ORIGINAL ARTICLE

INFECTION AND ASSOCIATED FACTORS IN CHILDREN AND ADOLESCENTS UNDERGOING ANTINEOPLASTIC CHEMOTHERAPY

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Highlights:

1. The prevalence of infection during the first cycle of chemotherapy treatment in children and adolescents with cancer is 47.5%.
2. The risk factors associated with infection were the use of invasive ventilation, non-invasive ventilation and use of corticosteroids.
3. The signs and symptoms associated with infection were diarrhea, adventitious sounds, dyspnea, headache, mental and behavioral alterations, fever, tachypnea, hepatomegaly and splenomegaly.

PRE-PROOF

(as accepted)

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ABSTRACT

Objective: To evaluate the infection prevalence in children and adolescents with cancer undergoing chemotherapy and identify the associated factors. **Methods:** This cross-sectional study reviewed 59 medical records of children and adolescents with cancer receiving chemotherapy in the pediatric oncology ward at a referral center in Campina Grande, Paraíba. We conducted descriptive and multivariate analyses using Poisson regression. **Results:** The study identified a 47.5% infection prevalence during the first cycle of chemotherapy in children and adolescents with cancer. Significant risk factors for infection included invasive ventilation, non-invasive ventilation, and corticosteroid use. Significant symptoms and signs included diarrhea, adventitious sounds, dyspnea, headache, altered mental and behavioral states, fever, tachypnea, hepatomegaly, and splenomegaly. **Conclusion:** We found a high infection prevalence during the first cycle of chemotherapy. This complication can delay cancer treatment, promote tumor growth, and reduce the effectiveness of the therapy used.

Keywords: Infections; Neoplasms; Child Health; Adolescent Health

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INTRODUCTION

In pediatric oncology, infections represent a complication with high morbidity and mortality rates. Infections remain a significant concern during chemotherapy, despite advances in prevention and treatment that have improved survival rates. These infectious complications can cause delays in chemotherapy cycles, emergency surgeries, and the use of invasive devices.[1,2]

Currently, cancer is classified as the leading cause of death and a major obstacle to life expectancy worldwide.[3] This comorbidity in children and adolescents represents a complex challenge that significantly impacts the lives of the affected individuals and family dynamics. These ramifications include financial issues, changes in family routines, distancing, and intrafamily conflicts, among other changes.[4]

Moreover, cancer presents different primary locations, histological origins, and clinical behaviors.[5] The neoplasm most affecting individuals under 19 is leukemia[6]. According to the National Cancer Institute (INCA),[7] neoplasms are the second leading cause of death in the population, accounting for 16.6% of total deaths in the country. Researchers expected Brazil to have 4,310 new cases in males and 4,150 in females each year from 2020 to 2022.

The treatment of childhood cancer is structured into three modalities, which are *surgery*, *antineoplastic chemotherapy*, and *radiotherapy*, which can be combined or individualized, considering the disease staging, diagnosis, specific tumor characteristics, and the presence or absence of metastases.[5] Antineoplastic chemotherapy is the most used therapy in pediatric patients and is associated with multiple side effects, such as hair loss, weight loss, anorexia, nausea, and infections.[6,8]

Infections are a severe consequence of chemotherapy due to immunosuppression. A study conducted in Brazil found that infections were the second most common oncological emergencies, second only to febrile neutropenia.[9] However, studies on this problem are scarce in Brazil, and more clarification on associated factors is needed. Therefore, clinical studies on this topic are necessary, emphasizing the importance of summarizing frequent Nursing diagnoses in patients undergoing chemotherapy to guide nurses' clinical reasoning/diagnosis and support the implementation of an individualized Nursing process that is subject to early evaluation and intervention.

Considering this premise, the question arises: "What is the prevalence of the first infection episode after initiating chemotherapy and the associated factors in children and adolescents with cancer?". Furthermore, this article aims to evaluate the infection prevalence in children and adolescents with cancer undergoing chemotherapy and the associated factors, with an emphasis on the nursing team.

MATERIALS AND METHODS

This is a cross-sectional documentary study with a quantitative approach conducted with the medical records of children and adolescents admitted for antineoplastic treatment in the pediatric oncology ward of a referral center in Campina Grande, state of Paraíba. The manuscript's construction followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), meeting scientific requirements for observational studies.

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The sample size was defined based on a simple random sample statistical test for a finite population of 462 patients, estimating an infection proportion of 43% in the population of interest.[10] Considering a population of 462 children and adolescents diagnosed with malignant neoplasms registered between 2008 and February 2021 in the pediatric oncology sector of the referral hospital in Campina Grande, with a 95% confidence interval and a 0.05 margin of error, we determined a minimum estimate of 55,7 patients.

Data collection began in March 2021 and extended until July 2021. We gradually selected the medical records, and all were subjected to inclusion and exclusion criteria. The total number of records collected was 256; of these, we excluded 139 because they were incomplete, 38 were unrelated to neoplasms, 12 had benign neoplasm diagnoses, four were adult records, two were transferred for treatment, and two were duplicates. Ultimately, 59 records remained.

We collected data using a standardized adapted form with sociodemographic, clinical, and laboratory questions.[11,12] The form had seven sections containing information on gender, age, place of origin, type of cancer, infection risk factors, treatment used, signs and symptoms, infection foci, and laboratory tests, concluding with infection identification. We retrieved the patient records meeting the criteria from the archives and thoroughly read them to collect information. Thus, we collected clinical data relevant to the first cycle of chemotherapy.

The dependent variable considered was the diagnosis of infection, based on the presence of a medical diagnosis in the record. We identified associated factors in medical and nursing progress notes, nursing diagnoses, and laboratory and imaging test results. We tracked records from admission through the end of the first chemotherapy cycle.

We entered the collected data twice into Excel and exported it to the statistical software STATA version 15. We performed descriptive analysis using simple frequency, central tendency measures (mean and median), and variability measures (standard deviation and percentiles). The infection prevalence rate was calculated by dividing the number of existing cases by the at-risk population, multiplied by 100.

We used Poisson regression due to the high prevalence of the outcome to propose the predictive model and evaluate factors associated with infection. Prevalence Ratios (PR) with 95% Confidence Intervals (95% CI) were estimated. A bivariate analysis was conducted, selecting independent variables with a p-value less than 20% ($p < 0.20$) for multivariate analysis using the multiple regression model inserted by the Backward method. We removed variables with significance levels above 5% ($p > 0.05$) from the model. This procedure was repeated until

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all remaining variables had statistical significance ($p < 0.05$). The model's fit quality was assessed using Deviance statistics.

The study followed the principles of Resolution 466/12 of the Brazilian National Health Council. The Research Ethics Committee of the Federal University of Campina Grande approved it, and data collection began after this approval under Opinion No. 4.5333.765. Upon approval, we collected data from the medical records of patients treated at the service.

RESULTS

We evaluated 59 medical records of children and adolescents undergoing chemotherapy, with the majority being male (54.2%). The mean age was 7.3 years (SD = 5.2), with a minimum age of 0.8 years and a maximum of 17 years. Most patients were from Campina Grande (50.8%) (Table 1).

In this study, 28 patients presented infections at the beginning of chemotherapy, with an overall prevalence of 47.5%. When stratifying the types of infection, all patients diagnosed with an infection presented with febrile neutropenia. Additionally, 23.7% had bacterial infections, 8.5% had fungal infections, and 6.8% had viral infections.

Table 1 – Sociodemographic Data, Underlying Disease, Risk Factors, Treatment Used, and Infection Focus (n=59). Campina Grande/Paraíba, Brazil, 2023

Variable	N	%
Age		
Mean ± standard deviation	7.31±5.24	
Median (minimum-maximum)	5.65 (0.8-17)	
Sex		
Male	32	54.2
Female	27	45.8
Place of Birth		
Campina Grande	30	50.8
Other municipalities	28	47.5
Ignored	1	1.7
Underlying Disease		
Leukemia	35	59.3
Lymphoma	10	16.9
Soft tissue tumors	4	6.8
Wilms tumor	3	5.1
Neuroblastoma	2	3.4
Bone tumors	2	3.4
Medulloblastoma	1	1.7
Esophageal adenocarcinoma	1	1.7

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Other malignant neoplasms	1	1.7
Treatment Used		
Chemotherapy	48	81.4
Chemotherapy + Radiotherapy	5	8.5
Chemotherapy + Surgery	4	6.8
Chemotherapy + Radiotherapy + Surgery	2	3.4
Infection Focus		
Not identified	14	23.7
Soft tissues	10	16.9
Pulmonary	9	15.3
Bloodstream	7	11.9
Catheter	4	6.8
Urinary	3	5.1
Upper respiratory	1	1.7

Source: The author.

Regarding laboratory tests, blood cultures were positive in 15.3% of the patients, identifying microorganisms such as *Klebsiella pneumoniae*, *Klebsiella spp*., *Acinetobacter baumannii*, *Acinetobacter lwoffii*, *Staphylococcus lentus*, *Escherichia coli*, and other Gram-negative bacteria. Moreover, 1.7% of patients had positive urine cultures, with *Escherichia coli* being highlighted. Stool cultures showed positivity in 5.1% of patients, identifying *Klebsiella sp.*, *Klebsiella oxytoca*, and *Klebsiella pneumoniae.*

Bivariate Data Analysis

Sex was not significantly associated with infection. However, age showed a significant association ($p < 0.05$). Among the types of cancer analyzed, we did not observe any significant association with infection (Table 2).

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Table 2 – Sociodemographic Factors and Types of Cancer Associated with Infection (n=59). Campina Grande/Paraíba, Brazil, 2023

	Infection		P-value*	PR[95% CI]
	No	Yes		
Sex				
Male	17 (54.84%)	14 (45.16%)	0.923	1.03 [0.60; 1.77]
Female	15 (53.57%)	13 (46.43%)		
Age				
Mean ± standard deviation	8.6±5.65	5.9±4.44	**0.049**	0.94 [0.89; 0.99]
Median (min.-max.)	6.055 (0.8-17)	4.45 (0.8-16.2)		
Leukemia				
No	16 (51.61%)	15 (48.39%)	0.099	1.71 [0.90; 3.25]
Yes	8 (28.57%)	20 (71.43%)		
Lymphoma				
No	25 (80.65%)	6 (19.35%)	0. 628	0.82 [0.36; 1.85]
Yes	24 (85.71%)	4 (14.29%)		
Others				
No	21 (67.74%)	10 (32.26%)	0.164	0.53 [0.22; 1.29]
Yes	24 (85.71%)	4 (14.29%)		

* Univariate Poisson model; PR - Prevalence Ratio; 95% CI - 95% Confidence Interval
Source: The author.

Among the investigated risk factors (Table 3), we found significant associations with infection for symptoms such as a history of neutropenia, use of invasive devices, non-invasive ventilation (NIV), and corticosteroid use ($p < 0.05$).

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Table 3 – Risk Factors for Infections (n=59). Campina Grande/Paraíba, Brazil, 2023

	Infection		P-value*	PR[95% CI]
	No	Yes		
History of Neutropenia				
No	22 (70.97%)	9 (29.03%)	**0.025**	1.92 [1.08; 3.39]
Yes	11 (40.74%)	16 (59.26%)		
Port-A-Cath				
No	29 (93.55%)	2 (6.45%)	0. 659	0.69 [0.13; 3.55]
Yes	27 (96.43%)	1 (3.57%)		
Use of Catheters				
No	31 (100%)	0 (0.00%)	**0.000**	2.29 [1.69; 3.10]
Yes	24 (85.71%)	4 (14.29%)		
Invasive Ventilation				
No	31 (100%)	0 (0.00%)	**0.000**	2.19 [1.65; 2.92]
Yes	26 (92.86%)	2 (7.14%)		
NIV				
No	31 (100%)	0 (0.00%)	**0.000**	2.35 [1.72; 3.21]
Yes	23 (82.14%)	5 (17.86%)		
Parenteral Nutrition				
No	30 (96.77%)	1 (3.23%)	0.941	1.05 [0.25; 4.39]
Yes	27 (96.43%)	1 (3.57%)		
Use of Corticosteroids				
No	20 (66.67%)	10 (33.33%)	**0.006**	2.61 [1.31; 5.20]
Yes	7 (25%)	21 (75%)		

* Univariate Poisson model; PR - Prevalence Ratio; 95% CI - 95% Confidence Interval
Source: The author.

Regarding signs and symptoms, we found significant associations with infection prevalence for diarrhea, hypotension, bradycardia, cough, adventitious sounds, dyspnea, tachypnea, headache, altered mental and behavioral states, fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and mucositis ($p < 0.05$) (Table 4).

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Table 4 - Signs and Symptoms Associated with Infection (n=59). Campina Grande/Paraíba, Brazil, 2023

	Infection		P-value*	PR[95% CI]
	No	Yes		
GASTROINTESTINAL				
Abdominal Pain				
No	23 (74.19%)	8 (25.81%)	0.396	1.26 [0.73; 2.18]
Yes	18 (64.29%)	10 (35.71%)		
Diarrhea				
No	29 (93.55%)	2 (6.45%)	**0. 002**	2.07 [1.32; 3.24]
Yes	19 (67.86%)	9 (32.14%)		
Vomiting				
No	20 (64.52%)	11 (35.48%)	0.560	1.17 [0.68; 2.01]
Yes	16 (57.14%)	12 (42.86%)		
CARDIOVASCULAR				
Tachycardia				
No	28 (90.32%)	3 (9.68%)	0.148	1.51 [0.86; 2.66]
Yes	22 (78.57%)	6 (21.43%)		
Hypotension				
No	31 (100%)	0 (0.00%)	**0.000**	2.24 [1.67; 3.01]
Yes	25 (89.29%)	3 (10.71%)		
Delayed Peripheral Perfusion				
No	30 (96.77%)	1 (3.23%)	0.941	1.05 [2.54; 4.39]
Yes	27 (96.43%)	1 (3.57%)		
Bradycardia				
No	31 (100%)	0 (0.00%)	**0.000**	2.24 [1.67; 3.01]
Yes	25 (89.29%)	3 (10.71%)		
RESPIRATORY				
Cough				
No	27 (87.10%)	4 (12.90%)	**0.001**	2.28 [1.39;3.74]
Yes	14 (50.00%)	14 (50.00%)		
Adventitious Sounds				
No	30 (96.77%)	1 (3.23%)	**0.000**	2.78 [1.79; 4.33]
Yes	15 (53.57%)	13 (46.43%)		
Dyspnea				
No	30 (96.77%)	1 (3.23%)	**0.007**	1.92 [1.19; 3.09]
Yes	23 (82.14%)	5 (17.86%)		
Tachypnea				
No	30 (96.77%)	1 (3.23%)	**0.000**	2.32 [1.54; 3.50]
Yes	19 (67.86%)	9 (32.14%)		
CNS				
Headache				
No	31 (100%)	0 (0.00%)	**0.000**	2.35 [1.72; 3.21]
Yes	23 (82.14%)	5 (17.86%)		

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Altered Mental and Behavioral States				
No	31 (100%)	0 (0.00%)	**0.000**	2.24 [1.67; 3.01]
Yes	25 (89.29%)	3 (10.71%)		
OTHERS				
Fever				
No	24 (77.42%)	7 (22.58%)	**0.000**	7.03 [2.36; 20.95]
Yes	3 (10.71%)	25 (89.29%)		
Skin Rash				
No	31 (100%)	0 (0.00%)	**0.000**	2.48 [1.78; 3.45]
Yes	21 (75.00%)	7 (25.00%)		
Lymphadenopathy				
No	26 (83.87%)	5 (16.13%)	0.213	1.41 [0.82; 2.44]
Yes	20 (71.43%)	8 (28.57%)		
Hepatomegaly				
No	28 (90.32%)	3 (9.68%)	**0.001**	2.2 [1.37; 3.52]
Yes	16 (57.14%)	12 (42.86%)		
Splenomegaly				
No	28 (90.32%)	3 (9.68%)	**0.028**	1.74 [1.06; 2.87]
Yes	20 (71.43%)	8 (28.57%)		
Mucositis				
No	30 (96.77%)	1 (3.23%)	**0.000**	2.65 [1.73; 4.08]
Yes	16 (57.14%)	12 (42.86%)		

* Univariate Poisson model; PR - Prevalence Ratio; 95% CI - 95% Confidence Interval
Source: The author.

Multivariate Data Analysis

The multivariate analysis using Poisson regression identified invasive ventilation, NIV, corticosteroid use, diarrhea, adventitious sounds, dyspnea, tachypnea, headache, altered mental and behavioral states, fever, hepatomegaly, and splenomegaly as independent significant variables associated with infection ($p < 0.05$) (Table 5).

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Table 5 – Final Model of Risk Factors Associated with Infection Obtained with Poisson Regression (n=59). Campina Grande/Paraíba, Brazil, 2023

	P-value*	PR[95% CI]
Invasive Ventilation		
No	0.008	3.86 [1.42; 10.55]
Yes		
NIV		
No	0. 004	4.01 [1.57; 10.23]
Yes		
Use of Corticosteroids		
No	0.019	1.87 [1.11; 3.15]
Yes		
Diarrhea		
No	0.045	1.52 [1.01; 2.28]
Yes		
Adventitious Sounds		
No	0.005	2.71 [1.36; 5.42]
Yes		
Dyspnea		
No	0.023	2.43 [1.13; 5.23]
Yes		
Tachypnea		
No	0.035	0.48 [0.24; 0.95]
Yes		
Headache		
No	0.010	3.07 [1.31; 7.24]
Yes		
Altered Mental and Behavioral States		
No	0.004	4.23 [1.56; 11.41]
Yes		
Fever		
No	0.001	5.75 [2.11; 15.66]
Yes		
Hepatomegaly		
No	0.006	0.20 [0.65; 0.63]
Yes		
Splenomegaly		
No	0.001	0.41 [0.24; 0.70]
Yes		

PR - Prevalence Ratio; 95% CI - 95% Confidence Interval
P-value Deviance Statistics = 0.999

Source: The author.

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DISCUSSION

Infections in children and adolescents with cancer during the first cycle of chemotherapy are a severe public health issue affecting these patients' quality of life. These individuals are at high risk of severe and potentially fatal infections, particularly during the first chemotherapy cycle due to immunosuppression. The intensity of induction treatment can increase treatment duration, hospitalization costs, and risk of death, and may compromise the efficacy of antineoplastic therapy protocols.[13]

The present study estimated an infection prevalence of 47.5% during the first cycle of chemotherapy. All infection cases were associated with febrile neutropenia. These data corroborate a study conducted in Brazil, where the predominant oncological emergencies were infectious, with febrile neutropenia being the most frequent. International studies have shown that infection prevalence in children and adolescents with cancer varies between 43.4% in Mexico, 9.4% in India, and 36% in Germany and Switzerland.[11,12,14,15] This variability in prevalence percentages may be associated with the context of the country where the research was conducted, diagnostic methods, and hospital care protocols.

In the multivariate analysis, the variables identified as statistically significant ($p < 0.05$) for infection occurrence included *risk factors* such as invasive ventilation, NIV, corticosteroid use, and *signs and symptoms* such as diarrhea, adventitious sounds, dyspnea, headache, mental and behavioral alterations, fever, tachypnea, hepatomegaly, and splenomegaly.

The study results confirmed a higher frequency of infection in patients using invasive and non-invasive ventilation compared to those who did not. Mechanical ventilation use, associated with other factors such as patient age, comorbidities, indiscriminate antibiotic use, and oral and hand hygiene practices, increases the risk of ventilator-associated pneumonia, especially in immunocompromised patients.[16,17]

In addition, adventitious sounds and dyspnea were significant signs and symptoms associated with infection. These findings align with identifying infection foci, where pulmonary infection was this research's second most prevalent infection focus. A study on the profile of onco-hematological emergencies in children and adolescents also highlighted the predominance of respiratory infections, particularly types of pneumonia.[11]

Diarrhea's clinical manifestation also showed a significant association with infection due to gastrointestinal dysfunction caused by chemotherapy-induced mucositis. This condition is also associated with nausea and vomiting. Additionally, adverse disturbances in the intestinal

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microbiota can promote immunological dysregulation and increase patient mortality risk. This symptom was observed in a study with healthcare professionals who identified dietary and infectious factors as primary causes of diarrhea.[18,19]

Patients may exhibit various behaviors during chemotherapy influenced by the duration of diagnosis and treatment. Symptoms associated with mental and behavioral alterations, such as anxiety and distress, can appear shortly after diagnosis and treatment initiation and may return at the end of treatment due to fear of disease recurrence. Psychological symptoms are also associated with cancer treatment's adverse effects, such as nausea, vomiting, diarrhea, and constipation.[20]

Chemotherapy-induced immunosuppression can trigger multiple complications due to the recruitment of cells involved in the infection and the cytotoxicity of chemotherapy that directly affects the spleen and liver, organs responsible for metabolizing most drugs. These effects can be cumulative and dose-dependent or might be overlooked during clinical examination, making toxicity monitoring and timely treatment crucial to reduce mortality caused by such complications.[21]

High doses of corticosteroids used in chemotherapy can compromise patient health, leading to adverse effects like hyperglycemia, hypertension, dyslipidemia, bruising, obesity, skin lesions, mental and behavioral alterations, and immunosuppression, which directly increase infection rates. The degree of immunosuppression raises susceptibility to opportunistic infections, potentially worsened by corticosteroid use.[22]

Another common clinical manifestation in cancer patients is fever, due to immunosuppression caused by chemotherapy agents, underlying disease, and exposure to biological agents. In neutropenic patients, the magnitude of the inflammatory response mediated by neutrophils can mutate, making fever the earliest sign of infection. If the infection is not quickly diagnosed and treated, it can lead to multiple hospitalizations and potentially death.[23]

The final model obtained in this study has many implications for clinical practice. It is valuable for describing the relationship between infection and associated factors. Considering that nursing is integrated into the multidisciplinary team providing care, knowledge of the final model facilitates nursing care planning related to the educational role that the profession exercises for its subordinates, the multidisciplinary team, patients, and families. The goal is to prevent and minimize infection risks and intervene early, as this complication can delay cancer treatment, promote tumor growth, and reduce cure chances.

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Moreover, nursing is based on the Nursing Care Systematization (SAE) as a resource to develop qualified actions for patients and families. It is an exclusive nurse activity that organizes the care process, providing greater patient safety, improved care quality, and increased professional autonomy.[24]

In the study by Calegari *et al.*,[25] they identified frequent nursing diagnoses in cancer patients: ineffective protection, risk of impaired oral mucosa, risk of falls, acute pain, hyperthermia, constipation, and imbalanced nutrition: less than body requirements. These diagnoses are associated with cancer and infection-associated factors, corroborating the results identified in this study and highlighting the importance of nursing process presence from academic training to professional practice to support diagnosis development and intervention proposal and evaluation.

For future studies, due to the scarcity of national and international research on this topic, we recommend conducting national studies with prospective and multicentric design, with larger samples to confirm the results and establish their external validity according to each location's reality.

This study had limitations, such as the inability to monitor new infection cases in the same patient due to the cross-sectional design of the research. Additionally, as a documentary study, there was difficulty in following signs and symptoms until infection diagnosis because of disorganized records and insufficiently recorded information.

CONCLUSION

We found a prevalence of 47.5% of infection during the first cycle of chemotherapy in children and adolescents with cancer. The variables identified as statistically significant for infection occurrence included risk factors such as invasive ventilation, NIV, corticosteroid use, and signs and symptoms such as diarrhea, adventitious sounds, dyspnea, headache, mental and behavioral alterations, fever, tachypnea, hepatomegaly, and splenomegaly.

This study contributes to understanding the factors associated with infection in children and adolescents diagnosed with cancer undergoing chemotherapy. Early recognition of these factors through clinical and laboratory evaluation can facilitate planning and implementing evidence-based interventions focused on prevention and early treatment.

These findings highlight the need for emphasizing continuous care and evaluation by the nursing team, which has the most prolonged contact period with the patient and performs the most preventive measures. We hope these results support the planning and implementation

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of nursing actions anchored in the Nursing Care Systematization (SAE), aiming to prevent infections and consequently improve the quality of life and treatment response of patients undergoing antineoplastic therapy. Such measures should extend from academic training to professionals working directly with these patients, enabling them to plan and execute actions based on scientific evidence.

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