Korean J Clin Lab Sci. 2021;53(4):309-316

https://doi.org/10.15324/kjcls.2021.53.4.309

Korean Society for Clinical Laboratory Science

Korean Journal of CLINICAL LABORATORY SCIENCE

REVIEW ARTICLE

Diagnosis and Prognosis of Sepsis

Chang-Eun Park

Department of Biomedical Laboratory Science, Molecular Diagnostics Research Institute, Namseoul University, Cheonan, Korea

패혈증의 진단 및 예후예측

박창은

남서울대학교 임상병리학과·분자진단연구소

ARTICLE INFO

Received November 28, 2021
Revised December 2, 2021
Accepted December 6, 2021

Key words
Biomarker
Cytokine
Laboratory detection
Multi-markers
Sepsis

ABSTRACT

Sepsis is a physiological response to a source of infection that triggers mechanisms that compromise organ function, leading to death if not treated early. Biomarkers with high sensitivity, specificity, speed, and accuracy that could differentiate sepsis from non-infectious systemic inflammatory response syndrome (SIRS) could bring about a revolution in sepsis treatment. Given the limitations and time required for microbial verification of pathogens, the accurate diagnosis of infection before employing antibiotic therapy is important and clinically necessary. Procalcitonin (PCT), lactate, C-reactive protein (CRP), cytokines, and proadrenomedullin (ProADM) are the common biomarkers used for diagnosis. The procalcitonin (PCT)-guided antibiotic treatment in patients with acute respiratory infections effectively reduces antibiotic exposure and side effects while improving survival rates. The evidence regarding sepsis screening in hospitalized patients is limited. Clinicians, researchers, and healthcare decision-makers should consider these findings and limitations when implementing screening tools, future research, or policy on sepsis recognition in hospitalized patients. The use of biomarkers in pediatric sepsis is promising, although such use should always be correlated with clinical evaluation. Biomarkers may also improve the prediction of mortality, especially in the early phase of sepsis, when the levels of certain pro-inflammatory cytokines and proteins are elevated.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total sequential organ failure assessment (SOFA) score at least two points consequent to the infection. Septic patients were previously predominantly cared for in intensive care units (ICUs), but this is now changing with more septic patients being cared for in hospital wards [1]. The response to sepsis is the result of complicated interactions between mechanisms of inflammation, anti-inflammation, humoral and cellular adaptive mechanisms and circulatory changes, the accurate detection of procalcitonin (PCT) in serum is crucial for effective early diagnosis and very helpful for further treatment guidance.

Acute respiratory infections are caused by bacteria, viruses, and other causes and are often treated with antibiotic therapy. Sepsis has contributed to the development of multidrug-resistant bacterial pathogens [2].

Corresponding author: Chang-Eun Park
Department of Biomedical Laboratory Science, Molecular Diagnostics Research Institute, Namseoul University, 91 Daehak-ro, Seonghwan-eup, Seobuk-gu, Cheonan 31020, Korea
E-mail: eun2777@hanmail.net
ORCID: https://orcid.org/0000-0003-4259-7928

pISSN 1738-3544 eISSN 2288-1662

The infection blood biomarker procalcitonin has been proposed as an adjunct to clinical judgment and traditional clinical parameters to guide antibiotic prescribing practices in patients with acute respiratory infections. PCT measurements increase within 6~12 hr of infection in response to pro-inflammatory mediator release after bacterial invasion, are highest in patients who have bacteraemia, and correlate with disease severity and clinical outcome of patients with infection [3].

PCT concentrations rapidly fall by about 50% each day during resolution of infection and are therefore useful in monitoring the clinical course and supporting decisions to discontinue antibiotic treatment. A large US study, found PCT kinetics over 72 hr to be a strong and independent predictor of mortality. Early identification of non-responders to antibiotic and other medical treatment might also help to prevent adverse events [4]. It has been argued that sepsis has no reference standard for identification and diagnosis, with early signs and symptoms being non-specific [5]. The known presence of specific biomarkers during the response to an infectious insult makes possible the potential clinical use of such biomarkers in screening, diagnosis, prognosis (risk stratification), therapeutic response monitoring, and rational use of antibiotics (determination of adequate treatment length, for example).

C-reactive protein (CRP), one of the biomarkers that has been in longer use in pediatric sepsis, is a non-specific, acute-phase protein that increases 4~6 hr after exposure to an inflammatory trigger (infectious or not) and has an 8 hr doubling time, peaking from 36 ~50 hr after the trigger stimulus. Elevation of PCT levels usually occurs earlier during the course of infection than elevation of CRP levels, peaking at approximately 24~36 hr. Recently, The interleukin-6 (IL-6) and IL-8 to increase its specificity in the diagnosis of infections [6].

Sepsis alerts mediated by technology embedded in electronic medical records have also been proposed as an effective screening mechanism [7]. The most effective method of screening patients in acute care is not clear, therefore the purpose of this review was to examine the application of sepsis screening tools or alert mechanisms for early recognition of sepsis in general hospitalized.

MAIN BODY

Overall the frequency and time to use of diagnostic measures (lactate orders, blood cultures) improved significantly, whereas results pertaining to treatment (fluids and vasopressors) were inconsistent across studies with some but not all demonstrating improvement [8]. A biomarker may be defined as a characteristic that can be objectively measured and assessed as an indicator of normal biological processes, pathological processes, and/or pharmacological responses to a therapeutic intervention.

1. Procalcitonin (PCT)

PCT is thought to have pro-inflammatory effects similar to CRP. PCT, a sensitive biomarker of inflammation, is a U.S. Food and Drug Administration (FDA) approved marker of blood infection for guiding antibiotic therapy [9]. PCT should always be interpreted carefully in the context of medical history and other clinical information as recommended in the Surviving Sepsis Campaign (SSC) [10].

Normal serum values are below 0.05 ng/mL, and a value of 2.0 ng/mL suggests a significantly increased risk of sepsis and/or septic shock. Values <0.5 ng/mL represent a low risk while values of 0.5~2.0 ng/mL suggest an intermediate likelihood of sepsis and/or septic shock.

2. Lactate

Sepsis may progress rapidly to septic shock that is often associated with micro-and macro-circulatory dysfunction Lactate levels have been a useful marker for organ dysfunction and may also serve as an endpoint for resuscitation in patients with sepsis. The 2013 SSC

international guidelines lists a lactate level >2 mmol/L as one of the criteria defining severe sepsis and a lactate level >4 as defining septic shock [11]. Serial lactate measurements may be useful in monitoring treatment effectiveness to various therapeutic interventions, and therefore, is recommended in the sepsis bundle for septic shock, especially when the initial level is high. A normal lactate level is often interpreted as indicating a good prognosis in sepsis, but studies suggest that this may be a false assurance. Elevated levels of lactate are not considered specific for either the diagnosis of sepsis, or predicting mortality, unless thoughtfully coupled with the overall clinical trials.

3. C-reactive protein (CRP)

Serum concentrations can increase up to 1,000-folds during acute inflammatory events, which increases its value as a biomarker of infection and inflammation compared to other acute phase reactants. In patients with CRP concentrations >10 mg/dL, decreasing concentrations in the first 48 hr was associated with a mortality of 15%, whereas mortality reached 61% for patients in whom the CRP concentration increased [12]. An increase in CRP concentration above 2.2 mg/dL over the 48 hr period was predictive of inadequate antibiotic therapy with a sensitivity of 77% and a specificity of 67% [13].

4. Cytokines

Interleukin-6 (IL-6), IL-8 and IL-10 have been the most widely studied cytokines to diagnose sepsis, evaluate the level of the inflammatory response and help determine the prognosis for the patient. IL-6 is a prototype of proinflammatory cytokine, IL-8 is a major chemokine, and IL-10 represents an important anti-inflammatory cytokine. IL-6 and IL-10 levels are correlated with the mortality rate in septic patients [14]. IL-8 has been used to predict the severity of sepsis in pediatric patients, although the utility of IL-8 has not been confirmed in adults [15].

5. D-dimer

D-dimer was shown to predict the presence of bacteremia in septic patients and was correlated with sepsis severity [16].

6. Proadrenomedullin (ProADM)

ProADM is a potent vasodilator that belongs to the calcitonin peptide superfamily with PCT. ProADM has been shown to improve clinical pneumonia risk scores ProADM has been used as a prognostic marker, either alone or in risk stratification with other hormonal propeptides in patients with sepsis and severe pneumonia [17]. Correlation with severity and potential use as a risk stratifier ProADM was promising marker of diagnosis of infection in febrile neutropenic patients.

7. Multi-marker approach to sepsis

When used as a single marker, failed to provide useful information, no single marker accurately reflects the rapid immunological changes of sepsis. With optimal cutoff values, the combination of baseline alpha-2 macroglobulin and 72 hr PCT offered a 75% negative predictive value (95% CI 54~96%), and differentiated bacterial sepsis from systemic inflammatory response syndrome (SIRS) [17]. When combined with another biomarker, including interleukin 8 (IL-8), increased CRP levels are apparently a good diagnostic predictor in the first 24 hr. The different biomarkers down to a panel 3 markers that best predicted the development of sepsis: IL-1 receptor antagonist (IL-1ra), protein C and neutrophil gelatinase associated lipocalin (NGAL). For accuracy to predict severe sepsis (0.80) [19]. NGAL was promising biomarker of acute kidney injury (organ dysfunction) also, using the early increase in cases of acute kidney failure (48 hr prior to the increase of creatinine) and early introduction of renal protection measures. The utilizing the results of three more traditional biomarkers (PCT, CD64 and soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) [20]. A risk model for estimating mortality in

children with septic shock using five biomarkers (C-C chemokine ligand 3 (CCL3), IL- 8, heat shock protein 70 kDa 1B (HSPA1B), granzyme B (GZMB), and matrix metallopeptidase 8 (MMP8) was created and validated [21].

8. Sepsis-related sequential organ failure assessment (SOFA) score

The SOFA score is a mortality prediction score that is based on the degree of dysfunction of six organ systems. The score is calculated on admission and every 24 hr until discharge using the worst parameters measured during the prior 24 hr. The scores can be used in a number of ways: As individual scores for each organ to determine progression of organ dysfunction. As the sum of scores on one single ICU day. As the sum of the worst scores during the ICU stay. It is believed to provide a better stratification of the mortality risk in ICU patients given that the data used to calculate the score is not restricted to admission values. These changes may be quantified by calculating the SOFA score [22]. Clinical laboratory tests are essential in determining pulmonary function (arterial blood gases), hepatic function (bilirubin) and renal function (creatinine). The status of the coagulation system is determined by measuring the number of platelets.

9. Experimental analytes

Several new biomarkers have been proposed recently ranging from cytokines to small cellular proteins. These markers offer the potential to improve the diagnosis and treatment of sepsis. High IL-3 levels are associated with poor prognosis and high mortality rate, even after adjusting for prognostic indicators [23]. Tumor necrosis factor (TNF)-α converting enzyme (TACE) is a transmembrane protease enzyme that cleaves membrane-bound TNF to produce soluble TNF. Patients with sepsis had substantially elevated levels of basal TACE activity that were refractory to lipopolysaccharide stimulation [24]. The peptidoglycan (PGN) recognition protein 1 (PGLYRP1) as a ligand for TREM-1, a known proinflammatory receptor expressed on monocytes/macrophages and neutrophils [25]. Vaspin, a visceral adipose tissue-derived serpin, was first identified as an insulin-sensitizing adipose tissue hormone, and its anti-inflammatory function has recently been demonstrated a weak positive correlation between the concentration of vaspin and CRP [26]. A recent study showed that using a panel of biomarkers consisting of angiopoietin-1, angiopoietin-2, and bicarbonate was a better predictor of severity in pediatric septic patients [27]. The miRNAs have been suggested as biomarkers in the context of sepsis, In patients with sepsis, which are most likely due to a lack in standardization of sample collection, data normalization, and analysis [28]. Recently, there have been increasing data indicating that kallistatin, testican-1, presepsin, and mid-regional pro-adrenomedullin or bio-ADM are promising biomarkers significant in diagnosis and monitoring of sepsis. The HMGB-1 is promptly released subsequent to the infection. Also, it has been reported to have pro-inflammatory effects, and high plasma levels have been associated to sepsis.

Further, it has been correlated directly to sepsis severity and organ dysfunction [29]. Initial neutrophil to lymphocyte ratio (NLR) may be a helpful prognostic biomarker for sepsis and that high NLR may indicate unfavorable prognoses in patients with sepsis. However, these findings should be interpreted with caution due to the aforementioned limitations. The types of recently reported circulating biomarkers for evaluating sepsis were classified and arranged (Table 1).

10. Molecular diagnosis kits

A commercially available kit for molecular diagnosis of sepsis has been reported, has high specificity and sensitivity, and is used as a rapid diagnostic method [38]. SeptiCyte Lab (Immunexpress Inc., Seattle, WA, USA) is the first RNA-based technology that targets specific human inflammatory markers using 2.5 mL whole blood for sepsis determination in 4~6 hr. SeptiCyte provides a robust way to detect whether a pathogen is present based on the host response but

Table 1. The outlined markers were classified into relevant circulating biomarkers being evaluated within sepsis

Category	Biomarker	Characteristic	References
Chemokines	Interleukin (IL-8)	Pro-inflammatory cytokines are involved in chemotaxis during the inflammation for diagnosis	[30]
	Monocyte chemoattractant protein (MCP-1)	Role in the progression of sepsis to the immunosuppressive phase to predict	[31]
	Macrophage inflammatory protein (MIP)/Macrophage migration inhibitory factor (MIF)	Highly related members of the CC chemokine subfamily, CC chemokine (or β-chemokine) proteins have two adjacent cysteines (amino acids), near their amino terminus	[32]
	Osteopontin (OPN)	Matricellular protein that mediates diverse biological functions. OPN is involved in normal physiological processes and is implicated in the pathogenesis of a variety of disease states	[33]
	Regulated on Activation, Normal T Cell (RANTES)	Valuable sensitivity and specificity	[34]
Cell markers	Triggering receptor expressed on myeloid cells-1 (TREM-1)	Expression increases after the exposition of neutrophil to bacteria showed better prognostication than procalcitonin and C-reactive protein	[35]
	Presepsin (the receptor of lipopolysaccharide-lipopoly-saccharide binding protein [LPS-LBP] complexes)	Measured during the first week of treatment in ICU patients to predict all-cause mortality with respect to 30 days and 6 months	[36]
	Toll-like receptor (TLR) 2 and 4	Induced organ failure	[37]

requires a higher volume of blood and initial sample preparation SeptiCyte Lab is a host response-targeted, reverse transcription-quantitative PCR (RT-qPCR)-based test that quantifies the relative expression levels of four RNA biomarkers (carcinoembryonic antigen-related cell adhesion molecule 4 [CEACAM4], lysosomal-associated membrane protein 1 [LAMP1], phospholipase A2 group VII [PLA2G7] and placenta-specific protein 8 [PLAC8]) known to be involved in innate immunity and the host response to infection.

An emerging technology termed "integrated comprehensive droplet digital detection" (IC3D) (Velox Biosystems, Irvine, CA, USA) claims to selectively detect individual bacterial species directly from small quantities of whole blood within 1 to 4 hr (190). The IC3D technology is limited in the number of targets that it can detect in a single sample but is capable of skipping sample preparation entirely to accomplish the simplest and most direct testing from blood samples. This may be of significant value for rapidly tracking the spread of individual organisms in the context of outbreaks. In a one-step, culture- and amplification-free process, the IC3D method provides quantitative bacterial detection with single-cell sensitivity. IC3D combines DNAzyme-based sensors with real-time droplet microencapsulation and a particle counter.

CONCLUSIONS

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Septic shock defined by hypotension despite fluid resuscitation and serum lactate level >2 mmol/L. Clinical diagnotic severe sepsis or septic shock type of PCT algorithm and procalcitonin cutoffs used discontinuation at day 4, 7, and 10; recommendation against antibiotic: <1.0 μg/L or >50% drop to previous value [39]. Serial measurements of CRP are useful in assessing the response to antimicrobial treatment. CRP values that fail to decrease or continue to rise after 48 hours of antibiotic therapy suggest treatment failure. On admission and 24 hours later, the diagnostic accuracy of CRP alone for severe sepsis in children with febrile neutropenia was lower than that of PCT and IL-6. The 40% of the sepsis patients remain culture negative [40]. It is important to differentiate culture negative sepsis patients from those with noninfectious SIRS, as these disease conditions require different therapeutic regimens. An accurate and timely diagnosis of sepsis allows prompt and appropriate treatment. Sepsis screening and response are complex processes of care that involve various disciplines necessitating

roles of each of the professionals be made explicit. This immunosensor could be promisingly used for clinical early diagnosis of bacterial infections and also for guiding antibiotic therapy due to its ability for highly sensitivity detection. Use of procalcitonin to guide antibiotic treatment in patients with acute respiratory infections reduces antibiotic exposure and side-effects, and improves survival. Validation of the predictive risk model for severe sepsis in patients with high-risk febrile neutropenia in the first 24 hr of admission. Sepsis can lead to death if prompt action is not taken early. Therefore, the diagnostic flow is important, and it is important to distinguish sepsis from non-septicemia. It is expected to be used in the diagnosis of sepsis caused by the recent COVID-19, and is expected to be used as a diagnostic biomarkers.

요 약

패혈증은 감염원에 의한 생리학적 반응으로 장기의 기능을 손상시켜 조기에 치료하지 않으면 사망에 이르게 하는 기전을 유발한다. 이에 높은 감도, 특이도, 신속 정확도를 가진 바이오마커는 병원균의 미생물학적 검증에 필요한 제한성과 경과 시간을 감안할 때 패혈증을 비감염성 전신성 염증 반응 증후군(SIRS)과 구별하는 것이 획기적일 것으로 판단된다. 또한 항생제를 사용하기 전에 정확한 감염 진단이 중요하고 임상적으로 요구된다. 해당하는 후보물질인 프로칼시토닌, 젖산, C-반응성 단백질, 사이토카인, 프로아드레노매듈린(ProADM)이 진단에 활용된다. 급성 호흡기 감염 환자에서 프로칼시토닌으로 유도되는 항생제 치료는 항생제 노출과 항생제 부작용을 효과적으로 감소시키면서 사망률을 개선한다. 입원환자에 있어서 패혈증 선별검사에 대한 근거 마련은 제한적이다. 임상의사, 연구원 및 건강검진 의사의 전문가 집단은 일반 입원 환자의 패혈증 인식에 대한 스크리닝 도구, 향후 연구 또는 정책을 시행할 때 새로운 바이오마커의 발견과 한계점을 고려해야 한다. 바이오마커 사용은 항상 임상 평가와 상관관계가 있어야 하지만 소아 패혈증에서도 특히 바이오마커의 사용은 기대된다. 따라서 바이오마커의 활용에 있어서 특정된 전염증성 사이토카인 및 단백질 수준이 상승하는 것에 대해 패혈증의 초기 단계에서 사망률을 예측하는 것에 대해 향상된 진단법을 제공할 수 있다.

Acknowledgements: Funding for this paper was provided by Namseoul University year 2021.
Conflict of interest: None
Author's information (Position): Park CE, Professor.

REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303-1310. https://doi.org/10.1097/00003246-200107000-00002
2. Lawrence KL, Kollef MH. Antimicrobial stewardship in the intensive care unit: advances and obstacles. Am J Respir Crit Care Med. 2009;179:434-438. https://doi.org/10.1164/rccm.200809-1394CP
3. Kutz A, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, et al. Prognostic value of procalcitonin in respiratory tract infections across clinical settings. Crit Care. 2015;19:74. https://doi.org/10.1186/s13054-015-0792-1
4. Schuetz P, Birkhahn R, Sherwin R, Jones AE, Singer A, Kline JA, et al. Serial procalcitonin predicts mortality in severe sepsis patients: results from the multicenter procalcitonin monitoring sepsis (MOSES) study. Crit Care Med. 2017;45:781-789. https://doi.org/10.1097/CCM.0000000000002321
5. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:762-774. https://doi.org/10.1001/jama.2016.0288
6. Kitanovski L, Jazbec J, Hojker S, Derganc M. Diagnostic accuracy of lipopolysaccharide-binding protein for predicting bacteremia/clinical sepsis in children with febrile neutropenia: comparison with interleukin-6, procalcitonin and C-reactive protein. Support Care Cancer. 2014;22:269-277. https://doi.org/10.1007/s00520-013-1978-1
7. Amland RC, Hahn-Cover KE. Clinical decision support for early recognition of sepsis. Am J Med Qual. 2016;31:103-110. https://doi.org/10.1177/1062860614557636
8. Gyang E, Shieh L, Forsey L, Maggio P. A nurse-driven screening tool for the early identification of sepsis in an intermediate care unit setting. J Hosp Med 2015;10:97-103. https://doi.org/10.1002/jhm.2291
9. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis. 2018;18:95-107. https://doi.org/10.1016/S1473-3099(17)30592-3
10. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, et al. Surviving sepsis campaign: association between performance metrics and outcomes in a 7.5-year study. Crit Care Med. 2015;43:3-12. https://doi.org/10.1097/CCM.0000000000000723
11. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for

management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:580-637. https://doi.org/10.1097/CCM.0b013e31827e83af
12. Liu S, Hou Y, Cui H. Clinical values of the early detection of serum procalcitonin, C-reactive protein and white blood cells for neonates with infectious diseases. Pak J Med Sci. 2016;32:1326-1329. https://doi.org/10.12669/pjms.326.11395
13. Povoa P, Coelho L, Almeida E, Fernandes A, Mealha R, Moreira P, et al. Early identification of intensive care unit-acquired infections with daily monitoring of c-reactive protein: a prospective observational study. Crit Care. 2006;10:R63. https://doi.org/10.1186/cc4892
14. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the genetic and inflammatory markers of sepsis (GenIMS) study. Arch Intern Med. 2007;167:1655-1663. https://doi.org/10.1001/archinte.167.15.1655
15. Calfee CS, Thompson BT, Parsons PE, Ware LB, Matthay MA, Wong HR. Plasma interleukin-8 is not an effective risk stratification tool for adults with vasopressor-dependent septic shock. Crit Care Med. 2010;38:1436-1441. https://doi.org/10.1097/CCM.0b013e3181de42ad
16. Prucha M, Bellingan G, Zazula R. Sepsis biomarkers. Clin Chim Acta. 2015;440:97-103. https://doi.org/10.1016/j.cca.2014.11.012
17. Schuetz P, Aujesky D, Muller C, Muller B. Biomarker-guided personalised emergency medicine for all-hope for another hype? Swiss Med Wkly. 2015;145:w14079. https://doi.org/10.4414/smw.2015.14079
18. Kelly BJ, Lautenbach E, Nachamkin I, Coffin SE, Gerber JS, Fuchs BD, et al. Combined biomarkers discriminate a low likelihood of bacterial infection among surgical intensive care unit patients with suspected sepsis. Diagn Microbiol Infect Dis. 2016;85:109-115. https://doi.org/10.1016/j.diagmicrobio.2016.01.003
19. Shapiro NI, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM, et al. A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. Crit Care Med. 2009;37:96-104. https://doi.org/10.1097/CCM.0b013e318192fd9d
20. Andersen LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, Donnino MW. Etiology and therapeutic approach to elevated lactate levels. Mayo Clin Proc. 2013;88:1127-1140. https://doi.org/10.1016/j.mayocp.2013.06.012
21. Wong HR, Salisbury S, Xiao Q, Cvijanovich NZ, Hall M, Allen GL, et al. The pediatric sepsis biomarker risk model. Crit Care. 2012;16:R174. https://doi.org/10.1186/cc11652
22. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315:801-810. https://doi.org/10.1001/jama.2016.0287
23. Weber GF, Chousterman BG, He S, Fenn AM, Nairz M, Anzai A, et al. Interleukin-3 amplifies acute inflammation and is a potential therapeutic target in sepsis. Science. 2015;347:1260-1265. https://doi.org/10.1126/science.aaa4268
24. O'Callaghan DJ, O'Dea KP, Scott AJ, Takata M, Gordon AC. Monocyte tumor necrosis factor-alpha-converting enzyme catalytic activity and substrate shedding in sepsis and noninfectious systemic inflammation. Crit Care Med. 2015;43:1375-1385. https://doi.org/10.1097/CCM.0000000000000992
25. Read CB, Kuijper JL, Hjorth SA, Heipel MD, Tang X, Fleetwood AJ, et al. Cutting edge: identification of neutrophil PGLYRP1 as a ligand for TREM-1. J Immunol. 2015;194:1417-1421. https://doi.org/10.4049/jimmunol.1402303
26. Motal MC, Klaus DA, Lebherz-Eichinger D, Tudor B, Hamp T, Wiegele M, et al. Increased plasma vaspin concentration in patients with sepsis: an exploratory examination. Biochem Med (Zagreb). 2015;25:90-96. https://doi.org/10.11613/BM.2015.011
27. Wang K, Bhandari V, Giuliano JS Jr, O Hern CS, Shattuck MD, Kirby M. Angiopoietin-1, angiopoietin-2 and bicarbonate as diagnostic biomarkers in children with severe sepsis. PLoS One. 2014;9:e108461 https://doi.org/10.1371/journal.pone.0108461
28. Benz F, Roy S, Trautwein C, Roderburg C, Luedde T. Circulating microRNAs as biomarkers for sepsis. Int J Mol Sci. 2016;17:78. https://doi.org/10.3390/ijms17010078
29. Kumar S, Tripathy S, Jyoti A, Singh SG. Recent advances in biosensors for diagnosis and detection of sepsis: a comprehensive review. Biosens Bioelectron. 2019;124-125:205-215. https://doi.org/10.1016/j.bios.2018.10.034
30. Stryjewski GR, Nylen ES, Bell MJ, Snider RH, Becker KL, Wu A, et al. Interleukin-6, interleukin-8, and a rapid and sensitive assay for calcitonin precursors for the determination of bacterial sepsis in febrile neutropenic children. Pediatric Crit Care Med. 2005;6:129-135. https://doi.org/10.1097/01.PCC.0000149317.15274.48
31. Bozza FA, Salluh JI, Japiassu AM, Soares M, Assis EF, Gomes RN, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. Crit Care. 2007;11:R49 https://doi.org/10.1186/cc5783
32. Tsujimoto H, Ono S, Majima T, Kawarabayashi N, Takayama E, Kinoshita M, et al. Neutrophil elastase, MIP-2, and TLR-4 expression during human and experimental sepsis. Shock. 2005;23:39-44. https://doi.org/10.1097/01.shk.0000145936.31967.d7
33. Vaschetto R, Nicola S, Olivieri C, Boggio E, Piccolella F, Mesturini R, et al. Serum levels of osteopontin are increased in SIRS and sepsis. Intensive Care Med. 2008;34:2176-2184. https://doi.org/10.1007/s00134-008-1268-4
34. Mikolajczyk TP, Nosalski R, Szczepaniak P, Budzyn K, Osmenda G, Skiba D. et al. Role of chemokine RANTES in the regulation of perivascular inflammation, T-cell accumulation, and vascular dysfunction in hypertension. FASEB J. 2016;30:1987-1999. https://doi.org/10.1096/fj.201500088R
35. Wright SW, Lovelace-Macon L, Hantrakun V, Rudd KE, Teparrukkul P, Kosamo S, et al. sTREM-1 predicts mortality in hospitalized patients with infection in a tropical, middle-income country. BMC Med. 2020;18:159. https://doi.org/10.1186/s12916-020-01627-5
36. Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, et al. Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. Crit Care. 2014;18:507. https://doi.org/10.1186/s13054-014-0507-z
37. Mansur A, von Gruben L, Popov AF, Steinau M, Bergmann I, Ross D, et al. The regulatory toll-like receptor 4 genetic polymorphism rs11536889 is associated with renal, coagulation and hepatic organ failure in sepsis patients. J Transl Med. 2014;12:177. https://doi.org/10.1186/1479-5876-12-177

38. Sinha M, Jupe J, Mack H, Coleman TP, Lawrence SM, Fraley SI. Emerging technologies for molecular diagnosis of sepsis. Clin Microbiol Rev. 2018;31:e00089-17. https://doi.org/10.1128/CMR.00089-17
39. Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, et al. Effect of sodium selenite administration and procalcitonin-guided therapy on mortality in patients with severe sepsis or septic shock: a randomized clinical trial. JAMA Intern Med. 2016;176:1266-1276. https://doi.org/10.1001/jamainternmed.2016.2514
40. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34:344-353. https://doi.org/10.1097/01.ccm.0000194725.48928.3a