

Bölüm 4

SEPSİSTE MEDİATÖRLER ve ÖNEMİ

Harun YILDIZ¹
Berzan EKMEN²
Makbule Beyza ŞEN³

1. GİRİŞ

Sepsis vücudun enfeksiyona karşı verdiği cevaptır ve önemli bir mortalite ve morbidite nedenidir. Hastanede ölüm nedenlerinde ilk sıralarda yer almaktır ve ülkeler için ciddi bir maliyete neden olmaktadır. Amerika'da yılda ortalama 750 000 sepsis vakası görülmektedir ve yılda ortalama 215 000 ölüm (tüm ölümlerin %9.3'ü) sepsisten kaynaklanmaktadır. Bu da yılda 16 milyar doları aşan bir maliyete neden olmaktadır (1).

Sepsis tanımları 2016 yılına kadar sistemik enflamatuvardır yanıt sendromu (SIRS) kriterlerine dayanıyordu. SIRS vücudun enfeksiyon ve/veya enfeksiyon dışı etkenlere vücudun verdiği enflamatuvardır yanıtına denilmektedir (2).

Eski tanımlamalarda SIRS kriterlerine ilaveten enfeksiyon şüphesi de varsa sepsis denilmektedir. Bu klinik tabloya organ disfonksiyonu ve sıvı resüsitasyonuna cevap veren hipotansiyon varsa şiddetlisepsis, eğer sıvı resisütasyonu yetmiyor, inotrop ihtiyacı varsa septik şok denilmektedir (3).

Sistemik enflamatuvardır yanıt sendromu (SIRS) (1): Ateş $>38^{\circ}\text{C}$ ya da $<36^{\circ}\text{C}$

Kalp atım hızı $>90/\text{dk}$

Solunum sayısı $>20/\text{dk}$ ya da arteriyal $\text{CO}_2 < 32 \text{ mmHg}$ Lökosit sayısı $>12.000/\text{mm}^3$ ya da $<4.000/\text{mm}^3$

¹ Dr., Ankara Etlik Şehir Hastanesi, dr.harunyildiz@yahoo.com, ORCID iD: 0000-0002-1918-2575

² Öğr. Gör., Lokman Hekim Üniversitesi, Sağlık Hizmetleri Meslek Yüksekokulu,
ORCID iD: 0000-0001-6260-6196

³ Arş. Gör., Lokman Hekim Üniversitesi, Eczacılık Fakültesi, Biyokimya AD,
ORCID iD: 0000-0003-4015-5595

ve eksojen vazopressörlerle karşı vazomotor yanıtın belirlenmesinde önemli bir rol oynadığı görülmektedir. Ayrıca NO, miyokard fonksiyonunu derinden etkiler ve muhtemelen miyokard depresan maddesi olarak görev yapan son aracıdır. NO'nun septik hastada kardiyovasküler fonksiyondaki bu merkezi rolünün tanınması, NO konsantrasyonunu değiştirmeye girişimlerini teşvik etmiştir (49).

KAYNAKÇA

1. Seremet Keskin, A. (2020). Sistemik İnflamatuvar Yanıt Sendromu Ve Septik Şok Belirtileri Olan Hastalarda Prokalsitoninin Tanısal Ve Prognostik Değeri. Gevher Nesibe Journal, 5(8), 45–52. doi: 10.46648/gnj.101
2. Bone, R.C., Bak, R.A., Cerra, F.B., Dellinger, R.P., Fein, A.M., Knaus, W.A., ve Sibbald, W.J. (1992). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest, 101(6), 1644- 1655.
3. De, O.R. (2010). Toplum Kökenli Sepsis: 125 Olgunun Retrospektif İncelenmesi. 15(1), 11–15.
4. Dellinger, R.P., Levy, M.M., Rhodes, A., Annane, D., Gerlach, H., Opal, S.M ... ve Moreno,
- R. (2013). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med, 41, 580-637.
5. Seymour, C.W., Liu, V.X., Iwashyna, T.J., Brunkhorst, F.M., Rea, T.D., Scherag, A., ... ve Deutschman, C.S. (2016). Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama, 315(8), 762-774.
6. Garnacho-Montero, J. et al. (2014). Prognostic and diagnostic value of eosinopenia, C- reactive protein, procalcitonin, and circulating cell-free DNA in critically ill patients admitted with suspicion of sepsis. Crit. Care, 18(3), 1–9. doi: 10.1186/cc13908.
7. Charles, P. E. et al. (2008). Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either gram-negative or gram-positive bacteria. BMC Infect. Dis., 8, 1–8. doi: 10.1186/1471-2334-8-38.
8. Centers for Disease Control and Prevention (CDC). (2018). Hospital Toolkit for Adult Sepsis Surveillance.
9. Tan, M., Lu, Y., Jiang, H., ve Zhang, L. (2019). The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis. J. Cell. Biochem., 120(4), 5852–5859. doi: 10.1002/jcb.27870.
10. Schuetz, P. (2011). Procalcitonin Algorithms for Antibiotic Therapy Decisions. Arch. Intern. Med., 171(15), 1322. doi: 10.1001/archinternmed.2011.318.
11. Jensen, J. U., Heslet, L., Jensen, T. H., Espersen, K., Steffensen, P., ve Tvede, M. (2006). Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit. Care Med., 34(10), 2596–2602. doi: 10.1097/01.CCM.0000239116.01855.61.
12. Lippi, G. (2019). Sepsis biomarkers: Past, present and future. Clin. Chem. Lab. Med., 57(9), 1281–1283. doi: 10.1515/cclm-2018-1347.

13. Fuller, B.M., ve Dellinger, R.P. (2012). Lactate as a hemodynamic marker in the critically ill. *Curr Opin Crit Care*, 18(3), 267-272.
14. Huckabee, W.E. (1961). Abnormal resting blood lactate. I. The significance of hyperlactatemia in hospitalized patients. *Am J Med*, 30, 833-839.
15. Huckabee, W.E. (1961). Abnormal resting blood lactate. II. Lactic acidosis. *Am J Med*, 30, 840-848.
16. Borregaard, N., ve Herlin, T. (1982). Energy metabolism of human neutrophils during phagocytosis. *J Clin Invest*, 70(3), 550-557.
17. Dugas, A.F., Mackenhauer, J., Salciccioli, J.D., Cocchi, M.N., Gautam, S., ve Donnino,
18. M.W. (2012). Prevalence and characteristics of nonlactate and lactate expressors in septic shock. *J Crit Care*, 27(4), 344-350.
19. Mallat, J., Rahman, N., Hamed, F., Hernandez, G., ve Fischer, M.O. (2022). Pathophysiology, mechanisms, and managements of tissue hypoxia. *AnaesthesiaCritical Care and Pain Medicine*, 41(4), 101087. doi: 10.1016/j.accpm.2022.101087.
20. Schumacker, P.T., ve Samsel, R.W. (1989). Oxygen delivery and uptake by peripheral tissues: physiology and pathophysiology. *Crit Care Clin*, 5(2), 255-269. Tejero, J., Shiva, S., ve Gladwin, M.T. (2019). Sources of vascular nitric oxide and reactive oxygen species and their regulation. *Physiol. Rev.*, 99(1), 311-379. doi:10.1152/physrev.00036.2017.
21. Huang, J.B., Chen, Z.R., Yang, S.L., ve Hong, F.F. (2023). Nitric Oxide Synthases in Rheumatoid Arthritis. *Molecules*, 28(11), 4414.
22. Giroud, C., Moreau, M., Mattioli, T.A., Balland, V., Boucher, J.L., Xu-Li, Y. (2010). Role of Arginine Guanidinium Moiety in Nitric-oxide Synthase Mechanism of Oxygen Activation. *Journal of Biological Chemistry*, 285(10), 7233-7245.
23. Tejero, J., Shiva, S., ve Gladwin, M.T. (2019). Sources of Vascular Nitric Oxide and Reactive Oxygen Species and Their Regulation. *Physiol Rev*, 99(1), 311-79.
24. Hauser, B., Radermacher, P., Thiemer, C., Matejovic, M. (2004). NITRIC OXIDE, BACTERIA, AND HOST DEFENSE IN SEPSIS: WHO NEEDS WHAT? *Shock*, 22(6), 588- 590.
25. Tay, J.E.F., Ulaganathan, V., Kua, G.Y.L., Adan, M.A., Lim, S.Y. (2022). Nutritional Status of Orang Asli in Malaysia. *Malaysian Journal of Medical Sciences*, 29(3), 17-29.
26. Luo, Y., Zhu, Y., Basang, W., Wang, X., Li, C., Zhou, X. (2021). Roles of Nitric Oxide in the Regulation of Reproduction: A Review. *Front Endocrinol (Lausanne)*, 12.
27. Liy, P.M., Puji, N.N.A., Jose, S., Vidyadarshan, S. (2021). Nitric oxide modulation in neuroinflammation and the role of mesenchymal stem cells. *Exp Biol Med*, 246(22), 2399-406.
28. Lambden, S. (2019). Bench to bedside review: therapeutic modulation of nitric oxide in sepsis—an update. *Intensive Care Med Exp*, 7(1), 64.
29. Król, M., Kepinska, M. (2020). Human Nitric Oxide Synthase—Its Functions, Polymorphisms, and Inhibitors in the Context of Inflammation, Diabetes and Cardiovascular Diseases. *Int J Mol Sci*, 22(1), 56.
30. Zhou, L., Zhu, D.Y. (2009). Neuronal nitric oxide synthase: Structure, subcellular localization, regulation, and clinical implications. *Nitric Oxide*, 20(4), 223-30.
31. Yuyun, M.F., Ng, L.L., Ng, G.A. (2018). Endothelial dysfunction, endothelial nitric oxide bioavailability, tetrahydrobiopterin, and 5-methyltetrahydrofolate in cardiovascular disease. Where are we with therapy? *Microvasc Res*, 119, 7-12.

32. Cinelli, M.A., Do, H.T., Miley, G.P., Silverman, R.B. (2020). Inducible nitric oxide synthase: Regulation, structure, and inhibition. *Med Res Rev*, 40(1), 158–89.
33. Hu, S., Pi, Q., Xu, X., Yan, J., Guo, Y., Tan, W., et al. (2021). Disrupted eNOS activity and expression account for vasodilator dysfunction in different stage of sepsis. *Life Sci*, 264, 118606.
34. Hu, S., Pi, Q., Luo, M., Cheng, Z., Liang, X., Luo, S., et al. (2021). Contribution of the NLRP3/IL-1 β axis to impaired vasodilation in sepsis through facilitation of eNOS proteolysis and the protective role of melatonin. *Int Immunopharmacol*, 93, 107388.
35. Tenopoulou, M., Doulias, P.T. (2020). Endothelial nitric oxide synthase-derived nitric oxide in the regulation of metabolism. *F1000Res*, 9, 1190.
36. Wei, J.X., Jiang, H.L., Chen, X.H. (2023). Endothelial cell metabolism in sepsis. *World J Emerg Med*, 14(1), 10.
37. Luo, M., Luo, S., Cheng, Z., Yang, X., Lv, D., Li, X., et al. (2020). Tubeimoside I improves survival of mice in sepsis by inhibiting inducible nitric oxide synthase expression. *Biomedicine & Pharmacotherapy*, 126, 110083.
38. Wilmes, V., Scheiper, S., Roehr, W., Niess, C., Kippenberger, S., Steinhorst, K., et al. (2020). Increased inducible nitric oxide synthase (iNOS) expression in human myocardial infarction. *Int J Legal Med*, 134(2), 575–81.
39. Sharawy, N., Lehmann, C. (2020). Molecular mechanisms by which iNOS uncoupling can induce cardiovascular dysfunction during sepsis: Role of posttranslational modifications (PTMs). *Life Sci*, 255, 117821.
40. Tuteja, N., Chandra, M., Tuteja, R., Misra, M.K. (2004). Nitric Oxide as a Unique Bioactive Signaling Messenger in Physiology and Pathophysiology. *J Biomed Biotechnol*, 2004(4), 227–37. Kourosh-Arami, M., Hosseini, N., Mohsenzadegan, M., Komaki, A., Joghataei, M.T. (2020). Neurophysiologic implications of neuronal nitric oxide synthase. *Rev Neurosci*, 31(6), 617–36. Winkler, M.S., Kluge, S., Holzmann, M., Moritz, E., Robbe, L., Bauer, A., ... et al. (2017). Markers of nitric oxide are associated with sepsis severity: an observational study. *CritCare*, 21(1), 189.
41. Chandra, A., Enkhbaatar, P., Nakanob, Y., Traber, L.D., Traber, D.L. (2006). SEPSIS: EMERGING ROLE OF NITRIC OXIDE AND SELECTINS. *Clinics*, 61(1), 71–76.
42. Saha, B.K., Burns, S.L. (2020). The Story of Nitric Oxide, Sepsis and Methylene Blue: A Comprehensive Pathophysiologic Review. *Am J Med Sci*, 360(4), 329–37. Ataei Atabadi, E., Golshiri, K., Jüttner, A., Krenning, G., Danser, A.H.J., Roks, A.J.M. (2020). Nitric Oxide-cGMP Signaling in Hypertension. *Hypertension*, 76(4), 1055–68.
43. Spiller, F., Oliveira Formiga, R., Fernandes da Silva Coimbra, J., Alves-Filho, J.C., Cunha, T.M., Cunha, F.Q. (2019). Targeting nitric oxide as a key modulator of sepsis, arthritis and pain. *Nitric Oxide*, 89, 32–40.
44. Serreli, G., Deiana, M. (2023). Role of Dietary Polyphenols in the Activity and Expression of Nitric Oxide Synthases: A Review. *Antioxidants*, 12(1), 147.
45. Wardi, G., Brice, J., Correia, M., Liu, D., Self, M., & Tainter, C. (2020). Demystifying Lactate in the Emergency Department. *Annals of Emergency Medicine*, 75(2), 287–298.
46. Symeonides, S., & Balk, R. A. (1999). Nitric oxide in the pathogenesis of sepsis. *Infectious Disease Clinics of North America*, 13(2), 449–463.