

Bölüm 2

GÜNÜMÜZDEKİ VE GELECEKTEKİ SEPSİS BİYOBELİRTEÇLERİ

Çiğdem ARABACI¹

GİRİŞ

Sepsis, sistemik enflamasyonla karakterize vücudun bakteriyel, fungal veya viral enfeksiyona immünolojik cevabıdır (1). Septik yanıt; enflamatuvar ve antiinflamatuvar süreçleri, humoral ve hücrel reaksiyonları ve dolaşım anormalliklerini içeren karmaşık bir olaylar zinciridir (2,3). Sepsis teşhisi, hastanın semptomları, radyolojik incelemeler, biyobelirteçlerin araştırılması ve enfeksiyondan sorumlu olan mikroorganizmanın tanımlanması gibi laboratuvar testleri ile birleştirilen klinik bulgulara dayanarak konur. Sepsis vakalarında, teşhis ve tedavinin belirlenmesi çok önemlidir. Teşhisteki gecikme ve yanlış antibiyotik tedavisi hastaların sağ kalım oranını etkiler. Sepsisin erken teşhisi ise uygun antibiyotik rejimlerinin hızlı bir şekilde uygulanmasını ve yetersiz tanı ve terapötik müdahalelerin önlenmesini sağlar (4).

Biyobelirteçler, biyolojik ve patolojik süreçleri değerlendirebilen, kan ve vücut sıvılarında ölçülebilir miktarda bulunan moleküllerdir. Sepsis tanısında kullanılan biyobelirteçler erken tanı, risk sınıflandırma, değerlendirme ve prognoz tahmininde rol oynayabilirler (5,6). Bu değerlendirmeler uygun bir tedavi oluşturmak ve hastayı iyileştirmek için kritik bir öneme sahiptir. İdeal bir biyobelirteçte aranan özellikler ise; biyokimyasal olarak stabil

¹ Tıbbi Mikrobiyoloji Uzmanı, S.B.Ü. Okmeydanı Eğitim ve Araştırma Hastanesi
cigdem.arabaci@okmeydani.gov.tr

lecek biyobelirteçlerin bakteriyel enfeksiyonların ve sepsisin tanı, tedavi ve prognoz takibinde kullanımı için gelecekte yapılacak daha çok çalışmaya ihtiyacı vardır.

KAYNAKLAR

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* 2001 29(7):1303-13 10.
2. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med.* 2003;348(2):138-1 50.
3. Gullo A, Bianco N, Berlot G. Management of severe sepsis and septic shock: challenges and recommendations. *Crit Care Clin.* 2006; 22(3):489-501.
4. World Health Organization - <https://www.who.int/sepsis/en/>.
5. Definitions Working Group Bethesda. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001;69 (3):89-95.
6. Marshall JC, Reinhart K; International Sepsis Forum. Biomarkers of sepsis. *Crit Care Med.* 2009;37(7):2290-2298.
7. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Crit Care.* 2010;14 (1):R15.
8. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006 34(6):1589-15 96.
9. Zambon M, Ceola M, Almeida-de- Castro R, et al. Implementation of the Surviving Sepsis Campaign guidelines for severe sepsis and septic shock: we could go faster. *J Crit Care.* 2008;23(4):455-4 60.
10. Vincent JL, Donadello K, Schmit X. Biomarkers in the critically ill patient: C-reactive protein. *Crit Care Clin.* 2011;27 (2):241-251.
11. Müller B, Becker KL, Schächinger H, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med.* 2000;28 (4):977-983.
12. Selberg O, Hecker H, Martin M, et al. Discrimination of sepsis and systemic inflammatory response syndrome by determination of circulating plasma concentrations of procalcitonin, protein complement 3a, and interleukin-6. *Crit Care Med.* 2000;28 (8):2793-2798.
13. Suprin E, Camus C, Gacouin A, et al. Procalcitonin: a valuable indicator of infection in a medical ICU? *Intensive Care Med.* 2000;26 (9):1232-1238.
14. Schmit X, Vincent JL. The time course of blood C-reactive protein concentrations in relation to the response to initial antimicrobial therapy in patients with sepsis. *Infection.* 2008;36 (3):213-219.
15. Assicot M, Gendrel D, Carsin H, et al. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet.* 1993;341 (8844):515-518.
16. Kopterides P, Siempos II, Tsangaris I, et al. Procalcitonin-guided algorithm

- ms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Med.* 2010;38 (11):2229– 2241.
17. O'Grady NP, Barie PS, Bartlett JG, et al. American College of Critical Care Medicine; Infectious Diseases Society of America. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med.* 2008;36 (4):1330–1349.
 18. Boussekey N, Leroy O, Alfandari S, et al. Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. *Intensive Care Med.* 2006;32(3):469-472.
 19. Pettilä V, Hynninen M, Takkunen O, et al. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. *Intensive Care Med.* 2002;28 (9):1220–1225.
 20. Oberholzer A, Souza SM, Tschoeke SK, et al. Plasma cytokine measurements augment prognostic scores as indicators of outcome in patients with severe sepsis. *Shock.* 2005;23 (6):488–493.
 21. Pinsky MR, Vincent JL, Deviere J, et al. Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality. *Chest.* 1993;103 (2):565–575.
 22. Qiu P, Cui X, Barochia A, et al. The evolving experience with therapeutic TNF inhibition in sepsis: considering the potential influence of risk of death. *Expert Opin Investig Drugs.* 2011;20 (11):1555-15 64.
 23. Ramírez P, Ferrer M, Gimeno R, et al. Systemic inflammatory response and increased risk for ventilator-associated pneumonia: a preliminary study. *Crit Care Med.* 2009;37(5):1691-169 5.
 24. Spyridaki A, Raftogiannis M, Antonopoulou A, et al. Effect of clarithromycin in inflammatory markers of patients with ventilator-associated pneumonia and sepsis caused by Gram-negative bacteria: results from a randomized clinical study. *Antimicrob Agents Chemother.* 2012;56(7):3819-38 25.
 25. Jerala R. Structural biology of the LPS recognition. *Int J Med Microbiol* 2007;297 (5):353–363.
 26. Choi JH, Shin WS. Pathogenesis of sepsis and concepts of immunotherapy. *Korean J Infect Dis.* 2000;32 (2):148–157.
 27. Linscheid P, Seboek D, Zulewski H, et al. Autocrine/paracrine role of inflammation-mediated calcitonin gene-related peptide and adrenomedullin expression in human adipose tissue. *Endocrinology.* 2005;146 (6):2699–2708.
 28. Hinson JP, Kapas S, Smith DM. Adrenomedullin, a multifunctional regulatory peptide. *Endocr Rev.* 2000;21 (2):138–167.
 29. Christ-Crain M, Morgenthaler NG, Struck J, et al. Mid-regional pro-adrenomedullin as a prognostic marker in sepsis: an observational study. *Crit Care.* 2005;9 (6):R816–R824.
 30. Al Shuaibi M, Bahu RR, Chaftari AM, et al. Pro-adrenomedullin as a novel biomarker for predicting infections and response to antimicrobials in

- feb- rile patients with hematologic malignancies. *Clin Infect Dis.* 2013;56 (7):943– 950.
31. Suberviola B, Castellanos-Ortega A, Ruiz Ruiz A, et al. Hospital mortality prognostication in sepsis using the new biomarkers suPAR and pro-ADM in a single determination on ICU admission. *Intensive Care Med.* 2013;39 (11):1945–1952.
 32. Sundén-Cullberg J, Norrby-Teglund A, Rouhiainen A, et al. Persistent elevation of high mobility group box-1 protein (HMGB1) in patients with severe sepsis and septic shock. *Crit Care Med.* 2005;33 (3):564–573.
 33. Hatada T, Wada H, Nobori T, et al. Plasma concentrations and importance of High Mobility Group Box protein in the prognosis of organ failure in patients with disseminated intravascular coagulation. *Thromb Haemost.* 2005;94 (5):975–979.
 34. Gibot S, Massin F, Cravoisy A, et al. High-mobility group box 1 protein plasma concentrations during septic shock. *Intensive Care Med.* 2007;33 (8):1347– 1353.
 35. Petrovsky N, Socha L, Silva D, et al. Macrophage migration inhibitory factor exhibits a pronounced circadian rhythm relevant to its role as a glucocorticoid counter-regulator. *Immunol Cell Biol.* 2003;81 (2):137–143.
 36. Calandra T, Echtenacher B, Roy DL, et al. Protection from septic shock by neutralization of macrophage migration inhibitory factor. *Nat Med.* 2000;6 (2):164–170.
 37. Bozza FA, Gomes RN, Japiassú AM, et al. Macrophage migration inhibitory factor levels correlate with fatal outcome in sepsis. *Shock.* 2004;22 (4):309–313.
 38. Corina Seeger et al. *Acute care testing handbook 2014* (alt text for link: “Get the free ebook on acute care testing by Radiometer”)
 39. Andersen WL, Mackenhauer J, Roberts JC, et al. Etiology and therapeutic approach to elevated lactate. *Mayo Clin Proc.* 2013;88(10):1127–1140.
 40. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013; 41(2): 580-637.
 41. Henriques, GMOM. (2013). The endothelin system. Hiroaki Matsuno (Ed.). In *Innovative rheumatology*. London: IntechOpen. DOI: 10.5772/53738.
 42. Kayaalp, O. (2012). Otakoidler. Oğuz Kayaalp (Ed.) Akılcı tedavi yönünden tıbbi farmakoloji içinde. (13.baskı, s.130-135). İstanbul: Güneş Tıp Kitabevi.
 43. Ehrenreich H, Burd PR, Rottem M, et al. Endothelins belong to the assortment of mast cell-derived and mast cell-bound cytokines. *New Biol.* 1992;4 (2):147-156.
 44. Suzuki T, Kumazaki T, Mitsui Y. Endothelin-1 is produced and secreted by neonatal rat cardiac myocytes in vitro. *Biochem Biophys Res Commun.* 1993;191 (3):823-830.
 45. Weitzberg E, Lundberg JM, Rudehill A. Elevated plasma levels of endothelin in patients with sepsis syndrome. *Circ Shock.* 1991;33 (4):222- 227.
 46. Dupuy AM, Philippart F, Péan Y, et al. Role of biomarkers in the manage-

- ment of antibiotic therapy: an expert panel review: I – currently available biomarkers for clinical use in acute infections. *Ann Intensive Care*. 2013; 3 (1):22.
47. Bopp C, Hofer S, Bouchon A, et al. Soluble TREM-1 is not suitable for distinguishing between systemic inflammatory response syndrome and sepsis survivors and nonsurvivors in the early stage of acute inflammation. *Eur J Anaesthesiol*. 2009;26(6):504-507.
 48. Hoffmann JJ. Neutrophil CD64 as a sepsis biomarker. *Biochem Med*. 2011;21(3):282-90.
 49. Icardi M, Erickson Y, Kilborn S, et al. CD64 index provides simple and pre- dictive testing for detection and monitoring of sepsis and bacterial infection in hospital patients. *J Clin Microbiol*. 2009;47(12):3914–3919.
 50. David S, Kümpers P, Van Slyke P, et al. Mending leaky blood vessels: the angiotensin-1/Tie2 pathway in sepsis. *J Pharmacol Exp Ther*. 2013;345(1):2–6.
 51. Ricciuto DR, Dos Santos CC, Hawkes M, et al. Angiotensin-1 and angiotensin-2 as clinically informative prognostic biomarkers of morbidity and mortality in severe sepsis. *Crit Care Med* 2011;39(4):702–710.
 52. Nemeth E, Ganz T. Ganz, The role of hepcidin in iron metabolism. *Acta Haematol*. 2009;122(2–3): 78-86.
 53. Yapakcı E, Tarcan A, Celik B, et al. Serum pro-hepcidin levels in term and preterm newborns with sepsis. *Pediatr Int*. 2009; 51(2): 289-292.
 54. Wu TW, Tabangin M, Kusano R, et al. The utility of serum hepcidin as a biomarker for late-onset neonatal sepsis. *J Pediatr*. 2013;162(1); 67-71.
 55. Andaluz-Ojeda D, Bobillo F, Iglesias V, et al. A combined score of pro- and anti-inflammatory interleukins improves mortality prediction in severe sepsis. *Cytokine*. 2012;57(3):332–336.
 56. Gibot S, Béné MC, Noel R, et al. Combination biomarkers to diagnose sepsis in the critically ill patient. *Am J Respir Crit Care Med*. 2012;186 (1):65–71.
 57. Shapiro NI, Trzeciak S, Hollander JE, 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 (1):96–104.
 58. LaRosa SP, Opal SM. Biomarkers: the future. *Crit Care Clin*. 2011;27:407–19.
 59. Johnson SB, Lissauer M, Bochicchio GV, et al. Gene expression profiles differentiate between sterile SIRS and early sepsis. *Ann Surg*. 2007;245(4):611–21.
 60. Schneider CP, Angele MK, Hartl WH. Activated partial thromboplastin time waveform analysis as specific sepsis marker in cardiopulmonary bypass surgery. *Crit Care*. 2010;14(1):104.
 61. Delannoy B, Guye ML, Slaiman DH, et al. Effect of cardiopulmonary bypass on activated partial thromboplastin time waveform analysis, serum procalcitonin and C-reactive protein concentrations. *Crit Care*. 2009;13(6):R180.