ORIGINAL RESEARCH

Presenting Symptoms in Sepsis: Is the Mnemonic "SEPSIS" Useful?

Kanokpit Wattanapaiboon[1]
Sarach Banditlerdruk[1]
Veerapong Vattanavanit [ID][2]

[1]Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand; [2]Critical Care Medicine Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

Background: The mnemonic "SEPSIS" (S = Slurred speech or confusion, E = Extreme shivering or muscle pain, fever, P = Passing no urine all day, S = Severe breathlessness, I = It feels like you are going to die, S = Skin mottled or discolored) has been developed by the World Sepsis Day committee, so as to raise public awareness of the symptomatic presentation of sepsis. However, this mnemonic has not been validated.

Methods: A retrospective, observational, single-center study was performed. All adult septic patients presenting at the emergency department of Songklanagarind Hospital from 2016 to 2019 were included and followed up until either hospital discharge or death.

Results: The study included 437 patients, comprising patients with sepsis (n = 250) and those with septic shock (n = 187). Patients presented with symptoms according to the mnemonic as follows: S = 97 (22.2%), E = 240 (54.9%), P = 18 (4.1%), S =181 (41.4%), I = 5 (1.1%), and S = 5 (1.1%). Sixty-five patients (14.9%) did not present with any sepsis-specific symptoms according to the mnemonic. Compared with patients who had at least one mnemonic symptom, a higher proportion of patients without mnemonic symptoms had underlying immunosuppression (24.6% vs 8.3%, P < 0.01) and were diagnosed with intraabdominal infection (38.5% vs 12.1%, P < 0.01). In a multivariable adjusted logistic regression model, vague-presenting symptoms were independently associated with in-hospital mortality (adjusted odds ratio 2.17, 95% confidence interval 1.30−3.61, P = 0.03).

Conclusion: Two components of the mnemonic "SEPSIS" were rarely reported: it feels like you are going to die and skin mottled or discolored. Using the mnemonic might lead to missed diagnoses, especially in immunosuppression and intraabdominal infection. This mnemonic should be revised for the local context.

Keywords: sepsis, symptom, mnemonic

Introduction

Sepsis is a syndrome defined as an inappropriate response of the host immune system to infection causing life-threatening organ dysfunction.[1] Sepsis is a global health problem related to 11 million deaths each year.[2] Early recognition and timely treatment are crucial and associated with improved outcomes in sepsis patients.[3]

The symptomatic presentation of sepsis remains a problematic issue for clinicians.[4] Sepsis patients typically present with symptoms of infection and organ dysfunction. Some symptoms of sepsis are easy to identify, such as fever and chills, productive cough, or dysuria. However, in some patients, particularly the elderly or immunocompromised, these symptoms might be vague or atypical.[5]

The Global Sepsis Alliance and its founding members established the first World Sepsis Day as a platform for sepsis declaration with the goals of raising

Correspondence: Veerapong Vattanavanit
Critical Care Medicine Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand
Tel +66-84-8456228
Fax +66-74-429385
Email vveerapong@gmail.com

public awareness of sepsis and improving the quality of sepsis management.[6] The mnemonic "SEPSIS" was created for simple recall of sepsis symptoms including Slurred speech or confusion, Extreme shivering or muscle pain, fever, Passing no urine all day, Severe breathlessness, It feels like you are going to die, and Skin mottled or discolored.[7]

Most of the available epidemiological data on sepsis come from developed countries.[8] In Thailand and other low- and middle-income Asian countries, the symptoms of sepsis might be different from those in western countries; thus, the utility of the mnemonic "SEPSIS" is questionable.

To better characterize the symptoms of sepsis, the primary objective of this study was to evaluate the presenting symptoms of septic Thai patients compared with the mnemonic "SEPSIS".

Methods
Study Design and Setting
We conducted a retrospective study of all adult sepsis or septic shock patients admitted to Songklanagarind Hospital, Southern Thailand from January 2016 to December 2019. Songklanagarind Hospital is an academic tertiary-care hospital with 816 non-ICU beds and 10 medical ICU beds. At the time of the study, sepsis management in our hospital followed our sepsis protocol adapted from the Surviving Sepsis Campaign 2012 and 2016 guidelines.[3,9] The study protocol was approved by our Institutional Review Board (REC 62–105-14-1). Patient consent to review their medical records was not required by the research ethics committee, as the data collected from electronic medical records were anonymous, confidential, and did not contain information that could identify individual patients.

Study Population
Patients were included if they were 18 years of age or older and admitted to a medical ward or a medical intensive care unit with a primary diagnosis of sepsis or septic shock, defined by the sepsis-3 criteria[1] (see Supplementary appendix). Septic shock is a subset of sepsis in which the risk of mortality substantially increased. The exclusion criteria were development of sepsis after hospital admission and incomplete data.

Data Collection and Definitions
The collected data included sex, age, comorbidities, diagnosed as sepsis or septic shock, time of diagnosis, time to antibiotic administration, Sequential Organ Failure Assessment (SOFA) score, source(s) of infection, results of hemoculture, symptoms from mnemonic "SEPSIS", chief complaint, presenting symptoms, length of stay in the ICU, length of stay in the medical ward, and discharge type.

Chief Complaint and Presenting Symptoms
The chief complaint and presenting symptoms were abstracted from the nursing triage, ED physician, resident and/or attending staff notes. The chief complaint was defined as the symptom(s) that was(were) the reason for the visit to the hospital.[10] Presenting symptoms were categorized as obvious and vague symptoms adapted from the study of Filbin et al[11] Obvious symptoms were symptoms that immediately led the clinician to consider infection. Vague symptoms were symptoms that did not include any of the obvious symptoms (see Supplementary appendix).

Outcome Measures
Primary outcomes were the prevalence of presenting "SEPSIS" symptoms in septic patients. Secondary outcomes were the prevalence of obvious and vague sepsis symptoms and factors associated with in-hospital mortality.

Statistical Analysis
The sample size was determined by using population proportion formula.[12] We expected that 80% of septic patients had at least one mnemonic symptom with 5% marginal error and 95% confidence interval. The minimum of 246 septic patients was required.

Categorical data are expressed as percentages. Continuous data are shown as mean ± standard deviation or median with minimum and maximum interquartile range (IQR) depending on the distribution of the data. The data were tested for normality using the Shapiro–Wilk test. Continuous variables and proportions were compared between groups using the Student's t-test or Mann–Whitney U-test and chi-square tests, respectively. We assessed the association between clinical characteristics and in-hospital mortality using multivariable logistic regression analysis. Variables that were associated with in-

hospital mortality (P < 0.1) were introduced into a multiple logistic regression model after testing for association. Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to identify the significant independent factors influencing in-hospital mortality. Two-tailed values of P < 0.05 were deemed statistically significant. All statistical analyses were computed with Stata version 16 (StataCorp, College station TX, USA).

Results

During the 4-year period, 437 patients met the study inclusion criteria. Of those, 250 patients (57.2%) were diagnosed with sepsis. The most common identified source of infection was pneumonia (218/437, 49.9%). Nearly 66% of infections were community-acquired. Overall, in-hospital mortality was 31.8% (Table 1).

Fever accounted for 42.1% of chief complaints. Patients presented with symptoms according to the mnemonic "SEPSIS" as follows: S = 97 (22.2%), E = 240 (54.9%), P = 18 (4.1%), S = 181 (41.4%), I = 5 (1.1%), and S = 5 (1.1%), respectively. Sixty-five patients (14.9%) did not present with any sepsis-specific symptoms according to the mnemonic (Table 2).

More than two thirds of patients (268/437, 61.3%) had obvious symptoms, of which the most common was fever and/or chills. The most common vague symptom was fatigue (71/437, 16.2%) (Table 2).

Compared with those who had at least one mnemonic symptom, a higher proportion of septic patients without any symptoms according to the mnemonic had underlying immunosuppression (24.6% vs 8.3%, P < 0.01) and were diagnosed intraabdominal infection (38.5% vs 12.1%, P < 0.01) (Table 3).

Compared with patients with obvious symptoms, those who presented with vague symptoms were older (median age, 72 vs 65 years, $P < 0.01$) and more often diagnosed with intraabdominal infection (24.9% vs 10.4%, P < 0.01). The mortality rate was significantly higher in the group with vague symptoms (39.6% vs 26.9%, P < 0.01) (Table S2).

Factors related to in-hospital mortality (Table S3) were introduced into a multiple logistic regression model. We performed univariable and multivariable logistic regression analysis of patient characteristics associated with in-hospital mortality. In multivariable adjusted logistic regression analysis, SOFA score, the presence of septic shock, pneumonia as the source of infection, and vague symptoms were independently associated with in-hospital mortality (Table 4).

Discussion

This study revealed that using the mnemonic "SEPSIS" regarding the recommendation of Word Sepsis day will lead to misdiagnosis of nearly 15% of sepsis patients. Two components of symptoms in the mnemonic were rarely stated: I feel like I am going to die and skin mottled. Two thirds of patients presented with obvious symptoms. However, patients with vague symptoms were associated with higher in-hospital mortality.

The definition of sepsis has changed over time. The sepsis-3 definition emphasized the presence of organ dysfunction in sepsis using the SOFA score.[1] The components of SOFA include six major systems or organs: respiration; coagulation; liver; and the cardiovascular, central nervous, and renal systems. The SOFA score, when used as part of the definition of sepsis, is a better predictor of mortality than older definitions.[1] However, some debate over the use of SOFA might result in late detection of sepsis.[13]

The mnemonic "SEPSIS" has been used with sepsis symptoms to alert people to recognize sepsis in the World Sepsis Day Campaign. Some components of the mnemonic represent organ dysfunction in the SOFA score. Slurred speech or confusion reflects central nervous system dysfunction, passing no urine all day reflects renal dysfunction, severe breathlessness reflects respiratory dysfunction, and skin mottled or discolored reflects tissue hypoperfusion. In our study, components E (extreme shivering or muscle pain, fever) and S (severe breathlessness) were the two most often reported. These results were related to our most common source of infection being pneumonia, as in our previous sepsis studies.[14,15] Concordant with the source of infection, the respiratory system is the most common site of organ dysfunction in sepsis. A Spanish study reported that the highest incidence of organ failure in sepsis was respiratory failure, accounting for 74.9%.[16]

We found that two items in the mnemonic had been rarely reported: it feels like you are going to die and skin mottled or discolored. The first one was a patient's statement, which might not have been documented. The second one was a sign of tissue hypoperfusion. It is difficult to detect abnormal skin perfusion by itself unless it is in the late stage, especially in Thai patients with dark skin. Coudroy et al reported that nearly half of septic shock patients had skin mottling and 65% presented on the day of admission.[17]

Table 1 Baseline Characteristics of Patients (n = 437)

Characteristics	Values
Male	257 (58.8)
Age, median (IQR), y	67 (57.0–79.5)
Diagnosis	
Sepsis	250 (57.2)
Septic shock	187 (42.8)
Co-morbidities	
Hypertension	149 (34.1)
Diabetes mellitus	110 (25.2)
Malignancy	95 (21.7)
Chronic kidney disease	82 (18.8)
Coronary artery disease	68 (15.6)
Immunosuppression	47 (10.8)
Stroke	38 (8.7)
Chronic lung disease	35 (8.0)
Cirrhosis	27 (6.2)
Antibiotic time, median (IQR), min	60 (40–120)
SOFA score, median (IQR)	6 (4–9)
Source(s) of infection	
Pneumonia	218 (49.9)
Intraabdominal infection	70 (16.0)
Urinary tract infection	62 (14.2)
Primary bacteremia	32 (7.3)
Skin and soft-tissue infection	26 (5.9)
Tropical infection	10 (2.3)
Infective endocarditis	3 (0.7)
CNS infection	2 (0.5)
Unable to identify source of infection	25 (5.7)
Type of infection	
Community	288 (65.9)
Health care associated	149 (34.1)
Hemoculture	
No growth	332 (76)
Growth	105 (76)
Escherichia coli	36 (34.3)
Klebsiella species	21 (20)
Staphylococcus aureus	12 (11.4)
Others	49 (46.7)
ICU length of stay, median (IQR), day	1 (0–5)
Ward length of stay, median (IQR), day	6 (0–15)
Outcomes	
Death	139 (31.8)
Discharged	282 (64.5)
Transferred	16 (3.7)

Note: Data are presented as number (%) unless otherwise specified.
Abbreviations: CNS, central nervous system; ICU, intensive care unit; IQR, interquartile range; SOFA, sequential organ failure assessment.

Table 2 Sepsis-Presenting Symptoms (n = 437)

Symptoms	Value
Chief complaints	
Fever	184 (42.1)
Dyspnea	110 (25.2)
Others	143 (32.7)
Symptoms as "SEPSIS"	
Slurred speech of confusion	97 (22.2)
Extreme shivering or muscle pain, fever	240 (54.9)
Passing no urine all day	18 (4.1)
Severe breathlessness	181 (41.4)
It feels like you are going to die	5 (1.1)
Skin mottled or discolored	5 (1.1)
No "SEPSIS" symptoms	65 (14.9)
Presenting symptoms	
Obvious symptoms	268 (61.3)
Fever and/or chill	235 (53.8)
Cough with productive sputum	110 (25.2)
Dysuria	19 (4.3)
Report skin redness or concern soft-tissue infection	15 (3.4)
Referral for specific infectious diagnosis	39 (8.9)
Vague symptoms	169 (38.7)
Fatigue	71 (16.2)
Shortness of breath	70 (16.0)
Altered mental status	57 (13.0)
Diarrhea	33 (7.6)
Abdominal pain	27 (6.2)
Nausea, vomiting	26 (5.9)
Dry cough	13 (3.0)
Chest pain	12 (2.7)
Headache	4 (0.9)
Back pain	4 (0.9)
Focal neurological symptoms	4 (0.9)
Abnormal urine (bloody or cloudy)	4 (0.9)

Note: Data are presented as number (%) unless otherwise specified.

Nearly 15% of our sepsis patients had none of the symptoms represented by the mnemonic. They were more likely to have underlying immunosuppression and were more often diagnosed with intraabdominal infection compared with those who had at least one symptom. The immunocompromised state modifies the cardinal signs of inflammation, resulting in difficulty diagnosing sepsis.[18] As we know, intraabdominal infection is a common hidden source of infection in septic patients.[19]

We should be concerned about septic patients who present with vague symptoms because they have a higher

Table 3 Characteristics of Septic Patients Without and with Symptoms in the Mnemonic of "SEPSIS" (n = 437)

Characteristics	No "SEPSIS" Symptom (n = 65)	Presence of "SEPSIS" Symptoms (n = 372)	P
Age	71 (61–82)	67 (57–79)	0.17
Male	37 (56.9)	220 (59.1)	0.74
Underlying co-morbidities			
Hypertension	20 (30.8)	129 (34.7)	0.54
Diabetes mellitus	11 (16.9)	99 (26.6)	0.09
Malignancy	17 (26.2)	78 (21.0)	0.35
Immunosuppression	16 (24.6)	31 (8.3)	<0.01
Chronic kidney disease	14 (21.5)	68 (18.3)	0.53
Coronary artery disease	19 (29.2)	49 (13.2)	<0.01
Stroke	3 (4.6)	35 (9.4)	0.20
Cirrhosis	4 (6.2)	23 (6.2)	0.99
Antibiotic time, min	12 (6.5–16.5)	12 (6.5–16.5)	0.52
SOFA score, median (IQR)	6 (4–9)	6 (4–9)	0.76
Sepsis	40 (61.5)	210 (56.5)	0.44
Septic shock	25 (38.5)	162 (43.5)	0.44
Type of infection			
Pneumonia	12 (18.5)	206 (55.4)	<0.01
Intraabdominal infection	25 (38.5)	45 (12.1)	<0.01
Skin and soft tissue	2 (3.1)	24 (6.5)	0.29
Urinary tract	10 (15.4)	52 (14.0)	0.77
Primary bacteremia	5(7.7)	27(7.3)	0.90
Infective endocarditis	0	3 (0.8)	0.47
CNS infection	0	2 (0.5)	0.55
Tropical infection	0	10 (2.7)	0.18
Outcomes			
In-hospital mortality	22 (33.8)	117 (31.5)	0.70
ICU length of stay, median (IQR), day	3 (1–7)	3 (1–7)	0.06
Ward length of stay, median (IQR), day	5 (1–11.5)	5 (1–11.5)	0.42

Note: Data are presented as number (%) unless otherwise specified.
Abbreviations: CNS, central nervous system; ICU, intensive care unit; IQR, interquartile range; SOFA, sequential organ failure assessment.

Table 4 Association Between Patient Characteristics and In-Hospital Mortality

Characteristics	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Age	1.01 (0.99–1.02)	0.30		
Primary bacteremia	2.02 (0.96–4.28)	0.07		
History of hypertension	1.96 (1.26–3.03)	<0.01	1.76 (1.02–3.04)	0.04
History of stroke	0.298 (0.10–0.88)	0.02	0.27 (0.08–0.87)	0.03
SOFA score	1.33 (1.24–1.44)	<0.01	1.34 (1.20–1.41)	<0.01
Septic shock	2.67 (1.75–4.10)	<0.01	1.76 (1.07–2.88)	0.02
Pneumonia	1.69 (1.11–2.58)	0.01	2.07 (1.27–3.40)	0.04
Vague symptoms	2.11 (1.38–3.24)	<0.01	2.17 (1.30–3.61)	0.03

Abbreviations: OR, odds ratio; SOFA, sequential organ failure assessment.

To our knowledge, this is the first study of symptomatic presentation of sepsis following the mnemonic "SEPSIS" in the Thai population and provided epidemiological data on sepsis in a local context. Overall, in-hospital mortality was 31.8%, higher than the recent Thai sepsis data[20] (21%) due to the inclusion of septic shock patients in the study. We confirmed the benefit of the SOFA score, which was significantly associated with mortality. Pneumonia was also associated with in-hospital mortality. Not only in the acute phase, He et al reported that pulmonary infection is also an independent risk factor for long-term mortality in sepsis patients.[21] The timing of antibiotic administration was not associated with in-hospital mortality, similar to our previous report.[15] Although this study was not designed to evaluate the effect of the timing of antibiotic administration, our results supported the position statement of the Infectious Disease Society of America against a fixed timing of antibiotic administration with inappropriate use.[22]

This study has several limitations. First, this was a single-center study in a tertiary academic medical center; therefore, variations in patient characteristics, practice protocols, and mortality may exist that are not representative of the general population. Second, this was a retrospective review that relied on chart review to obtain patient history information. The quality of the data depended on the completion of medical records. Third, patients with

mortality rate. Obscured infection commonly occurs in the elderly and intraabdominal infection was the common source of infection. Our findings were similar to those of a previous study by Filbin et al that confirmed the association of vague sepsis symptoms and in-hospital mortality.[11]

vague symptoms were older, which might be related to in-hospital mortality. However, we tried to adjust for age and other confounding factors.

Conclusion

Using the mnemonic "SEPSIS" might lead to misdiagnosis of sepsis in 15% of cases, especially in immunosuppression and intraabdominal infection. Septic patients with vague presentation were associated with higher in-hospital mortality. We suggest further research using big data with a multicenter study to better clarify sepsis symptoms and revision of the mnemonic for the local context.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no potential conflicts of interest.

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