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FEVER AND SEPSIS – DANGEROUS CONTROVERSIES

GROZNICA I SEPSA – OPASNE KONTROVERZE

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Summary

Introduction. Sepsis is the body's response to infection, leading to tissue and organ damage. Although fever was considered to be an important sign of sepsis, it has been shown that half of the critically ill patients with sepsis do not have fever at the time of diagnosis. Absence of high body temperature may be a serious disruption of the thermoregulatory response to infection and therefore a reflection of the disease severity. The aim of this study was to determine the percentage of patients with sepsis without fever, and to compare the clinical presentation and outcome of the disease in febrile and afebrile patients. **Material and Methods.** A retrospective study included 597 patients with sepsis who were divided into two groups: the first included patients with elevated body temperature (≥ 37.7 °C) and the second included patients who were afebrile (< 37.7 °C). Demographic data, clinical, laboratory and microbiological data, gas analysis parameters, length of hospitalization, and data on the disease outcome were collected and analyzed for all patients. **Results**. The results show that 41.9% of patients with sepsis did not have fever in the first 24 hours of hospitalization. In the group of afebrile patients, the average age was higher (67.38 ± 14.63 vs. 61.38 ± 18.96 years; $p < 0.001$) and comorbidities were more common. Patients with elevated body temperature had a significantly lower degree of organ dysfunction measured by the Sequential Organ Failure Assessment score compared to afebrile patients. There were 29.2% of patients with lethal outcome in the group of afebrile patients compared to 18.4% of deceased febrile patients. **Conclusion**. We conclude that the absence of fever does not rule out the diagnosis of sepsis, but on the contrary, it is associated with greater organ dysfunction and higher mortality, while the elderly are a particularly vulnerable group.

Key words: Fever; Sepsis; Body Temperature; Prognosis; Organ Dysfunction Scores; Risk Factors

Sažetak

Uvod. Sepsa predstavlja odgovor organizma na infekciju, dovodeći do oštećenja tkiva i organa. Iako se smatralo da je febrilnost vrlo važan znak sepse, dokazano je da polovina kritično bolesnih pacijenata sa sepsom nema povišenu telesnu temperaturu u momentu postavljnja dijagnoze sepse. Neuspeh povećanja telesne temperature može predstavljati ozbiljan poremećaj termoregulacionog odgovora na infekciju i samim tim odraz ozbiljnosti bolesti. Ciljevi ovog israživanja su utvrđivanje procenta obolelih od sepse bez povišene telesne temperature i poređenje kliničke slike i ishoda bolesti u odnosu na bolesnike sa povišenom telesnom temperaturom. **Materijal i metode.** Retrospektivnom studijom je obuhvaćeno 597 pacijenata obolelih od sepse, a pacijenti su podeljeni u dve grupe, od kojih je prva obuhvatala pacijente sa povišenom telesnom temperaturom (≥ 37,7° C), a druga grupa pacijente koji su afebrilni (< 37,7° C). Za sve pacijente prikupljeni su i analizirani demografski podaci, podaci o kliničkim i laboratorijskim vrednostima, parametri gasnih analiza kao i podaci o uzročniku bolesti, dužina hospitalizacije i podaci o ishodu bolesti. **Rezultati.** Rezultati pokazuju da čak 41,9% pacijenata obolelih od sepse nije imalo povišenu temperaturu u prvih 24 h hospitalizacije. U grupi afebrilnih bolesnika veća je prosečna starost i češći su komorbditeti. Oboleli sa povišenom telesnom temperaturom imali su značajno manji stepen organske disfunkcije meren Skorom za sekvencijalnu procenu otkazivanja organa u odnosu na afebrilne bolesnike. U grupi afebrilnih bolesnika preminulo je njih 29,2%, naspram18,4% preminulih febrilnih pacijenata. **Zaključak**. Odsustvo febrilnosti ne isključuje dijagnozu sepse, već nasuprot tome, povezuje se sa većom organskom disfunkcijom i većim mortalitetom, pri čemu posebno izloženu kategoriju čine stariji bolesnici.

Ključne reči: groznica; sepsa; telesna temperatura; prognoza; SOFA skor; faktori rizika

Introduction

Sepsis is defined as a life-threatening dysfunction of organs caused by the inappropriate response of the body to infection [1 - 3]. The definition of sepsis has changed, from the first definition in 1992, which implied the fulfillment of at least two criteria of systemic inflammatory response syndrome (SIRS), to the definition which is used today (SEPSIS-3) that implies dysfunction of organs caused by infection. As a measure of organ dysfunction, the increase of sequential organ failure assessment (SOFA) score by two or more points has been proposed [4, 5]. If it is not recognized in time and adequately treated, it can lead to septic shock, organ failure, and death [6]. Even though it represents one of the leading symptoms of sepsis, elevated body temperature does not occur in all patients [6–8]. The febrile response, in

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Abbreviations
SIRS – systemic inflammatory response syndrome
SOFA – sequential organ failure assessment

which the elevated body temperature is just a component, presents a complex physiological reaction that includes creation of immune reactants and the activation of numerous physiological, endocrinological, and immune components [1]. Since the definition of the disease changed in the last 40 years, the place and role of fever as a diagnostic parameter of sepsis has also changed, thus elevated body temperature was one of the four SIRS criteria for diagnosing sepsis [4, 10–13]. Although fever was considered to be an important sign of sepsis, it has been proven that half of the critically ill patients with sepsis do not have an elevated body temperature at the time of the diagnosis [14–16]. The results of recently conducted researches point to the fact that the absence of fever may represent a serious disorder of the thermoregulatory response to infection, therefore a reflection of the severity of the disease, suggesting the patient's immune status could be assessed based on the body temperature [14, 17, 18]. All of this has influenced the decision not to mention fever as a diagnostic parameter in the new criteria for diagnosing sepsis [11].

The aim of this research was to determine the distribution of afebrile patients with sepsis, to compare the severity of the clinical presentation of sepsis between febrile and afebrile patients, and to examine the prognostic significance of the body temperature in evaluating the outcome of sepsis.

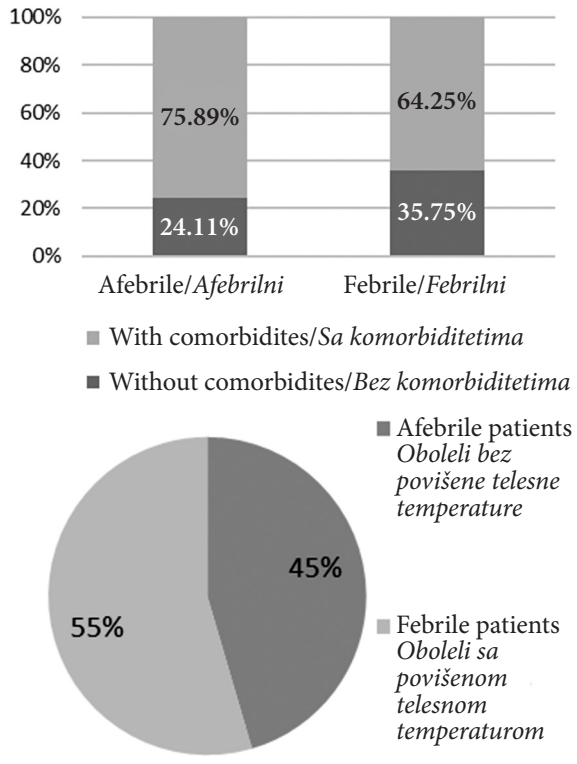
Material and Methods

The retrospective study included 597 patients diagnosed with sepsis and treated at the Clinic of Infectious Diseases of the Clinical Center of Vojvodina, during the period from January 2010 to December 2019. The data were collected from medical histories and entered into a specially created database. The study was approved by the Medical Ethics Committee of the Clinical Center of Vojvodina (number 00-47/2020). The inclusion criteria were: diagnosis of sepsis according to the SEPSIS-3 criteria [10] (the increase of the SOFA score by > 2 points, as a consequence of the infection) and the age of 18 years and over. All data were collected and analyzed from the medical records. Also, the data of clinical and laboratory test results of routinely measured parameters were recorded in the first 24 hours of hospitalization. The aforementioned laboratory tests were performed by using standard procedures at the Center for Laboratory Diagnostics of the Clinical Center of Vojvodina and the microbiology laboratory of the Institute of Public Health of Vojvodina.

Patients who met the inclusion criteria were divided into two groups: the first group included patients with elevated body temperature in the first 24 hours of hospitalization (≥ 37.7 °C) and the second group included patients who were afebrile in the first 24 hours of hospitalization (< 37.7 °C). This is in accordance with modern textbooks of infectious diseases and internal medicine stating that the normal body temperature is up to 37.2 °C in the morning, and up to 37.7 °C in the evening [1, 2]. Considering the fact that there is a circadian rhythm of body temperature, which is lowest at 6 a.m. and the highest during the afternoon hours, between 4 and 5 p.m. [1], as well as the fact that antipyretics were used to lower the elevated temperature, the highest recorded value in the first 24 hours of hospitalization was taken as the representative value of the body temperature. Statistical data processing was done using SPSS v. 23.0 program.

Results

The ratio between febrile and afebrile patients with sepsis and the prevalence of comorbidities among the mentioned groups is shown in **Graph 1**. Gender distribution, comorbidities, and fatal outcome among afebrile and febrile sepsis patients are shown in **Table 1**. The average age in febrile patients was 61.38 ± 18.96 years, while the average age in afebrile patients was 67.38 ± 14.63 years. Correlation analysis confirms the connection between body temperature and age. Namely, age statistically signifi-



Graph 1. The ratio between the febrile and afebrile patients with sepsis and the prevalence of comorbidities among the groups
Grafikon 1. *Odnos između febrilnih i afebrilnih pacijenata sa dijagnozom sepse i prevalencija komorbiditeta između grupa*

Table 1. Gender distribution, comorbidities, and fatal outcome among the afebrile and febrile patients with sepsis
Tabela 1*. Pol, komorbiditeti i smrtni ishod između febrilnih i afebrilnih pacijenata obolelih od sepse*

Comorbidity *Komorbiditeti*		Afebrile/*Afebrilni*		Febrile/*Febrilni*		Total/*Ukupno*		p/*p*
		No./*Br.*	%	No./*Br.*	%	No./*Br.*	%	
Hypertension *Hipertenzija*	Yes/*Da*	128	50.4	126	49.6	254	42.5	<0.001
	No/*Ne*	122	35.6	221	64.4	343	57.5	
Diabetes mellitus *Dijabetes melitus*	Yes/*Da*	78	50.0	78	50.0	156	26.1	0.017
	No/*Ne*	172	39.0	269	61.0	441	73.9	
Malignancy *Malignitet*	Yes/*Da*	24	40.7	35	59.3	59	9.9	0.835
	No/*Ne*	226	42.1	311	57.9	537	901	
Chronic renal insufficiency *Hronična bubrežna insuficijencija*	Yes/*Da*	49	79.1	13	20.9	62	10.4	0.009
	No/*Ne*	201	37.6	334	62.4	535	89.6	
Hematologic disease *Hematološko oboljenje*	Yes/*Da*	10	41.7	14	58.3	24	4.0	0.394
	No/*Ne*	240	41.9	333	58.1	573	96.0	
Liver cirrhosis *Ciroza jetre*	Yes/*Da*	4	36.4	7	63.6	11	2.2	0.636
	No/*Ne*	246	42.0	340	58.0	586	87.8	
Male/*Muškarci*		132	52.8	193	55.6	325	54.4	0.424
Female/*Žene*		118	47.2	154	44.4	272	45.6	
Total male + female/*Ukupno muškarci+žene*		250	100	347	100	597	100	
Fatal outcome/*Smrtni ishod*		73	29.2	64	18.4	137	22.9	0.002
Favorable outcome/*Povoljan ishod*		177	70.8	283	81.6	460	77.1	
Fatal outcome (younger than 65 years) *Smrtni ishod (mlađi od 65 godina)*		15	17.4	14	8.6	29	11.7	0.040
Favorable outcome (younger than 65 years) *Povoljan ishod (mlađi od 65 godina)*		71	82.6	148	91.4	460	88.3	

Table 2. Values of mean arterial pressure, heart rate, respiratory rate, Glasgow coma score and laboratory parameters of inflammation in the observed groups of patients
Tabela 2. *Vrednosti srednjeg arterijskog pritiska, srčane frekvencije, respiratorne frekvencije, Glasgow koma skora i laboratorijskih parametara između posmatranih grupa pacijenata*

Parameter/*Parametar*	Group/*Grupa*	Median/*Medijana*	IQR*	p/*p*
MAP* [mmHg]	Afebrile/*Afebrilni*	85	73 - 100	0.862
	Febrile/*Febrilni*	85	73 - 97	
RR*	Afebrile/*Afebrilni*	16	14 - 18	0.268
	Febrile/*Febrilni*	17	14 - 19	
HR*	Afebrile/*Afebrilni*	89	80 - 100	0.013
	Febrile/*Febrilni*	90	80 - 105	
GCS*	Afebrile/*Afebrilni*	15	14 - 15	0.210
	Febrile/*Febrilni*	15	14 - 15	
WBCs* [$10^9 10^9$/l]	Afebrile/*Afebrilni*	12.94	8.47 - 19.04	0.318
	Febrile/*Febrilni*	12.40	8.43 - 17.40	
NEUT* (aps.br) [$10^9 10^9$/l]	Afebrile/*Afebrilni*	11.15	6.87 - 16.84	0.464
	Febrile/*Febrilni*	10.40	7.03 - 15.14	
LYMPH* (aps.br) [$10^9 10^9$/l]	Afebrile/*Afebrilni*	0.90	0.52 - 1.34	0.941
	Febrile/*Febrilni*	0.91	0.51 - 1.32	
CRP* [mg/l]	Afebrile/*Afebrilni*	203.70	122 - 293.20	0.970
	Febrile/*Febrilni*	208.50	135.92 - 279.95	
PCT* [ng/ml]	Afebrile/*Afebrilni*	12.43	3.12 - 38.18	0.113
	Febrile/*Febrilni*	8.07	1.95 - 36.17	
Fibrinogen [mmol/l]	Afebrile/*Afebrilni*	5.79	4.35 - 6.90	0.006
	Febrile/*Febrilni*	6.08	5 - 7.60	

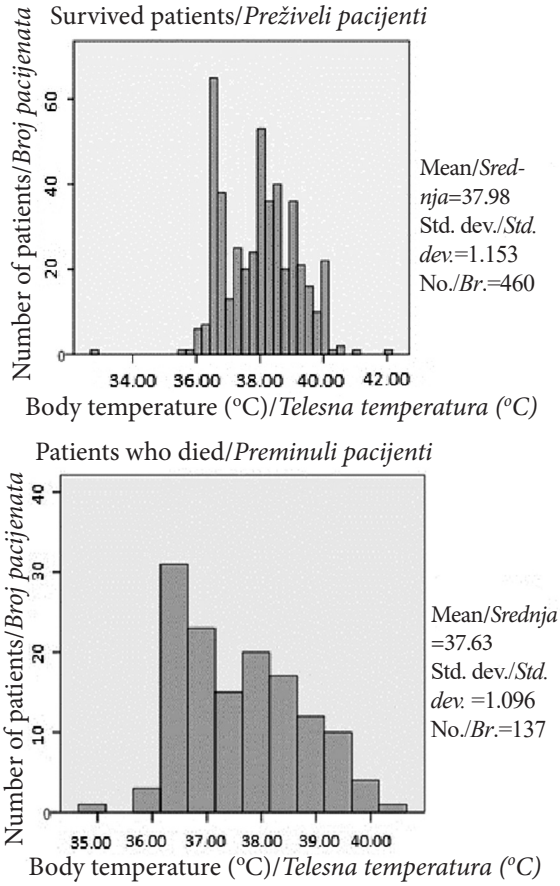
Legend: *MAP - mean arterial pressure; *HR - heart rate; *RR - respiratory rate; *GCS - Glasgow coma score; WBCs - white blood cells; *NEUT - neutrophils; *LYMPH - lymphocytes; *CRP - C-reactive protein; *PCT - procalcitonin; *IQR - interquartile range
*Legenda: *MAP - srednji arterijski pritisak; *HR - srčana frekvencija; *RR - respiratorna frekvencija; *GCS - Glasgov koma skor; WBCs - leukociti; *NEUT - neutrofili; *LYMPH - limfociti; *CRP - C-reaktivni protein; *PCT – procalcitonin; IQR - interkvartilni raspon*

Table 3. Degree of organ dysfunction in the studied groups of patients
Tabela 3. *Stepen organske disfunkcije između dve ispitivane grupe pacijenata*

	Group/Grupa	No./*Br.*	Arithmetic mean/*Aritmetička sredina*	Standard deviation/*Standardna devijacija*	p/*p*
SOFA	Afebrile/*Afebrilni*	250	4.36	2.69	< 0.001
	Febrile/*Febrilni*	347	3.62	2.17	
qSOFA	Afebrile/*Afebrilni*	250	0.88	0.82	0.620
	Febrile/*Febrilni*	347	0.85	0.86	
SIRS	Afebrile/*Afebrilni*	250	1.292	0.86	< 0.001
	Febrile/*Febrilni*	347	2.052	0.91	

Legenda: SOFA – Skor za sekvencijalnu procenu otkazivanja organa, SIRS – Sindrom sistemskog inflamatornog odgovora

cantly negatively correlated with body temperature in septic patients (Spearman's correlation coefficient is - 0.145, p < 0.001). Values of mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), Glasgow coma score (GCS), and laboratory parameters of inflammation in the observed groups of patients are shown in **Table 2**. The laboratory parameters of inflammation did not differ between the observed groups of patients. Patients with elevated body temperature had higher HR values **(Table 2)**. Compared to afebrile patients, patients with elevated body temperature had a significantly lower degree of organ dysfunction measured by the SOFA score. Also, these patients had higher SIRS values, which was expected given that fever is one of the SIRS criteria **(Table 3)**. The mean temperature value in patients who died was 37.6 ± 1.09, while in the group of survivors it was statistically significantly higher at 38.0 ± 1.15 ºC (p = 0.002) **(Graph 2)**.



Graph 2. Distribution of the highest measured body temperatures in the first 24 hours of hospitalization in patients who survived and patients who died
Grafikon 2. *Distribucija najviše izmerene telesne temperature u prva 24h hospitalizacije kod pacijenata koji su preživeli i kod pacijenata koji su preminuli*

Discussion

Our study shows that two of five patients diagnosed with sepsis did not have a body temperature above 37.7 °C. One of the reasons for excluding this parameter from the definitions of sepsis, as well as the clinically significant scores used for diagnosis (SOFA and quick SOFA), is probably the high percentage of sepsis cases with normal body temperature [11, 12]. Results similar to ours were reported by Bhavani et al. where 61.87% of patients did not develop high temperature; while in the study by Drewry et al. 52.17% of patients did not develop elevated body temperature [14, 17].

According to our data, fever was absent statistically significantly more often in older patients with sepsis than in younger patients which coincides with the results of the study by Bhavani et al., where the average age in the febrile group with rapid/slow rise in temperature was 54/56 years, while the average age in normothermic and hypothermic patients was 60 and 63 years [17]. Such data are in line with literature data claiming that old people are more often immunocompromised [1, 19]. A research by Norman DC et al. showed that the elderly, due to their "physiological immunodeficiency" often do not present with fever, leukocytosis, tachypnea or tachycardia [19–22]. In addition to the immunocompromised response, general activity decreases, causing lower daily rise in body temperature. Also, inherent mechanisms of thermoregulation are reduced. In his article, Yoshikawa T. confirmed that infections are one of the leading causes of morbidity and mortality in the elderly population [23]. The presence of comorbidities is observed in a significantly higher percentage of afebrile patients (≈3/4) compared to febrile patients (≈2/3).

This result corresponds to the results obtained in the study by Bhavani et al. [17]. One of the potential explanations is the well-known immunocompromised condition of chronically ill patients, which causes a weaker proinflammatory response, therefore lessening stimulation of the thermoregulatory center [1].

The values of the laboratory parameters show that statistically significantly lower values of fibrinogen were recorded in the group of afebrile patients. That may be interpreted as the reduced capacity of the pro-inflammatory response in these patients. The absence of differences in concentrations of other parameters of inflammation have been reported in numerous studies which confirmed these claims, and it has been pointed out that initially measured values of inflammation parameters have no prognostic significance, and that only their dynamic monitoring has prognostic significance in sepsis [24–29]. The patients with elevated body temperature had a significantly lower degree of organ dysfunction measured by the SOFA score compared to the afebrile patients, which differs from the study of Bhavani et al., where no statistically significant differences were found [17]. According to numerous literature data, a higher degree of organ dysfunction, as well as higher mortality can be associated with a weaker inflammatory response in afebrile patients [1, 2]. It is known that an increase in body temperature occurs due to pyrogenic cytokines (interleukin-1, interleukin-6, tumor necrosis alpha, interferon alpha), so the assumption is that the inability to increase body temperature is based on a weak immune response [14]. Statistically significantly higher mortality was found in the group of afebrile patients, where almost every third patient died (29.2%), compared to febrile patients, where every fifth patient died (18.4%). If we exclude patients older than 65 years, the result of higher mortality in the afebrile group does not change, like reported by other researchers [19, 30]. One advantage that is widely attributed to elevated body temperature is an immune protective mechanism. Namely, the defense against pathogens involves a tight temporal and spatial connection between the regulators of the immune system. The absence of elevated body temperature as a part of the response to infection could be a reflection of the weakened immune capacities of the individual, regardless of his/her age, indicating the necessity of greater caution in the treatment of these patients, their intensive monitoring, and a greater possibility of a complicated course and outcome of the disease.

Conclusion

Two out of five patients diagnosed with sepsis presented with a normal body temperature. Elevated body temperature, as a clinical symptom of sepsis, is more often absent in the elderly.

In the group of afebrile patients, a higher percentage of people presented with comorbidities. Afebrile patients have statistically significantly lower values of fibrinogen than febrile patients, while the mean values of other parameters of inflammation were not statistically significantly different in the observed groups of patients. Afebrile patients with sepsis showed a higher degree of organ dysfunction. Higher mortality was recorded in the group of afebrile patients compared to the group of febrile patients.

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