

# 15. Bölüm

---

## FEBRİL NÖTROPENİ

---

Sibel OYUCU ORHAN<sup>1</sup>

### Giriş

---

Febril nötropeni (FN), en iyi bilinen ve hayatı tehdit eden onkolojik acil lerden biridir. Hematolojik malignitelere bağlı kemoterapi alan hastalar, tedavi seyri boyunca %80'e kadar oranda; solid tümörlere bağlı kemoterapi alanlar ise %10-50 oranında en az bir kez FN ile komplike olmaktadır (1-3). Ateş olasılığı, nötropeninin süresi ve şiddetinin yanı sıra mutlak nötrofil sayısındaki (ANC) düşüş hızı ile artar (4). Mutlak nötrofil sayısının en düşük değeri, genellikle kemoterapinin bitiminden sonraki 7-10 gündür (5).

Sitotoksik antineoplastik tedavi alan kanser hastalarında myelopoez olumsuz olarak etkilendir ve gastrointestinal mukoza bütünlüğü bozulur. Bu hastalarda gastrointestinal sistemde kolonize olan bakteri ve/veya mantarlar, intestinal mukozal yüzeylerden transloke olarak invazif enfeksiyon için risk oluştururlar. Nötropenik hastalarda nötrofil aracılı inflamatuar cevap silik olacağından ateş enfeksiyonun ilk ve tek bulgusu olabilir (6). Nötropenik ateşin erken tanınıp empirik sistemik antibiyoterapisinin derhal başlanması, olası sepsise gidişin ve ölümün engellenmesi adına kritik önem arz etmektedir.

Kanser hastalarındaki nötropenik ateşin değerlendirilmesi ve yönetimi için uluslararası birçok rehber bulunmaktadır. Burada bahsedilecek öneriler genellikle; 2010 Infectious Diseases Society of America (IDSA), 2018 American Society of Clinical Oncology (ASCO)/IDSA ile National Comprehensive Cancer Network (NCCN) rehberleri referans alınarak yapılmıştır (5,7,8).

---

<sup>1</sup> Uzm.Dr., Bursa Uludağ Üniversitesi Hastanesi, İç Hastalıkları, Tıbbi Onkoloji,  
sibelyoyucu@yahoo.com

rik antifungal ajanlar (amfoterisin B, geniş spektrumlu azoller, ekino-kandinler) tedaviye eklenmelidir.

- E) Anti-fungal profilaksi alsın almasın, nötropenik ateşli her hastaya günlük galaktomannan antijeni bakılmalıdır.

**Cevaplar: 1.D 2.C 3.D**

## Kaynaklar

---

1. Rosenberg PS, Alter BP, Bolyard AA, et al. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. *Blood*. 2006;107(12):4628-4635. doi:10.1182/blood-2005-11-4370
2. Wisplinghoff H, Seifert H, Wenzel RP, et al. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. *Clinical Infectious Diseases*. 2003;36(9):1103-1110. doi:10.1086/374339
3. Zinner SH. Changing epidemiology of infections in patients with neutropenia and cancer: Emphasis on gram-positive and resistant bacteria. *Clinical Infectious Diseases*. 1999;29(3):490-494. doi:10.1086/598620
4. Melendez E, Harper MB. Risk of serious bacterial infection in isolated and unsuspected neutropenia. *Academic Emergency Medicine*. 2010;17(2):163-167. doi:10.1111/j.1553-2712.2009.00649.x
5. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2011;52(4). doi:10.1093/cid/cir073
6. Sickles EA, Greene WH, Wiernik PH. Clinical presentation of infection in granulocytopenic patients. *Archives of internal medicine*. 1975;135(5):715-719.
7. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical practice guideline update. *Journal of Clinical Oncology*. 2018;36(14):1443-1453. doi:10.1200/JCO.2017.77.6211
8. NCCN (2020). *Prevention and Treatment of Cancer-Related Infections*. (01.01.2021 tarihinde [https://www.nccn.org/professionals/physician\\_gls/default.aspx#infectionsadresinden](https://www.nccn.org/professionals/physician_gls/default.aspx#infectionsadresinden) ulaşılmıştır).
9. Willies GH, Woolf CJ. The site of action of corticosteroid antipyresis in the rabbit. *The Journal of Physiology*. 1980;300(1):1-6. doi:10.1113/jphysiol.1980.sp013146
10. Egi M, Morita K. Fever in non-neurological critically ill patients: A systematic review of observational studies. *Journal of Critical Care*. 2012;27(5):428-433. doi:10.1016/j.jcrc.2011.11.016
11. Safdar A, Armstrong D. Infections in patients with hematologic neoplasms and hematopoietic stem cell transplantation: Neutropenia, humoral, and splenic defects. *Clinical Infectious Diseases*. 2011;53(8):798-806. doi:10.1093/cid/cir492
12. Hübel K, Hegener K, Schnell R, et al. Suppressed neutrophil function as a risk factor for severe infection after cytotoxic chemotherapy in patients with acute nonlymphocytic leukemia. *Annals of Hematology*. 1999;78(2):73-77. doi:10.1007/s002770050475
13. Wood AJJ, Pizzo PA. Management of Fever in Patients with Cancer and Treatment-Induced Neutropenia. *New England Journal of Medicine*. 1993;328(18):1323-1332. doi:10.1056/nejm199305063281808

14. Schimpff SC, Young VM, Greene WH, et al. Origin of infection in acute nonlymphocytic leukemia. Significance of hospital acquisition of potential pathogens. *Annals of internal medicine*. 1972;77(5):707-714. doi:10.7326/0003-4819-77-5-707
15. Bodey GP. *Pseudomonas* bacteremia. Retrospective analysis of 410 episodes. *Archives of Internal Medicine*. 1985;145(9):1621-1629. doi:10.1001/archinte.145.9.1621
16. Holland T, Fowler VG, Shelburne SA. Invasive gram-positive bacterial infection in cancer patients. *Clinical Infectious Diseases*. 2014;59(Suppl 5):S331-S334. doi:10.1093/cid/ciu598
17. Sipsas NV, Bodey GP, Kontoyiannis DP. Perspectives for the management of febrile neutropenic patients with cancer in the 21st century. *Cancer*. 2005;103(6):1103-1113. doi:10.1002/cncr.20890
18. Raad I, Chaftari AM. Advances in prevention and management of central line-associated bloodstream infections in patients with cancer. *Clinical Infectious Diseases*. 2014;59:S340-S343. doi:10.1093/cid/ciu670
19. Gudiol C, Bodro M, Simonetti A, et al. Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. *Clinical Microbiology and Infection*. 2013;19(5):474-479. doi:10.1111/j.1469-0691.2012.03879.x
20. Montassier E, Batard E, Gastinne T, et al. Recent changes in bacteremia in patients with cancer: A systematic review of epidemiology and antibiotic resistance. *European Journal of Clinical Microbiology and Infectious Diseases*. 2013;32(7):841-850. doi:10.1007/s10096-013-1819-7
21. Treccarichi EM, Tumbarello M. Antimicrobial-resistant Gram-negative bacteria in febrile neutropenic patients with cancer: Current epidemiology and clinical impact. *Current Opinion in Infectious Diseases*. 2014;27(2):200-210. doi:10.1097/QCO.0000000000000038
22. Mikulska M, Viscoli C, Orasch C, et al. Aetiology and resistance in bacteraemias among adult and paediatric haematology and cancer patients. *Journal of Infection*. 2014;68(4):321-331. doi:10.1016/j.jinf.2013.12.006
23. Klastersky J, Ameye L, Maertens J, et al. Bacteraemia in febrile neutropenic cancer patients. *International Journal of Antimicrobial Agents*. 2007;30(SUPPL.1):51-59. doi:10.1016/j.ijantimicag.2007.06.012
24. Pagano L, Caira M, Nosari A, et al. Etiology of febrile episodes in patients with acute myeloid leukemia: Results from the hema e-Chart registry. *Archives of Internal Medicine*. 2011;171(16):1502-1503. doi:10.1001/archinternmed.2011.374
25. Gardner A, Mattiuzzi G, Faderl S, et al. Randomized comparison of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukemia. *Journal of Clinical Oncology*. 2008;26(35):5684-5688. doi:10.1200/JCO.2008.16.4681
26. Bow EJ, Meddings JB. Intestinal mucosal dysfunction and infection during remission-induction therapy for acute myeloid leukaemia. *Leukemia*. 2006;20(12):2087-2092. doi:10.1038/sj.leu.2404440
27. Saral R, Burns WH, Laskin OL, et al. Acyclovir Prophylaxis of Herpes-Simplex-Virus Infections. *New England Journal of Medicine*. 1981;305(2):63-67. doi:10.1056/nejm198107093050202
28. Saral R, Ambinder RF, Burns WH, et al. Acyclovir prophylaxis against herpes simplex virus infection in patients with leukemia. A randomized, double-blind, placebo-controlled study. *Ann Intern Med*. 1983 Dec;99(6):773-6. doi: 10.7326/0003-4819-99-6-773
29. Lee HS, Park JY, Shin SH, et al. Herpesviridae viral infections after chemotherapy without antiviral prophylaxis in patients with malignant lymphoma: Incidence and risk factors. *American Journal of Clinical Oncology: Cancer Clinical Trials*. 2012;35(2):146-150. doi:10.1097/COC.0.b013e318209aa41
30. Hirsch HH, Martino R, Ward KN, et al. Fourth European conference on infections in leukaemia (ECIL-4): Guidelines for diagnosis and treatment of human respiratory syncytial

- virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. *Clinical Infectious Diseases*. 2013;56(2):258-266. doi:10.1093/cid/cis844
- 31. Dignan FL, Clark A, Aitken C, et al. BCSH/BSBMT/UK clinical virology network guideline: Diagnosis and management of common respiratory viral infections in patients undergoing treatment for haematological malignancies or stem cell transplantation. *British Journal of Haematology*. 2016;173(3):380-393. doi:10.1111/bjh.14027
  - 32. Link H, Böhme A, Cornely OA, et al. Antimicrobial therapy of unexplained fever in neutropenic patients - Guidelines of the infectious diseases working party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Annals of Hematology*. 2003;82(SUPPL. 2). doi:10.1007/s00277-003-0764-4
  - 33. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American society of clinical oncology clinical practice guideline. *Journal of Clinical Oncology*. 2013;31(6):794-810. doi:10.1200/JCO.2012.45.8661
  - 34. Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Critical Care Medicine*. 2008;36(1):296-327. doi:10.1097/01.CCM.0000298158.12101.41
  - 35. Rosa RG, Goldani LZ. Cohort study of the impact of time to antibiotic administration on mortality in patients with febrile neutropenia. *Antimicrobial Agents and Chemotherapy*. 2014;58(7):3799-3803. doi:10.1128/AAC.02561-14
  - 36. 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. *Critical Care Medicine*. 2006;34(6):1589-1596. doi:10.1097/01.CCM.0000217961.75225.E9
  - 37. Ko BS, Ahn S, Lee YS, et al. Impact of time to antibiotics on outcomes of chemotherapy-induced febrile neutropenia. *Supportive Care in Cancer*. 2015;23(9):2799-2804. doi:10.1007/s00520-015-2645-5
  - 38. Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: Use of high-resolution computed tomography. *Journal of Clinical Oncology*. 1999;17(3):796-805. doi:10.1200/jco.1999.17.3.796
  - 39. Lyman GH, Lyman CH, Agboola O. Risk Models for Predicting Chemotherapy-Induced Neutropenia. *The Oncologist*. 2005;10(6):427-437. doi:10.1634/theoncologist.10-6-427
  - 40. Lyman GH, Dale DC, Friedberg J, et al. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: A nationwide study. *Journal of Clinical Oncology*. 2004;22(21):4302-4311. doi:10.1200/JCO.2004.03.213
  - 41. Schwenkglenks M, Jackisch C, Constenla M, et al. Neutropenic event risk and impaired chemotherapy delivery in six European audits of breast cancer treatment. *Supportive Care in Cancer*. 2006;14(9):901-909. doi:10.1007/s00520-006-0034-9
  - 42. Intragumtorntchai T, Sutheesophon J, Sutcharitchan P, et al. A predictive model for life-threatening neutropenia and febrile neutropenia after the first course of CHOP chemotherapy in patients with aggressive non-Hodgkin's lymphoma. *Leukemia and Lymphoma*. 2000;37(3-4):351-360. doi:10.3109/10428190009089435
  - 43. Ray-Coquard I, Borg C, Bachelot T, et al. Baseline and early lymphopenia predict for the risk of febrile neutropenia after chemotherapy. *British Journal of Cancer*. 2003;88(2):181-186. doi:10.1038/sj.bjc.6600724
  - 44. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American society of clinical oncology clinical practice guideline update. *Journal of Clinical Oncology*. 2015;33(28):3199-3212. doi:10.1200/JCO.2015.62.3488
  - 45. Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile

- neutropenia in adult patients with lymphomas and solid tumours. *European Journal of Cancer.* 2006;42(15):2433-2453. doi:10.1016/j.ejca.2006.05.002
46. Klastersky J, Paesmans M, Rubenstein EB, et al. The multinational association for supportive care in cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *Journal of Clinical Oncology.* 2000;18(16):3038-3051. doi:10.1200/JCO.2000.18.16.3038
  47. Carmona-Bayonas A, Jiménez-Fonseca P, Echaburu JV, et al. Prediction of serious complications in patients with seemingly stable febrile neutropenia: Validation of the clinical index of stable febrile neutropenia in a prospective cohort of patients from the FINITE study. *Journal of Clinical Oncology.* 2015;33(5):465-471. doi:10.1200/JCO.2014.57.2347
  48. Uys A, Rapoport BL, Anderson R. Febrile neutropenia: A prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score. *Supportive Care in Cancer.* 2004;12(8):555-560. doi:10.1007/s00520-004-0614-5
  49. Klastersky J, Paesmans M. The multinational association for supportive care in cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. *Supportive Care in Cancer.* 2013;21(5):1487-1495. doi:10.1007/s00520-013-1758-y
  50. Paesmans M, Klastersky J, Maertens J, et al. Predicting febrile neutropenic patients at low risk using the MASCC score: Does bacteremia matter? *Supportive Care in Cancer.* 2011;19(7):1001-1008. doi:10.1007/s00520-010-0925-7
  51. Rolston KVI. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. *Clinical Infectious Diseases.* 2005;40(SUPPL. 4). doi:10.1086/427331
  52. Viscoli C, Castagnola E. Planned progressive antimicrobial therapy in neutropenic patients. *British Journal of Haematology.* 1998;102(4):879-888. doi:10.1046/j.1365-2141.1998.00848.x
  53. Sepkowitz KA. Treatment of patients with hematologic neoplasm, fever, and neutropenia. *Clinical Infectious Diseases.* 2005;40(SUPPL. 4). doi:10.1086/427330
  54. Kern WV, Marchetti O, Drgona L, et al. Oral antibiotics for fever in low-risk neutropenic patients with cancer: A double-blind, randomized, multicenter trial comparing single daily moxifloxacin with twice daily ciprofloxacin plus amoxicillin/clavulanic acid combination therapy - EORTC infectious diseases group trial XV. *Journal of Clinical Oncology.* 2013;31(9):1149-1156. doi:10.1200/JCO.2012.45.8109
  55. Cornely OA, Wicke T, Seifert H, et al. Once-Daily Oral Levofloxacin Monotherapy versus Piperacillin/Tazobactam Three Times a Day: A Randomized Controlled Multicenter Trial in Patients with Febrile Neutropenia. *International Journal of Hematology.* 2004;79(1):74-78. doi:10.1007/BF02983537
  56. de Naurois J, Novitzky-Basso I, Gill MJ, et al. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Annals of Oncology.* 2010;21(SUPPL. 5). doi:10.1093/annonc/mdq196
  57. Freifeld AG, Sepkowitz KA. No place like home? Outpatient management of patients with febrile neutropenia and low risk. *Journal of Clinical Oncology.* 2011;29(30):3952-3954. doi:10.1200/JCO.2011.37.5758
  58. Wingard JR, Eldjerou L, Leather H. Use of antibacterial prophylaxis in patients with chemotherapy-induced neutropenia. *Current Opinion in Hematology.* 2012;19(1):21-26. doi:10.1097/MOH.0b013e32834da9bf
  59. Bow EJ. Fluoroquinolones, antimicrobial resistance and neutropenic cancer patients. *Current Opinion in Infectious Diseases.* 2011;24(6):545-553. doi:10.1097/QCO.0b013e-32834cf054

60. Averbuch D, Cordonnier C, Livermore DM, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: Guidelines of the 4th European conference on Infections in Leukemia (ECIL-4, 2011). *Haematologica*. 2013;98(12):1836-1847. doi:10.3324/haematol.2013.091330
61. Kibbler CC. Empirical antifungal therapy in febrile neutropenic patients: current status. *Current topics in medical mycology*. 1997;8(1-2):5-14. Accessed January 3, 2021. <https://europepmc.org/article/med/9504062>
62. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the infectious diseases society of America. *Clinical Infectious Diseases*. 2016;63(4):e1-e60. doi:10.1093/cid/ciw326
63. Aguilar-Guisado M, Espigado I, Martín-Peña A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *The Lancet Haematology*. 2017;4(12):e573-e583. doi:10.1016/S2352-3026(17)30211-9
64. Van de Wyngaert Z, Berthon C, Debarri H, et al. Discontinuation of antimicrobial therapy in adult neutropenic haematology patients: A prospective cohort. *International Journal of Antimicrobial Agents*. 2019;53(6):781-788. doi:10.1016/j.ijantimicag.2019.02.020
65. Hanna H, Afif C, Alakech B, et al. Central Venous Catheter-Related Bacteremia Due to Gram-Negative Bacilli: Significance of Catheter Removal in Preventing Relapse. *Infection Control & Hospital Epidemiology*. 2004;25(8):646-649. doi:10.1086/502455
66. Raad I, Hanna H, Boktour M, et al. Management of central venous catheters in patients with cancer and candidemia. *Clinical Infectious Diseases*. 2004;38(8):1119-1127. doi:10.1086/382874
67. Legrand M, Max A, Peigne V, et al. Survival in neutropenic Patients with severe sepsis or septic shock. *Critical Care Medicine*. 2012;40(1):43-49. doi:10.1097/CCM.0b013e-31822b50c2