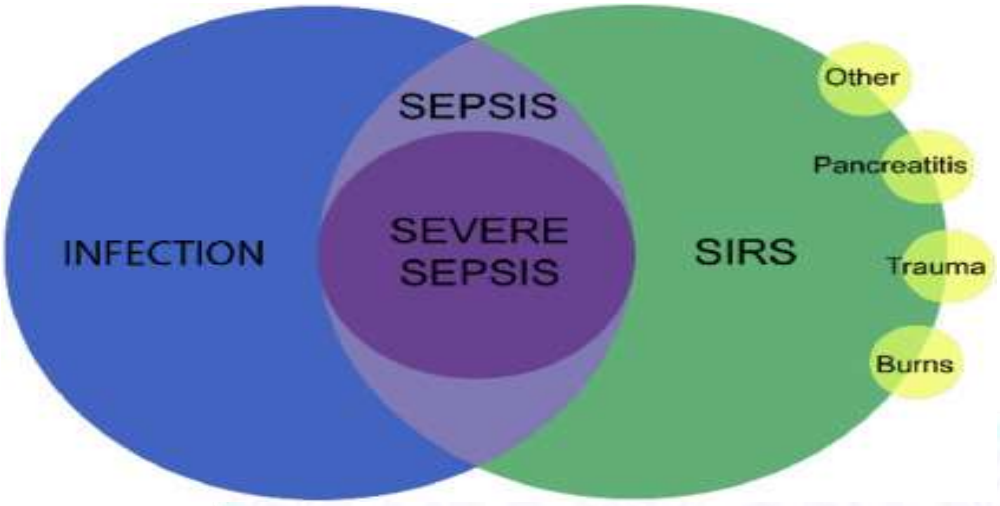

Fig. 1 Pathogenesis of sepsis.

Diagnostic criteria for systemic inflammatory response syndrome (SIRS)

Two or more of the following four criteria must be met:

1. Fever> 38 ° C or hypothermia <36 ° C;
2. Heart rate (HR)> 90 beats per minute;
3. Respiratory rate (RR)> 20 breaths per minute or $PaCO_2$ <32 mm Hg. if the patient is on mechanical ventilation;
4. Leukocytosis> 12x109 / l or leukopenia <4x109 / l or> 10% of immature leukocytes.

Despite all the advances in modern medicine, sepsis remains one of the most serious and often fatal complications of serious illness and injury. Sepsis was and remains one of the main complications of burn disease, being the main cause of death for severely burned people. That is why the issues of diagnosis and treatment of this complication do not cease to worry combustiologists and remain just as relevant at the beginning of the XXI century (Table 1).

Table 1.

Diagnostic criteria and classification of sepsis (RASKHI, Kaluga, 2004)

Syndrome	**Clinical and laboratory sign**
Systemic syndrome inflammatory reactions	Body temperature (more than 38 ° C or less than 36 ° C, tachycardia more than 90 beats per minute, shortness of breath more than 20 times per minute, leukocytosis less than 4x109 / L or more than 12x109 / L, or more than 10% of immature forms)
Sepsis	Systemic inflammatory response syndrome + documented infection (positive blood culture or presence of a focus of infection)
Severe sepsis	Sepsis + organ dysfunction
Septic shock	Sepsis + organ dysfunction + arterial hypotension

One of the modern promising methods for diagnosing sepsis is the procalcitonin test (PCT).

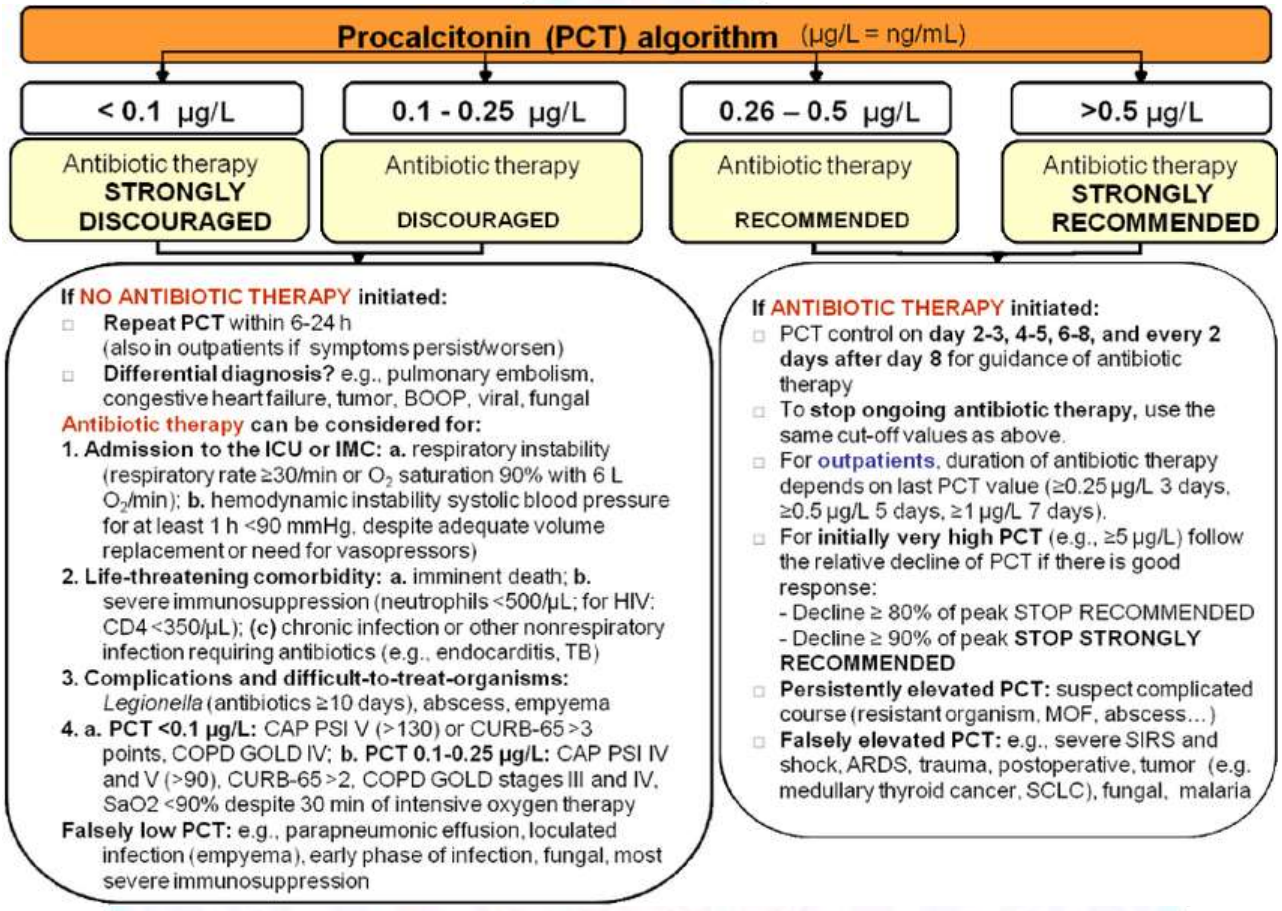

Fig: 2. Algorithm of antimicrobial therapy taking into account the PCT test.

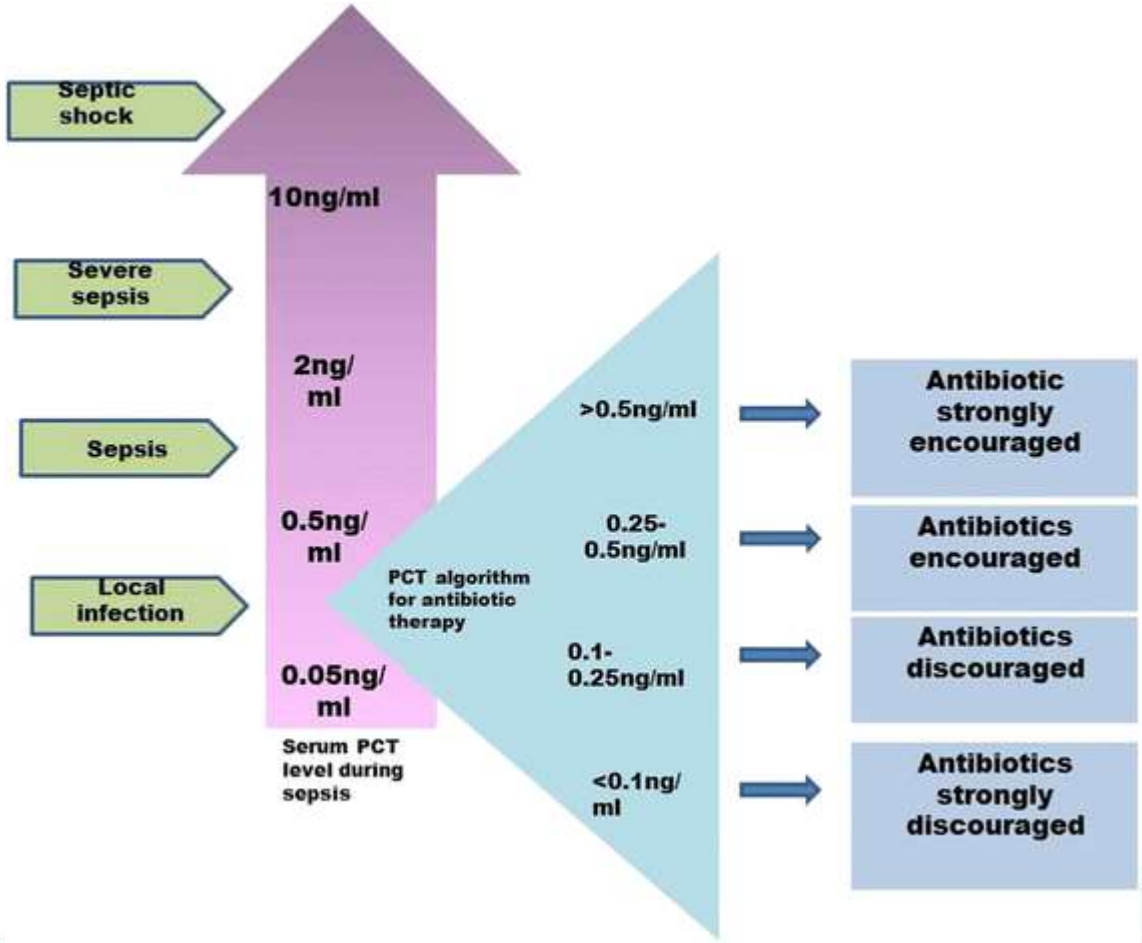

Fig: 3. Classification and diagnosis of burn sepsis.

In the pathogenesis of burn sepsis, an important role is played by proinflammatory cytokines - interleukin-6, tumor factor, interleukin-6, interleukin-8 and others, which form a specific response of the body, which is figuratively called "cytokine storm". Damage to various organs and tissues as a result of the action of interleukins leads to severe inflammatory disorders, accompanied by the development of interstitial edema (shock lung, shock kidney, etc.), the formation of a large number of circulating immune complexes, etc. (2003; Shafikov I.Z. et al., 2004; Pittet D. et al., 1995).

An analysis of microflora and its sensitivity to antibacterial agents was carried out in 45 patients, aged 16 to 75 years (mean age 41.5 ± 4.3), there were 29 men, 16 women. The area of deep burns ranged from 25% to 65 % of body surface (average 39.5 ± 5%).

The examination was carried out on admission, then on 4-5 and 10-15 days of treatment. Blood was taken from the central vein for sterility. The cultivation of microorganisms was carried out according to the standard method of microbiological blood examination on a double medium. The result was assessed by the presence of colonies of microorganisms. In addition, the analysis of wound cultures for microflora

was carried out. The isolated pathogenic and conditionally pathogenic microorganisms were found to have sensitivity to 15-20 antibiotics produced in the near and far abroad.

In blood cultures, with positive results, S. aureus (13 cases - 37.2%), Enterococcus (10 - 28.6%), Ps.aeruginosa (5 - 14.3%) prevailed, and 74.3% of pathogens were multiresistant strains (Table 3).

Table 3

The structure of pathogens isolated from the blood of burn patients

Type of pathogen	**Number of samples**		**Including resistant**	
	Abs.	**%**	**Abs.**	**%**
S. Aureus	13	37.2	11	31,4
Enterococcus	10	28,6	10	28,7
Ps. aeruginosa	5	14,3	2	5,8
S. Epidermidis	3	8,6	1	2,8
Candida	2	5,7	0	0
E. Coli	1	2,8	1	2,8
Acinetobacter	1	2,8	1	2,8
Total samples	35	100	26	74,3

From wounds with positive results, S. aureus (42 cases - 37.8%), bacteria of the Escherichia coli group (30 - 27.1%), Ps. aeruginosa (20 - 18%). Multidrug resistance of microorganisms seeded from wounds to antibacterial drugs was noted in 63.1% (Table 4).

Table 4

Causative agents of suppuration of burn wounds

Type of pathogen	**Number of samples**		**Including resistant**	
	Abs.	**%**	**Abs.**	**%**
S. Aureus	42	37,8	37	33,3
E. Coli	30	1 27,1	10	9,1
Ps. aeruginosa	20	18,0	11	9,9
S. Epidermidis	10	9,0	3	2,7
Streptococcus	4	3,6	4	3,6
Enterococcus	3	2,7	3	2,7
Acinetobacter	2	1,8	2	1,8
Total samples	111	100	70	63,1

The etiology of sepsis in burned patients is diverse: all types of microorganisms that inhabit a burn wound can cause its development. The most frequent causative agents of sepsis are S. Aureus and P. aeruginosa, which are isolated from burn wounds, according to our data, in 65-85% of patients, also prevailing in hemocultures of patients

with sepsis. When studying blood cultures, the "advantage" of gram-positive flora was highlighted: the ratio of sowing of S. aureus and P. aeruginosa strains in blood cultures of patients with burn sepsis is 2: 1. Less commonly, the causative agent of sepsis is E. Coli, Acinetobacter spp., Citrobacter spp., Enterobacter spp., (B-hemolytic streptococcus, non-sporogenic anaerobic bacteria. When these microorganisms are isolated from wounds, and even more so in blood culture, the prognosis is usually poor. In recent years, cases of sepsis caused by pathogenic fungi, mostly of the genus Candida, less often Actinomycetes, Phycomycetes, Zygomycetes, have become more frequent. The most severe course of sepsis is observed when the association of three or more microorganisms is isolated in the blood culture.

Sepsis can complicate the course of burn disease in any of its periods, starting with the period of shock. The so-called "early" sepsis developing in the next day after the injury (during the first 10-14 days) is characterized by a particularly high mortality rate. Early sepsis has a number of features compared to generalized infection that develops at a later date.

One of these features is the extreme difficulty of diagnosis. Moreover, the earlier sepsis develops, the greater difficulties the clinician faces. In this regard, the diagnostic criteria described by Bone B.C. et al. (1992), not only do not clarify, but even complicate the situation, since according to the classification proposed by the American consensus conference, all severely burned persons fall under the definition of sepsis.

When diagnosing "burn sepsis", most clinicians and pathologists are still guided by the diagnostic model, which includes the mandatory identification of "dense" bacteremia, septicopyemia. This is partly due to the peculiarities of the clinical course of burn disease: the early development of the systemic inflammatory response syndrome associated not only with infection.

This circumstance required further study of the severity of the clinical manifestations of SIRS in burn patients with different severity of the infectious process to determine the possibility of using the modern diagnostic concept of sepsis in this type of injury.

CONCLUSION

In the pathogenesis of sepsis in burn patients, early formation of a systemic inflammatory response and impaired immune reactivity are of great importance.

The dynamics of the development of the systemic inflammatory response in the early stages after trauma is influenced not only by the area and depth of burns, but also by the infectious process. The clinical signs of SIRS are more pronounced in those burned with sepsis than in patients with local and distant infectious complications. Its maximum manifestations coincide in terms with the generalization of the infection, confirmed by microbiological, histomorphological and immunological research

methods. Early diagnosis of sepsis allows timely correction of ongoing intensive care and improvement of the results of treatment of severely burned patients.

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