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Neutropenia: a narrative review.

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Abstract

Introduction: Neutropenia is one of the most common complications in patients receiving systemic treatment with chemotherapy; this is a heterogeneous population; therefore, its clinical presentation is non-specific, presenting asymptomatically or even showing very severe symptoms with signs of severe sepsis. Given those above, currently, the working groups need to consistently determine the different risk factors that contribute to the presentation of neutropenia to stratify the patient and thus optimally reduce complications.

Important points: This work emphasizes the analysis of risk factors, including the patient, the disease, and the treatment, according to stratification systems such as MASCC and CISNE. In addition, the clinical and microbiological foundations were evaluated to categorize the patient and include prophylactic support measures for the most frail groups, reducing the high risk of severe complications.

Conclusion: Neutropenia is an undesirable adverse event in managing oncohaematological treatment. The MASCC and CISNE risk stratification systems are valuable tools for selecting low-risk patients. However, other factors, such as the type of tumor and infection, may influence the stratification. Therefore, it is essential to manage each patient individually. The initiation of antimicrobial prophylaxis and the use of FECG can help reduce morbidity and mortality.

Keywords:
MeSH: Neutropenia, Chemotherapy-induced febrile neutropenia, Filgrastrim, Antibiotic prophylaxis.
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Introduction

Infections remain a frequent complication in the care of cancer patients, especially those who experience neutropenia during their disease.

The most frequent complication in patients with chemotherapy treatment is neutropenia. According to Ricardo Rabagliati B et al., approximately 40% of them have such a complication [1], which leads the patient to abandon treatment, delay subsequent cycles, prolong hospitalizations, and, in turn, increase morbidity and mortality [2].

Since the 1960s, neutropenia has been the main factor that predicts infection in cancer patients; therefore, facing this complication represents a challenge to reduce the risk factors that predispose it [3].

A prospective cohort study, "Patterns of chemotherapy-associated toxicity and supportive care in US oncology practice," found that 6% of adults with solid tumors treated with myelosuppressive chemotherapy presented neutropenia, one of the essential toxicities associated with treatment [4].

Freifeld et al., in their analysis, highlighted that patients with solid tumors receiving chemotherapy will have neutropenia lasting less than seven days, and only between 5% and 30% will have febrile neutropenia and clinically documented infections occur in 20% to 30% of febrile episodes; the intestinal tract, lungs, and skin are the most common sites of infection [5].

Neutropenia is considered a diagnostic and therapeutic emergency, a management that has evolved due to various recommendations from scientific societies and the results evidenced by them.

When dealing with this complication, we must focus on the three fundamental pillars: early diagnosis, priority therapy, and thorough evaluation, maintaining individualized management of this potentially serious complication for the patient's benefit [3].

This review allows us to establish simple parameters for the prophylaxis and prevention of neutropenia.

Definitions

According to the US National Comprehensive Cancer Network (NCCN), neutropenia is defined as an absolute neutrophil value (ANV) <1000 cells/microL, and severe neutropenia is generally defined as an NPV <500 cells/microL or an NPV 1000, which is expected to decrease to <500 cells/microL over the next 48 hours. The susceptibility to developing associated infection increases as the neutrophil count falls below 500 cells/microL and is higher in those with a prolonged duration greater than seven days [5].

Neutropenia can progress to febrile neutropenia (NF), so the Infectious Diseases Society of America (IDSA) defines fever as a temperature increase ≥ 38.3 °C taken orally or a temperature ≥ 38.0 °C lasting for 1 hour [6].

NF is the most frequent complication in patients, both for solid and hematological tumors; the latter being those with the most significant predisposition, increasing the morbidity and mortality rates for this cause.

Risk stratification

Neutropenia is considered a medical emergency since bacterial infections can show a sudden progression; likewise, mortality increases with each hour of delayed therapy, as in any septic patient. Thus, early recognition improves the probability of survival in patients at risk of neutropenic sepsis.

The American Society for Infectious Diseases reports that stratification is crucial to perform as a priority since it focuses on identifying risks that lead to increased morbidity. This evaluation also directs us to prioritize therapeutic management, including the need for intravenous antibiotics and prolonged hospitalizations. Based on these assessments, high-risk classifications require prolonged hospitalizations with broad-spectrum antibiotics [7]. In contrast, low-risk patients require outpatient management after observation or brief hospital admission.

At least three risk categories have been evaluated for such an assessment [8].

- Risk of developing febrile neutropenia.
- Risk of developing severe complications.
- Risk of lack of management response.

Risk of developing febrile neutropenia.

John R. Wingard, in the general description of neutropenic fever syndromes and the American Society for Infectious Diseases, determines certain factors that determine the presentation of febrile neutropenia [2]:

- Age over 65 years.
- Being a woman.
- Presence of comorbidities (chronic diseases)
- ECOG low.
- Malnutrition.

Factors determined by the disease:

- LDH increased.
- Myelopthisis.
- Advanced stages of the disease.

Factors determined by the treatment:

- Neoplasms that require the administration of intensified doses of chemotherapy.
- The nonprophylactic use of granulocyte colony stimulating factors (CSFGs).
- Use of cytotoxic regimens.

Risk of developing severe complications.

Validated scoring systems to determine the risk of severe complications include the Talcott score, Multinational Association for Supportive Care in Cancer (MASCC) score, and Clinical Stable Febrile Neutropenia (CISNE) score. Systems that assume the states of neutropenia and fever without evaluating the degree or duration.

In addition to the items categorized in these different scales, an exhaustive assessment of the risk of transmission of SARS-CoV-2 must also be carried out, predisposing the patient to severe acute respiratory syndrome secondary to the presence of this virus, which conditions complications and severe and irreversible sequelae [9].

Talcott, in his review, demonstrates four risk groups that they understand.

- Group I, patients admitted for another reason.
- Group II, patients with febrile neutropenia with already established comorbidities.
- Group III, patients only with leukemia who have not gone into remission after their treatment.
- Group IV includes the rest of the patients.

High-risk patients comprise groups I-III, and low-risk patients comprise group IV. It should be noted that these present a poor interpretation value due to the high number of hematological patients, distorting the value for solid tumors [10].

The MASCC is a scoring system that highlights various risk factors to classify severe complications, including age, disease burden, hypotension, active lung disease, type of cancer, dehydration requiring compensation, and presentation of the onset of fever [11]. This stratification has a maximum value of 26 points, with the highest value being the best prognosis; therefore, low risk is defined as a score >21 and increased risk <21, considering this group for priority

intervention and even for hospital management. In turn, the MASCC risk index can predict the probability of death, with a score <15: 29%, ≥15 but <21: 9%, ≥21: 2% [2].

The CISNE system is a clinical prediction model that predicts severe outcomes in presumed low-risk patients. The CISNE scale was validated in patients with solid tumors undergoing mild to moderate intensity chemotherapies who experience febrile neutropenia [12]. Based on your score, you are stratified as follows:

- Class I. Low risk. 0 points.
- Class II. Intermediate risk. 1 to 2 points.
- Class III High risk. ≥3 points.

In addition to the risk stratification systems described above, patient-related factors such as nutritional and psycho-emotional status should be further evaluated. Chemotherapy and dose intensity are also entirely related to the risk of presenting NF, a degree of toxicity greater than 20% in patients without treatment is considered high risk, and intermediate risk between 10 and 20% [13].

The role of antimicrobial prophylaxis

John R. Wingard M et al. revealed that during neutropenia, bacteraemia is the only sign of infection, and most of these arise from the patient's endogenous flora, with only 10 to 25% of patients identifying a specific infectious source [2].

The International Society of Immunocompromised Hosts and Eric Bow, in the description of fever syndromes due to neutropenia, made observations on bacterial infections, considering gram-negative germs as predisposing factors of severe conditions. Among the most common bacterial pathogens, Pseudomonas aeruginosa is found in particular, without underestimating gram-positive germs, including the most common Staphylococcus epidermidis, Staphylococcus aureus, and streptococci; in addition, the presence of resistant and nosocomial germs isolated in neutropenic patients with cancer [14]. Thus, the proportion of gram-positive and gram-negative bacteria as a cause of bacteremia remains at approximately 60:40% [15].

Gardner A and SYCho, HY C, in their review Opportunistic fungal infection in cancer patients, stated that fungal pathogens in neutropenia present infrequently and are rarely the cause of the first febrile episode; however, invasive fungal infections occur late as the etiologic agent of persistent or recurrent neutropenic fever [16]. Specific fungal germs are identified as causes of persistent or recurrent fever beyond the first week of neutropenia. Candida and Aspergillus represent the primary cause of invasive infections during neutropenia [17, 20].

SYCho, HY Choi. In an autopsy study of patients who died after prolonged febrile neutropenia between 1966 and 1975, 69% of patients had evidence of invasive fungal infections [21].

Given the above, many investigators have attempted to determine whether administering prophylactic antibacterial agents benefits clinical outcomes. Fluoroquinolones have been studied extensively and are preferred in patients at high risk of neutropenia and increased risk of infection.

Leibovici L et al. evaluated a 2012 meta-analysis of 109 randomized trials of neutropenic patients assessing whether the administration of prophylactic antibacterial agents provides a beneficial effect, showing that antibiotic prophylaxis was associated with a significantly lower incidence of fever and fewer clinically and microbiologically documented infections [22].

Based on the data analyzed, prophylaxis with fluoroquinolones is suggested for high-risk neutropenic patients receiving high-dose intensity chemotherapy regimens [23].
Gafter-Gvili A, in a systematic review with a meta-analysis of fluoroquinolone-based antibacterial chemoprophylaxis in neutropenic patients with hematological malignancies in the European Conference on Leukemia Infections group published between 2006 and 2014, reported fewer febrile episodes and fewer bloodstream infections but no demonstrated benefit on all-cause mortality [23].

Antibiotics with activity against gram-positive bacteria are not recommended, although they reduce fever and do not affect infection-related mortality. However, fluoroquinolone prophylaxis was associated with trends toward higher rates of colonization with resistant bacteria [5].

The role of granulocyte colony-stimulating factors (CSFs)

Bow Ed et al. emphasize that in several trials that support the use of FECG in the context of dose-dense chemotherapy for solid tumors such as hematological tumors, the benefit is significant in all indications since it decreases the incidence and duration of severe neutropenia and the time until NPV recovery [15].

Evidence suggests that FECG should be administered 1 to 3 days after chemotherapy, resulting in a lower risk of infection, significantly reducing infection-related events and antibiotic use [19].

The prophylactic use of FECG to reduce the risk of neutropenia is indicated when the risk is approximately >20%. Primary prophylaxis for preventing febrile neutropenia is recommended in high-risk patients based on age, medical history, disease characteristics, and toxicity of the chemotherapy regimen [20, 24].

Conclusions

Neutropenia has been considered an undesirable adverse event in managing oncohaematological treatment. Providing effective clinical management is part of the task; however, measures to reduce events become a challenge, so categorizing the patient according to risk stratification is essential.

Although there are two prognostic systems studied, MASCC and CISNE, the sensitivity was much higher than the specificity in both scales, and the two coincide in a high negative predictive value, so it is considered a valuable tool for selecting low-risk patients; instead, other factors not included in these scales, such as the type of tumor and the type of infection, could interfere with the stratification; therefore, we must consider that the patient must be managed individually, always considering their quality of life and psycho-emotional factors that contribute to complications. In addition, the primary objective should be to reduce morbidity and mortality, so that the initiation of antimicrobial prophylaxis should be highly effective for patients receiving dose escalation therapy; however, the risk of the appearance of resistant organisms must be considered as a factor that affects the choice of empirical medicine. FECG is recommended in high-risk patients who receive treatments with a greater risk of myeloid toxicity by 20% since it reduces the severity of neutropenia and its recovery period.

Abbreviations

ASCO: American Society of Clinical Oncology.
CISNE: Clinical Index of Stable Febrile Neutropenia.
GCGF: granulocyte colony-stimulating factor.
IDSA: Infectious Diseases Society of America.
LDH: lactate dehydrogenase.
MASCC: Multinational Association for Supportive Care in Cancer.
NCCN: United States National Comprehensive Cancer Network.
NF: febrile neutropenia.
AVN: absolute value of neutrophils

Administrative information

Additional Files

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Conflicts of interest

The author declares that they have no conflicts of competence or interest.

References

1. Rabagliati R, Bertín P, Cerón I, Rojas H, Domínguez I, Vera Á, et al. Epidemiology of febrile neutropenia in adult patients with acute leukemia and lymphoma: Cohort study in public and private hospitals in Santiago, Chile. Rev. Chil . infectol . 2014;31(6):721-728. doi: 10.4067/S0716-10182014000600013.
2. Wingard J. Risk assessment of adults with chemotherapy-induced neutropenia. UpToDate 2022:2(19):0-1. mascc.
3. Alcarraz C, Gil-Olivares F, Banda-Flores Claudia, Rabanal-Carretero Connie, Seas-Ramos Carlos, Ochoa-Woodell Theresa et al. Multidisciplinary Management of Febrile Neutropenia: Institutional Consensus. Lima Peru. Rev. Body Med. HNAAA 2021;14(2):236-241. doi: Alcarraz/UTF-8
4. Culakova E, Thota R, Poniewierski MS, Kuderer NM, Wogu AF, Dale DC, Crawford J, Lyman GH. Patterns of chemotherapy-associated toxicity and supportive care in US oncology practice: a nationwide prospective cohort study. Cancer Med. 2014 Apr;3(2):434-44. doi: 10.1002/cam4.200. Epub 2014 Feb 17. PMID: 24706592; PMCID: PMC3987093.
5. Thompson JA, Schneider BJ, Brahmer J, Achufusi A, Armand P, Berkenstock MK, et al. Management of Immunotherapy-Related Toxicities, Version 1.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Buy canc netw. 2022 Apr;20(4):387-405. doi: 10.6004/jnccn.2022.0020. PMID: 35390769.
6. Flowers CR, Seidenfeld J, Bow EJ, Karten C, Gleason C, Hawley DK, Kuderer NM, Langston AA, Marr KA, Rolston KV, Ramsey SD. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2013 Feb 20;31(6):794-810. doi: 10.1200/JCO.2012.45.8661 Epub 2013 Jan 14. PMID: 23319691.
7. Taplitz RA, Kennedy EB, Flowers CR. 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 Summary. J Oncol Pract. 2018 Apr;14(4):250-255. doi: 10.1200/JOP.18.00016. Epub 2018 Mar 8. PMID: 29517953.
8. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. Oncologist. 2005 Jun-Jul;10(6):427-37. doi: 10.1634/theoncologist.10-6-427. PMID: 15967836.
9. Cooksley T, Font C, Scotte F, Escalante C, Johnson L, Anderson R, Rapoport B. Emerging challenges in the evaluation of fever in cancer patients at risk of febrile neutropenia in the era of COVID-19: a MASCC position paper. Support Care Cancer. 2021 Feb;29(2):1129-1138. doi: 10.1007/s00520-020-05906-y. Epub 2020 Nov 23. PMID: 33230644; PMCID: PMC7682766.
10. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. J Clin Oncol. 1992 Feb;10(2):316-22. doi: 10.1200/JCO.1992.10.2.316. PMID: 1732432.
11. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, Gallagher J, Herrstedt J, Rapoport B, Rolston K, Talcott J. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol. 2000 Aug;18(16):3038-51. doi: 10.1200/JCO.2000.18.16.3038. PMID: 10944139.
12. Carmona-Bayonas A, Jiménez-Fonseca P, Virizuela Echaburu J, Antonio M, Font C, Biosca M, 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. J Clin Oncol. 2015 Feb 10;33(5):465-71. doi: 10.1200/JCO.2014.57.2347. Epub 2015 Jan 5. PMID: 25559804.
13. Rivas J. Febrile neutropenia: the hematologist's point of view. GAMO 2016;15(4):212-221. 2016/15_4

14. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011 Feb 15;52(4):e56-93. doi: 10.1093/cid/cir073. PMID: 21258094.

15. Wingard J, Bow E, Hall K, Bond S. Overview of neutropenic fever syndromes. UpToDate 2023:5(2):0-1. update.
16. Frater JL. How I investigate neutropenia. Int J Lab Hematol. 2020 Jun;42 Suppl 1:121-132. doi: 10.1111/ijlh.13210. PMID: 32543073.
17. Gardner A, Mattiuzzi G, Faderl S, Borthakur G, Garcia- Manero G, Pierce S, Brandt M, Estey E. Randomized comparison of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukemia. J Clin Oncol. 2008 Dec 10;26(35):5684-8. doi: 10.1200/JCO.2008.16.4681. Epub 2008 Oct 27. PMID: 18955453; PMCID: PMC4879706.

18. Wingard J, Bow E, Hall K, Bond S. Prophylaxis of infection during chemotherapy-induced neutropenia in high risk adults. UpToDate 2023:6(22):0-1. update.
19. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO; American Society of Clinical Oncology. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015 Oct 1;33(28):3199-212. doi: 10.1200/JCO.2015.62.3488. Epub 2015 Jul 13. PMID: 26169616.

20. Dale DC, Crawford J, Klippel Z, Reiner M, Osslund T, Fan E, Morrow PK, Allcott K, Lyman GH. A systematic literature review of the efficacy, effectiveness, and safety of filgrastim. Support Care Cancer. 2018 Jan;26(1):7-20. doi: 10.1007/s00520-017-3854-x. Epub 2017 Sep 22. PMID: 28939926; PMCID: PMC5827957.

21. Cho SY, Choi HY. Opportunistic fungal infection among cancer patients. A ten-year autopsy study. Am J Clin Pathol. 1979 Oct;72(4):617-21. doi: 10.1093/ ajcp /72.4.617. PMID: 495566.

22. Leibovici L, Paul M, Cullen M, Bucaneve G, Gafter-Gvili A, Fraser A, Kern WV. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer. 2006 Oct 15;107(8):1743-51. doi: 10.1002/cncr.22205. PMID: 16977651.

23. Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, van de Wetering MD, Kremer LC, Leibovici L. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev. 2012 Jan 18;1(1): CD004386. doi: 10.1002/14651858.CD004386.pub3. PMID: 22258955; PMCID: PMC4170789.

24. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis. 2011 Feb 15;52(4):e 56-93. doi: 10.1093/ cid /cir073 . PMID: 21258094.