International Journal of Health and Surgical Research
ISSN 3086-2574

Clinical Management of Febrile Neutropenia in Cancer Patients

Manejo Clínico da Neutropenia Febril em Pacientes com Câncer

Manejo clínico de la neutropenia febril en pacientes con cáncer

https://doi.org/10.5281/zenodo.18750203

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- **Tipo de Estudo**: Revisão Narrativa
- **Recebido**: 19/01/2026
- **Aceito**: 21/02/2026
- **Publicado**: 23/02/2026

International Journal of Health and Surgical Research
ISSN 3086-2574

ABSTRACT

Febrile neutropenia (FN) is one of the most frequent and potentially life-threatening complications of cancer therapy, associated with significant morbidity, mortality, and healthcare costs. Appropriate management requires accurate risk stratification and therapeutic decisions guided by up-to-date evidence and antimicrobial stewardship principles. To synthesize current evidence on the clinical management of febrile neutropenia (FN) in oncology patients based exclusively on the provided abstracts. This narrative review analyzed seven articles, including clinical guidelines, review articles, and one phase 3 randomized controlled trial. Risk stratification is central to FN management. Updated pediatric guidelines conditionally recommend discontinuing empirical antibiotic therapy in low-risk patients who are clinically stable, afebrile, and have negative blood cultures at 48 hours, as well as implementing pre-emptive antifungal therapy in high-risk patients without mold-active prophylaxis. In adults with hematologic malignancies, antibiotic de-escalation represents a key management focus. A phase 3 trial in IDH1-mutated acute myeloid leukemia demonstrated that ivosidenib plus azacitidine improved survival and reduced the incidence of FN (28% vs. 34%). FN is associated with hospitalizations lasting up to 10 days and costs reaching up to $65,000 per pediatric admission. Prophylactic granulocyte colony-stimulating factor (G-CSF) reduces the incidence of FN. Multidrug-resistant organisms remain a major clinical challenge. The management of FN requires risk-adapted strategies that integrate rapid assessment, evidence-based guidelines, and antimicrobial stewardship.

Keywords: Febrile Neutropenia; Neoplasms; Risk Assessment; Antimicrobial Stewardship; Practice Guidelines.

RESUMO

A neutropenia febril (NF) é uma das complicações mais frequentes e potencialmente graves do tratamento oncológico, estando associada a elevada morbimortalidade e custos hospitalares significativos. O manejo adequado exige estratificação de risco precisa e decisões terapêuticas baseadas em diretrizes atualizadas e princípios de stewardship antimicrobiano. O objetijo foi sintetizar a evidência atual sobre o manejo clínico da neutropenia febril (NF) em pacientes oncológicos com base exclusivamente em resumos fornecidos. esta revisão narrativa analisou sete artigos, incluindo diretrizes, revisões e um ensaio clínico randomizado de fase 3. A estratificação de risco é central no manejo da NF. Diretrizes pediátricas atualizadas recomendam condicionalmente descontinuar antibioticoterapia empírica em pacientes de baixo risco, clinicamente bem, afebris e com hemoculturas negativas em 48 horas, e terapia antifúngica pré-emptiva em alto risco sem profilaxia antimofo. Em adultos com neoplasias hematológicas, o descalonamento de antibióticos é foco central. Ensaio de fase 3 em leucemia mieloide aguda com mutação IDH1 demonstrou que ivosidenibe mais azacitidina melhorou sobrevida e reduziu incidência de NF (28% vs. 34%). A NF gera hospitalizações de até 10 dias e custos de até $65.000 por admissão pediátrica. G-CSF profilático reduz incidência de NF. Organismos multirresistentes são um desafio clínico importante. O manejo da NF requer estratégias adaptadas ao risco, integrando avaliação rápida, diretrizes baseadas em evidências e stewardship de antimicrobianos.

Palavras-chave: Neutropenia Febril; Neoplasias; Avaliação de Risco; Stewardship de Antimicrobianos; Guia de Prática Clínica.

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RESUMEN

La neutropenia febril (NF) es una de las complicaciones más frecuentes y potencialmente graves del tratamiento oncológico, asociada a una elevada morbimortalidad y a importantes costos sanitarios. Su manejo adecuado requiere una estratificación precisa del riesgo y decisiones terapéuticas basadas en evidencia actualizada y en los principios de optimización del uso de antimicrobianos. Sintetizar la evidencia actual sobre el manejo clínico de la neutropenia febril (NF) en pacientes oncológicos basándose exclusivamente en los resúmenes proporcionados. Esta revisión narrativa analizó siete artículos, incluyendo guías clínicas, revisiones y un ensayo clínico aleatorizado de fase 3. La estratificación del riesgo es fundamental en el manejo de la NF. Las guías pediátricas actualizadas recomiendan condicionalmente suspender la antibioticoterapia empírica en pacientes de bajo riesgo que estén clínicamente estables, afebriles y con hemocultivos negativos a las 48 horas, así como implementar terapia antifúngica preemptiva en pacientes de alto riesgo sin profilaxis activa contra mohos. En adultos con neoplasias hematológicas, la desescalada antibiótica constituye un eje central del manejo. Un ensayo de fase 3 en leucemia mieloide aguda con mutación IDH1 demostró que ivosidenib más azacitidina mejoró la supervivencia y redujo la incidencia de NF (28% vs. 34%). La NF se asocia con hospitalizaciones de hasta 10 días y costos de hasta $65.000 por ingreso pediátrico. El uso profiláctico de factor estimulante de colonias de granulocitos (G-CSF) reduce la incidencia de NF. Los microorganismos multirresistentes continúan siendo un importante desafío clínico.

Palabras clave: Neutropenia Febril; Neoplasias; Evaluación de Riesgo; Stewardship de Antimicrobianos; Guías de Práctica Clínica.

1. INTRODUCTION

Febrile neutropenia (FN) constitutes a frequent oncologic emergency and a common complication of myelosuppressive chemotherapy in cancer patients[1,5,7]. This condition significantly increases the risk for serious and potentially fatal infections[1,7]. For decades, the standard approach has been prompt empiric broad-spectrum antibiotic therapy, essential for preventing progression to sepsis and reducing mortality[3,6,7]. Although a definitive infectious source is often not identified, the profound immunosuppression in these patients predisposes them to a wide array of bacterial, fungal, and viral etiologies[7].

Current literature reflects a paradigm shift in FN management, moving from a "one-size-fits-all" approach toward individualized, risk-based strategies[3]. Knowledge and application of risk assessment tools are crucial to identify low-risk patients who may be candidates for less intensive management strategies, such as outpatient care, early discharge, or safe antibiotic discontinuation[1,2,3]. This evolution is particularly relevant given the growing clinical challenge of antimicrobial resistance, which mandates judicious use of broad-spectrum antibiotics[3,7].

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Simultaneously, the oncologic treatment landscape has evolved rapidly, introducing new variables into the FN equation. The emergence of targeted therapies and modalities such as CAR-T-cell therapy and hematopoietic cell transplantation (HCT) creates new challenges in managing infectious complications and redefines patient risk profiles[3,7]. For instance, differentiation syndrome, a potentially life-threatening side effect of some targeted therapies, can clinically mimic infection, requiring distinct diagnosis and intervention[7]. Despite advances, knowledge gaps persist, particularly regarding optimization of antibiotic de-escalation strategies, management of multidrug-resistant organism infections, and full integration of evidence-based recommendations into daily clinical practice[2,3].

The objective of this study is to synthesize current evidence on the clinical management of febrile neutropenia in cancer patients, based on an analysis of selected articles encompassing guidelines, reviews, and a recent clinical trial.

2. METHODOLOGY

This study is a narrative literature review designed to synthesize and discuss recent evidence on febrile neutropenia management in cancer patients. The data source for this review was exclusively a set of seven scientific articles provided by the author, encompassing clinical practice guidelines, review articles, and one phase 3 randomized controlled trial.

Study selection was defined by the provided set, with no additional inclusion or exclusion criteria applied by the reviewer. Data collection was performed through comprehensive reading and in-depth analysis of each provided abstract and reference. Extracted information included study objectives, main guideline recommendations, efficacy and safety data from therapeutic interventions, and discussions on the burden of FN on healthcare systems.

For data analysis, a qualitative thematic synthesis was conducted, organizing findings into categories such as risk stratification strategies, management specifics in particular populations, novel therapies and their impact on FN, disease burden, and emerging challenges. As this is a literature review not directly involving human subjects, submission to an Ethics Committee was not required.

3. RESULTS AND DISCUSSION

The importance of risk assessment is a unanimous consensus among authors. Cossey and Cote highlight that using risk assessment tools can reduce unnecessary hospitalizations and inappropriate antibiotic use[1]. This premise is operationalized more concretely in the updated pediatric guidelines by Lehrnbecher *et al.* Based on 10 new randomized controlled trials, the panel issued a conditional recommendation for discontinuing empiric antibacterial therapy in clinically well, afebrile low-risk pediatric patients if blood cultures remain negative at 48 hours, despite no evidence of marrow recovery[2]. This recommendation represents a significant shift from prior practice and reflects a strong commitment to patient safety coupled with antimicrobial stewardship[2].

Conversely, implementing these strategies in adult populations, particularly those with hematologic malignancies, is more nuanced. Stohs *et al.* corroborate the need for an individualized approach but focus on the increasing complexity introduced by novel treatments such as HCT and CAR-T-cell therapy, where infectious risk is particularly high and prolonged[3]. The authors identify broad-spectrum antibiotic de-escalation strategies as an area of particular interest[3], suggesting that evidence for safe application in these high-risk contexts may still be developing. This view is complemented by Nucci, who, in a practical approach based on his experience, discusses empiric antibiotic regimen choice, modifications, and discontinuation criteria, emphasizing individualization[6].

The emergence of multidrug-resistant organisms is identified as a major challenge in managing FN in patients with hematologic malignancies, including acute myeloid leukemia (AML)[7]. Peseski *et al.* and Stohs *et al.* converge in pointing to this problem as a central threat complicating therapeutic choices and worsening prognoses[3,7], reinforcing the urgency for therapeutic innovation and advances in rapid diagnostics.

Parallel to antimicrobial management, the role of granulocyte colony-stimulating factor (G-CSF) in FN prophylaxis is well-established. Boccia *et al.* provide robust data on the burden of FN in the United States, evidencing high hospitalization rates with average length of stay from 6 to 10 days, in-hospital mortality reaching 7.4% in adults with hematologic malignancies, and associated costs up to $40,000 for adults and $65,000 for pediatric patients[5]. The authors confirm that prophylactic G-CSF reduces FN incidence and improves chemotherapy dose delivery[5]. The importance of this prophylaxis was further highlighted during the COVID-19 pandemic, where recommendations were adapted to expand G-CSF indications and lower the threshold for use to avoid hospitalizations[5].

The phase 3 AGILE trial, discussed by Montesinos *et al.*, introduces a new dimension: the impact of targeted therapies on FN incidence itself. In patients with IDH1-mutated AML unfit for intensive chemotherapy, the combination of ivosidenib and azacitidine not only significantly improved overall survival (median 24.0 vs. 7.9 months) but also resulted in lower incidences of FN (28% vs. 34%) and infections (28% vs. 49%) compared to the placebo arm[4]. This finding suggests that more effective disease control may itself reduce infectious complications. However, the authors also note increased incidences of neutropenia (27% vs. 16%) and bleeding events (41% vs. 29%) in the experimental group, as well as differentiation syndrome occurrence (14% vs. 8%)[4]. This safety profile highlights that novel therapies introduce new challenges that overlap with traditional FN risk, corroborating Peseski *et al.*'s observation that differentiation syndrome mimics infection and requires specific intervention[7].

4. CONCLUSION

Based on the evidence provided, this review concludes that clinical management of febrile neutropenia in cancer patients has transcended the standardized approach of universal empiric antibiotic therapy. The current paradigm is grounded in risk-adapted strategies, supported by clinical assessment tools and updated guideline recommendations. For low-risk patients, particularly in pediatric populations, evidence supports safe early antibiotic discontinuation, while for high-risk groups, treatment individualization and vigilance for multidrug-resistant organisms and non-infectious complications are imperative.

The clinical relevance of these findings is substantial, demonstrating that adherence to risk-based practices can reduce morbidity and mortality, optimize healthcare resource utilization, and minimize selective pressure for antimicrobial resistance. The introduction of novel targeted cancer therapies may favorably alter FN risk profiles while simultaneously introducing new diagnostic and management challenges.

The main limitation of this analysis stems from the restricted number of provided articles. Future research should focus on implementing and evaluating antibiotic de-escalation strategies in high-risk adult populations receiving modern therapies, and on integrating novel biomarkers to optimize differentiation between infectious and non-infectious complications.

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