**ARTIGO REVISÃO**

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**Título –** Fatores de risco relacionados à infecção em pacientes pediátricos com câncer e neutropenia febril induzida por quimioterapia - uma revisão sistemática

**Título -** Factores de riesgo relacionados con la infección en pacientes pediátricos con cáncer y neutropenia febril inducida por quimioterapia: una revisión sistemática

**Title -** Risk factors related to infection in pediatric patients with cancer and febrile neutropenia induced by chemotherapy – a systematic review.

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**ABSTRACT**

**Background** - Febrile neutropenia induced by chemotherapy is the major risk factor for infection and death in cancer patients. The identification of these risk factors must take into consideration the heterogeneity of this population. **Objective** - to perform a systematic review of the studies addressing the risk factors related to infection among pediatric patients with cancer and febrile neutropenia and their epidemiological characteristics. **Contents -** The characteristics considered for selecting the articles were: population, exposition, comparison, outcome according to the acronym PECOS. The definition was as follows: P, patients under 18 years of age with febrile neutropenia induced by chemotherapy, E: presence of risk factors besides neutropenia; C no risk factors besides neutropenia; O, infection and S, original studies. The search was carried out using the PubMed, Virtual Health Library (Scielo, LILACs, and MEDLINE) and EMBASE. Sixty-three

observational studies were included, and The Critical Appraisal Skills Programme (CASP) was used to evaluate the methods and descriptions of observational studies. 46 variables with potential relationship with infection were identified. Type of cancer (44% of the studies), fever degree (30%), absolute neutrophil count (30%), platelets (30%) and C-reactive protein (30%) were the five most studied variables. **Conclusion** - This review identified current risk factors related to bacteremia in pediatric patients with cancer and febrile neutropenia.

**Keywords**: “Risk factors” “Bacteremia”, “Febrile Neutropenia”; “Child”.

## INTRODUCTION

Febrile neutropenia induced by chemotherapy is a major risk factor for infection in cancer patients [1, 2]. In clinical practice, decisions regarding the handling of infectious complications must be based on the number of circulating neutrophils. More specifically, levels of circulating neutrophils below 500 cells/mm³ indicate a severe bacterial infection [3, 4].

The identification of risk factors for severe infection and related complications must consider the heterogeneity of oncologic pediatric patients. Besides the phagocyte deficiency caused by cytotoxic agents, other factors such as alterations on the mucosal barrier, the presence of invasive devices, and defects in innate immunity caused by the underlying disease itself also contribute to the increased risk of infectious complications [4]. Patients who upon admission are identified as having a low risk of bacteremia and adverse events could receive ambulatorial treatment[5].

The Infectious Diseases Society of America provides guidelines for the risk stratification of severe infections in adult patients with febrile neutropenia [6, 7]. Although the diagnosis and treatment of children with chemotherapy-induced febrile neutropenia have improved in the last two decades, it is important to underscore that there are few validated schemes on risk stratification for the complications of febrile neutropenia in this age group [4, 8].

The aim of this work was to perform a systematic review of the studies addressing the risk factors related to infection among pediatric patients with cancer and febrile neutropenia and their epidemiological characteristics.

## METHODS

Publications were selected using the PRISMA methodology, which provides guidelines for the carrying out of meta-analysis and systematic reviews[9]. The characteristics considered for selecting the articles were: population, exposition, comparison, and outcome according to the

acronym PECOS[9,10]. The definition was as follows: P, patients under 18 years of age with chemotherapy-induced febrile neutropenia, E: presence of risk factors besides neutropenia; C no risk factors besides neutropenia; O, bacteremia and S, observational studies (cross-sectional, cohort, case-control), in addition to papers identified in other original and meta-analysis papers.

***Search strategy***

Publications were selected using the PRISMA methodology that guides practices for the performing meta-analyses and systematic reviews [9]. A systematic literature search was performed to identify relevant articles published between 2000 and 2017, not limited by language, using databases such as MedLine (Medical Literature Analysis and Retrieval System Online), LILACS (Latin America and Caribbean Literature in Health Sciences), SciELO (Scientific Electronic Library Online) and EMBASE. We used search terms from MeSH (Medical Subject Headings Section) of the National Library of Medicine ("risk"[MeSH Terms] OR "risk"[All Fields] OR "risk of"[All Fields]) AND ("bacteraemia"[All Fields] OR "bacteremia"[MeSH Terms] OR "bacteremia"[All Fields]) OR ("death"[All Fields] OR "mortality"[MeSH Terms]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) AND ("fever"[MeSH Terms] OR "fever"[All Fields]) AND ("neutropaenia"[All Fields] OR "neutropenia"[MeSH Terms] OR "neutropenia"[All Fields] OR "leukopenia"[MeSH Terms] OR "leukopenia"[All Fields]) and DeCS (Health Sciences Descriptors) from the BVS (Virtual Library in Health) portal.

***Studies selection***

**Inclusion criteria:** Published original papers evaluating risk factors for infections in patients under 18 years old with chemotherapy-induced febrile neutropenia.

**Exclusion criteria:** Papers including adult patients or patients with febrile neutropenia caused by hematopoietic stem cell transplantation.

***Data extraction and quality evaluation***

Two independent reviewers screened the titles and abstracts of the selected papers to find those that met the eligibility criteria. A third reviewer evaluated the divergences. Inclusion of each paper was determined after analyzing the type of study, population, objectives, and outcomes. **Figure 1** shows the article selection process.

The Critical Appraisal Skills Programme (CASP)[11] was used to analyze the methods and the descriptions of the observational studies. This evaluation was qualitative.

Figure 1 demonstrates in a diagram the process of selecting papers on infection in pediatric cancer patients with fever and neutropenia for this present review, elucidating the reasons why some papers did not fulfill the established criteria

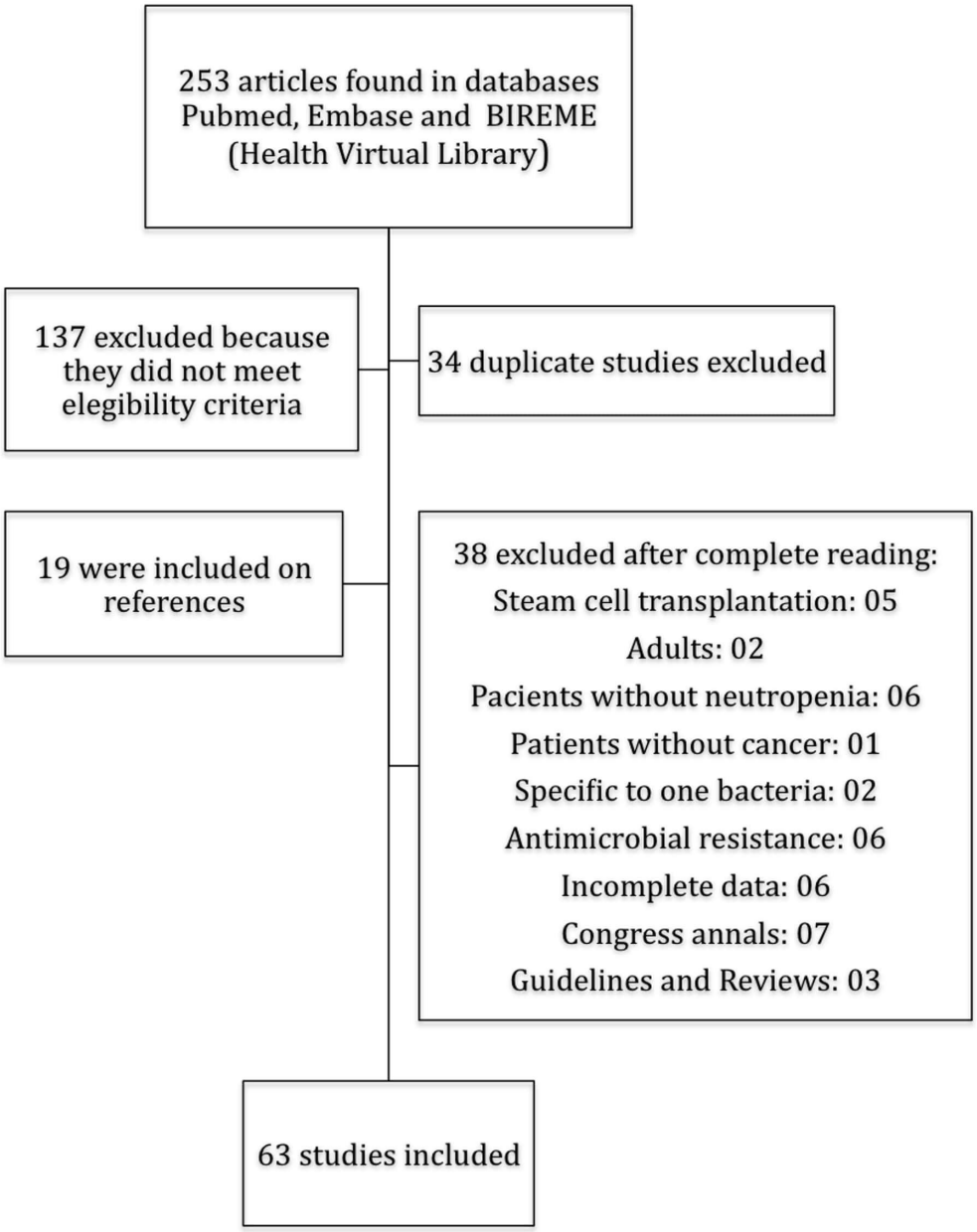
253 articles found in databases Pubmed, Embase and BIREME (Health Virtual Library)
137 excluded because they did not meet elegibility criteria
34 duplicate studies excluded
19 were included on references
38 excluded after complete reading:
Steam cell transplantation: 05
Adults: 02
Pacients without neutropenia: 06
Patients without cancer: 01
Specific to one bacteria: 02
Antimicrobial resistance: 06
Incomplete data: 06
Congress annals: 07
Guidelines and Reviews: 03
63 studies included

**Figure 1 –** Diagram of the selection of papers on infection in pediatric cancer patients with fever and neutropenia, systematic review, 2000-2017.

## RESULTS

Initially, 253 papers were selected. After analyzing the titles and abstracts, 34 papers were excluded due to duplication and 137 were excluded for not fulfilling the inclusion criteria. From the 83 remaining papers 38 were excluded, 14 of them for including adult patients, hematopoietic stem cell transplantations, or not oncological or not neutropenic patients, 7 of them for being Congress abstracts that presented only partial results, 3 for being review papers, and 8 for being studies on specific bacteria and the acquisition of resistance. Another six studies were excluded due to incomplete data (absence of information about the kind of population analyzed, the number of patients involved and the prevalence of bacteremia). The evaluation of the references in the selected papers found 19 more studies.

Papers were analyzed using the *CASP checklist,* a program for the critical evaluation of the methodology and the results of scientific papers[11]. CASP does not use a quantitative scoring system, but helps determine the most relevant, reliable, and applicable papers to the clinical practice. Through this checklist, 46% (29/63) of the included papers fulfilled all the analyzed criteria.

Sixty-three papers were evaluated and classified as observational studies, 34 being prospective and 29 retrospectives. The details of each study are presented in the Supplementary Material (Appendix 1).

### *Definition of febrile neutropenia*

Twenty percent of the papers used the most internationally used definition of neutropenia (absolute neutrophil count < 500 cells/$mm^3$ or < 1000 cells/$mm^3$ with an expected decline in 48 hours)[3, 12], but other definitions were found, such as absolute neutrophil count < 1000

cells/$mm^3$ in 10.7% of papers and < 500 cells/$mm^3$ in 50.7% of papers. A study considered neutropenia < 500 cells/$mm^3$ or < 580 cells/$mm^3$ with an expected decline in the number of neutrophils[13].

The body region used to measure temperature in the included studies varied from oral region (9%), axillary region (38.4%), auricular (1.5%) and 51.1% of the studies did not clarify in which body region was used for temperature measurement.

The medium number of febrile neutropenia episodes per study was 248.7 (variation from 26 to 1171 episodes). The smallest number of children evaluated is presented in the Hodge et al[14] study, that evaluated specific cytokines levels, normally not included in clinical protocols, like Th1 and regulatory T cells in febrile neutropenia with confirmed infection. The study found a raise in the percentage of CD25, CD127, CD8 and CD3 (p=0.005) and a reduction of Th1 cytokines (p=0.001) in patients with bacteremia compared with patients with negative cultures. The study with the largest number of episodes [5] retrospectively analyzed clinical and laboratorial characteristics registered in electronic records in a long period (5 years) and found monocytes levels > 155 to indicate a low risk of bacteremia (rate of 6.1%) with sensibility = 94%, specificity = 17% and Odds Ratio (OR) = 0.31 (95% confidence interval (CI 0.16 – 0.60) compared to others cutoff values for monocytes.

***Outcomes used in the studies***

Bacteremia rates varied from 6.4% to 61% (median 19.7%) between studies. Some studies evaluated infectious adverse events as the primary outcome and included other manifestations besides bacteremia. Ammann et al considered an adverse event as a microbiologically defined infection, radiologically confirmed pneumonia, death, necessity of ITU and life threatening complications according to the decision of the doctor in charge[15]. In a prospective study, Bothra et al considered adverse events as invasive infection (positive blood and urine culture), hemodynamic instability and death[16]. In another study, Chaudhuri et al considered septic shock, neutropenic enterocolitis, respiratory failure, disseminated intravascular coagulation and death as primary outcomes[17].

The most mentioned foci of infection were the lower respiratory tract, mucositis and urinary and gastrointestinal tracts, and the rates of neutropenia without focus of infection varied from 8% to 94% (median 53.7%). The majority of the studies did not report criteria for focus of infection definition. Fifty-seven percent of the studies found a larger prevalence of Gram positive microorganisms, with the Coagulase-negative *Staphylococcus* (CoNS) being the most quoted.

***Analyzed Variables***

The 63 analyzed papers evaluated 46 variables with potential relation to bacteremia and/or severe infectious complications in pediatric cancer patients with fever and neutropenia (Table 1). The most mentioned and analyzed variables were type of cancer (44%), degree of body temperature (30%), absolute neutrophil count (30%), platelets (30%), and C-reactive protein (30%). We observed a correlation between the type of cancer and the occurrence of an infectious event in 8/27 (29.6%) of the studies that analyzed that variable[18-25]. Hematological cancer showed the biggest association.

**Table 1** – Analysis of 63 studies on risk of infection in pediatric cancer patients with fever and neutropenia.

| **Clinical variables (No./%)** | **References** | **Laboratorial variables (No./%)** | **References** |
|---|---|---|---|
| Age (21/33) | 1, 2, 15, 17, 18, 20, 22, 25, 33, 37-45, 47, 48, 68 | Absolute neutrophil count (19/31,1) | 1,2,15,16,18,19, 20,23,35,38,40, 45,47,48,57,61, 62,64,65 |
| Sex (17/27) | 1, 15, 17, 18, 20, 25, 27, 37-41, 44, 45, 47, 48, 67 | Absolute monocyte count (11/ 17,5) | 2,18,19,20,27,3 9,40,48,49, 50, 65 |

| | | | |
|---|---|---|---|
| Type of cancer (28/44) | 1,15,16,18,19,20-25,33, 39, 40, 44, 45, 47-50, 56-58, 61-64, 67 | Absolute phagocyte count (4/6,3) | 1,2,15,61 |
| Type of chemotherapy (20/31,7) | 1,15,17,18,20,24, 26,31,39-44,49,56,61,65-67 | Lymphocyte (1/ 1,5) | 20 |
| Duration of fever (5/8) | 17,38,41,47,61 | Leukocytes (8/ 12,6) | 2,16,18,20,31,40,47,49 |
| Degree of body temperature (18/28,5) | 1,15,18,20,25,29, 33,35,38,40,44,47,49,50,56,61,62, 65 | Hemoglobin (10/ 15,9) | 1,15,16,18,31,33,40,41,47,49 |
| Length of hospitalization (3/ 4,7) | 39,41,45 | Platelets (18/ 28,6) | 1,2,15,16,18,20, 21,27,31,33,35, 40,41,48,49,58, 62,65 |
| Intensive care hospitalization (1/1,5) | 41 | Procalcitonin (7/ 11) | 20,48,53-55,72,73 |
| Duration of antimicrobial therapy (2/ 3,1) | 13,68 | Positive culture (3/ 4,8) | 16,38,41 |
| Use of central venous catheter (12/19) | 1,16,18,20,25,26, 27,37,40,45,49,65 | Previous bacteremia (6/ 9,5) | 1,15,18,40,45,67 |

| | | | |
|---|---|---|---|
| Bone marrow involvement (9/14,2) | 18,20,23,40,49,50,56, 62, 67 | Previous colonization (1/ 1,6) | 19 |
| Number of episodes of FN (7/11) | 1,15,18,20,40,56, 67 | Glucose (2/ 3,2) | 48, 70 |
| Duration of neutropenia (11/17.4) | 17,22,23,38,41,42,43,45,57,61, 63 | Renal function (4/ 6,3) | 18, 40, 48, 61 |
| Inpatient febrile neutropenia (2/ 3,1) | 1, 15 | LDH[a] (1,1,5) | 48 |
| Granulocyte colony stimulating factor (7/11) | 1, 15, 18, 19, 20, 40, 64 | Aspartate aminotransferase/ Alanine aminotransferase (2/ 3,1) | 18, 40 |

[a]LDH = lactic dehydrogenase.

[b]MPC-1 = monocyte chemotactic protein.

[c]MBL = mannose-binding lectin.

[d]MASP-2 = mannose-binding lectin-associated serine protease-2.

Forty-nine papers identified clinical and laboratorial risk factors related to infection in pediatric cancer patients with fever and neutropenia. Forty-three variables had meaningful associations with bacteremia or with severe infectious events, with the type of chemotherapy being the most mentioned. Bakhshi et al described the frequency of foci of infections and phases of chemotherapy in patients with acute

lymphoblastic leukemia (ALL) under 15 years, and found higher rates of urinary infection, gastroenteritis, and sepsis in the induction and intensification phases (p< 0.001)[26].

Fourteen papers established a score for prediction of risk for infectious adverse events with 4 variables: chemotherapy more intense than the maintenance of ALL (OR 8.8; CI 95% 2.0-39.8), hemoglobin > 9 (OR 10.0; CI 95% 4.8-20.8), total leukocyte count < 300 (OR 5.2; CI 95% 2.7-10.1), platelets <50.000 (OR 4.7; CI 95% 2.3-9.5). Punctuations ≥9 had a sensibility of 92% and specificity of 51%[15]. Madsen et al assessed the reproducibility of a model proposed by Rackoff for the prediction of bacteremia using a retrospective analysis of variables extracted from the medical records of the hospital[27, 28]. His new model of prediction classified patients as being at high risk of bacteremia if absolute monocyte count (AMC) <100 and body temperature >39.5 ºC, intermediate risk if AMC <100, and temperature <39.5 ºC, and low risk if AMC >100 and temperature <39.5 ºC (OR of high risk vs intermediate risk 11.8; 95% CI 1.7–81.8), and (OR of intermediate risk vs low risk 10.2; 95% CI 1.2–83.4)[20].

Inflammatory markers such as the acute phase proteins and cytokines were evaluated by numerous studies to predict infection, with C-reactive protein (CRP) and procalcitonin being the most utilized and related to bacteremia and its complications. El-Maghraby et al assessed three inflammatory markers (CRP, interleukin 8 and monocyte chemotactic protein-1 - MCP-1) and found that CRP had the best performance, with values >90 mg/L related to bacteremia caused by gram negative bacteria and *S.aureus* (p= 0.038)[29]. Badurdeen et al investigated the values of 10 cytokines and found that Interleukin 8 (p< 0.02), Interleukin 10 (p< 0.001), Interleukin 6 (p<0.006) and CRP > 90 mg/dl (p<0.01) were discriminatory between the bacteremia group and the group with negative cultures[14].

## DISCUSSION

In 2017, the International Pediatric Fever and Neutropenia Guideline Panel[30] presented updated recommendations for the management of febrile neutropenia in children with cancer. Although these guidelines contained more information than the previous edition, considering that temporal and geographic variations can alter scores performance, it was not possible to recommend only one model for risk stratification[4]. Miedema and collaborators[31] published a study in 2011 to verify the applicability of a risk stratification model for bacteremia

proposed by Ammann in 2004[18] in which 4 variables were used (bone marrow involvement, OR 2.4; maximum body temperature > 39.8 ºC, OR 3.2; comorbidity with need of hospitalization, OR 2.3; and absolute neutrophil count < 500, OR 2.4) with a sensibility of 37%, a negative predictive value of 96% and a specificity of 95%. The performance of the 2011 model was worse than the original 2004 model with a difference in sensibility between the tests of 10% (95% CI 4%-16%). The authors attributed this to differences between chemotherapy protocols in Switzerland (original article) and in the Netherlands, thus demonstrating that promising results in one population do not guarantee equally promising results in another population with different genetic and environmental factors[31]. Santolaya et al[21] carried out a multicentric study to analyze the risk score for invasive bacterial infection based on a model previously established by their team in 2001[32] in which 5 factors (CRP > 90 *g/l*, hypotension, leukemia relapse, platelets < 50.000 and chemotherapy in the last 7 days), measured in the first 24 hours of hospitalization, could discriminate between children at high and low risk of invasive bacterial infection (sensibility = 92%, specificity = 76%, positive predictive value = 82% and negative predictive value = 90%). This study demonstrated that their previously established model for risk stratification could be highly effective when applied to a population with similar clinical, social, and geographic characteristics.

For this reason, the most recent guideline for febrile neutropenia in children recommends that the choice of strategy for infection risk stratification should consider not only the capacity of the institution in applying complex measures of evaluation, but also the geographic variation of existing studies[4].

Papers on prediction and stratification of risk in children with neutropenia include prospective and retrospective observational studies with variations in inclusion criteria, and definitions of febrile neutropenia and adverse outcomes. To homogenize the pediatric populations of the various studies, this review chose to exclude patients with bone marrow transplant, once this is a specific population submitted to a more intense chemotherapy regime and they present a higher severity disease. Risk stratification cannot be applied in such patients.

One of the greatest challenges in the evaluation of papers was the divergence in the definitions of fever, which varied in the degree of temperature, number of febrile peaks, and place of measurement (oral, axillary, or auricular regions). The most used measurement of body temperature in Brazil is the axillary, with oral and rectal measurements being rarely performed in clinical practice [33] The Infectious Disease Society of America (IDSA)[7] guideline considers fever in neutropenic patients as an oral temperature >38.3 ºC or an oral temperature >38 ºC sustained for over one hour. Only three studies (4.5%) have used that definition (19, 34, 35).

In 1966, Bodey et al demonstrated the importance of the duration and the severity of neutropenia for the increased risk of severe infectious complications, and since then, the internationally accepted definition of neutropenia (absolute neutrophil count < 500 cell/*mm³* or < 1000 cell/*mm³* with an expected decline in 48 hours) is based on its calculations of relative risk[3, 12]. In this study 50.7% of the papers utilized the cutoff point of < 500 neutrophils/*mm³* and 20% of papers considered Bodey's definition.

The Centers for Disease Control and Prevention (CDC) defines bacteremia or bloodstream infection, as an isolation of pathogenic microorganisms in one or more blood cultures if the microorganism is not related to an infectious process in another focus [36]. In patients with neutropenia the term used is MBI-LCBI (mucosal barrier injury laboratory-confirmed bloodstream infection), which considers the chemotherapy-induced damage to mucosal barrier and the growth of intestinal microorganisms in at least one blood culture. Most papers found in this review were published before this CDC definition existed and therefore, they do not consider the breaking of the mucosal barrier in their definition of bacteremia. Furthermore, few papers comment on contaminating commensal microorganisms of the skin. To consider bloodstream infection by these pathogens, two blood cultures associated with symptoms of sepsis (fever, shivering, orthostatic hypotension) are recommended[26].

The two largest frequencies of bacteremia were reported in an Indian study (61%), which included patients hospitalized between 1992 and 2002, and in an American study (60%) which included patients with high-risk neuroblastoma in the induction phase[26, 37]. Such frequencies

might be related to socioeconomic status in the first study and with the aggressiveness of the underlying disease and its treatment in the second study.

Further, older publications and publications from developing nations found a larger percentage of gram-negative bacteria. Improvements in medical care conditions such as the use of long-term invasive devices can justify the differences in the prevalence of different microorganisms.

## CONCLUSION

The present review identified the most currently studied parameters related to infection in pediatric cancer patients with chemotherapy-induced fever and neutropenia. Clinical factors such as type of cancer, chemotherapy phase and hypotension, combined with laboratorial parameters such as monocyte count, platelets and inflammatory markers can improve the discrimination between patients who will have infectious complications from those who will not. This information can assist in the elaboration of local protocols to identify patients at major risk of developing bacterial infections in the course of febrile neutropenia. The identification and stratification of risk in this population has to consider the capacity of each institution to apply more or less complex evaluation measures and the geographic variation of the existing studies. Beyond this, the necessity of using well established criteria for the definition of febrile neutropenia, bloodstream infection, and other foci of infection is clear.



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**Supplementary material – Appendix 1** - Characteristics of risk factors related to bacteremia in pediatric cancer patients with febrile neutropenia, systematic review 2000-2017.

| Ref | First autor, year, local | Type of study | Population (n) | Objectives | Outcome | CASP (%) |
|---|---|---|---|---|---|---|
| 1 | Fleischhack, 2000, Germany | Retrospective | Febrile Neutropenic children (122) | Evaluate the relevance of procalcitonin in comparison to CRP, IL6, IL8, IL2R for predicting infection in Febrile Neutropenia | Comparison of relevance of procalcitonin in comparison to CRP, IL6, IL8, IL2R for predicting infection in FN | 66 |
| 2 | Klaasen, 2000, Canada | Prospective | Febrile Neutropenic children (227) | Derive and validate an existing clinical prediction score that identifies low risk of bacterial infection in Febrile Neutropenia | Absolute Monocite Count was capable of predicting bacteremia and AMC > 100 excluded severe bacterial infection with sensibility = 84% (95% CI 61% to 100%), specificity = 42% (95% CI 38% to 46%) and negative predictive value = 92% (95% CI 76% to 100%) | 100 |
| 3 | Baorto, 2001, USA | Retrospective | Febrile Neutropenic children (1171) | Identify the clinical and laboratorial parameters associated with low risk of Febrile Neutropenia | Absolute Monocite Count > 155 as a target for low risk obtained the smallest rate of bacteremia of 6,1% with sensibility = 94%, specificity = 17% and OR 0,31 (95% CI 0,16 - 0,60) compared to other Absolute Monocyte Count cutoff values | 91 |
| 4 | Soker, 2001, Turkey | Prospective | Febrile Neutropenic children (48) | Investigate the IL1beta, TNFalfa, IL2R, IL6 and IL8 as infection indicators in Febrile Neutropenia | IL-6, sIL-2R and IL-8 were significantly higher in the beginning of FN compared to the controls ($p < 0.001$, $p < 0.001$, and $p < 0.001$). | 75 |
| 5 | Mathur, 2002, Índia | Prospective | Febrile Neutropenic children (119) | Determine the etiology, risk factors and outcome in FN in children with hematological cancer | Bacteremia was more frequent in ANC between 0-200 than between 201-500 (p 0.01) | 66 |
| 6 | Alexander, 2002, USA | Retrospective | Febrile Neutropenic children (188) | Evaluate the risk prediction of adverse events in Febrile Neutropenia | High risk patients have more adverse event (33% x 5% 955 CI 3,39-25,95 OR 10,01) p <0.001. | 91 |
| 7 | Santolaya, 2002, Chile | Prospective | Febrile Neutropenic patients < 18 years (263) | Evaluate the model of risk prediction of invasive bacterial infection previously established | The model previously established with five risk factors during the first 24 hours of hospitalization presented useful to discriminate the children with high and low risk for invasive bacterial infection with Sensibility = 92%, specificity = 76%, positive predictive value = 82% and negative predictive value = 90%. | 100 |
| 8 | Ammann, 2003, Switzerland | Retrospective | Febrile Neutropenic patients < 18 years (285) | Determine the risk factors for severe bacterial infection | Independent variables associated to higher risk of severe bacterial infection: bone marrow involvement (OR 6.40; 95% CI ,2.66– 15.2); lack of clinical signs of viral infection (OR 3.00; 95% CI, 1.45–6.17); elevated CRP (OR 2.36; 95% CI, 1.40–3.94); low leukocyte count (OR 1.99; 95% CI, 1.32–3.03); presence of central venous catheter (OR 1.92; 95% CI, 1.02–3.63); hemoglobin (OR of low Hb 0.58; 95%CI,0.37–0.93); pre-b-cell leukemia (OR of other diagnoses 0.48; 95% CI, 0.25–0.91). Risk score presented sensibility = 96%, specificity = 26% and negative predictive value =91% (score <=3 was defined as Low Risk) | 100 |
| 9 | Ammann, 2004, Switzerland | Retrospective | Febrile Neutropenic patients < 17 years (364) | Define risk predictors for bacteremia | Four variables for the risk score of bacteremia in Febrile Nutropenia patients: blood marrow commitment OR 2.4 (1.3–4.6); maximum temperature > 39.8°C OR 3.2 (1.5–7.1); comorbidity that require hospitalization OR 2.3 (1.3–4.2) and Absolute Neutrophil Count< 500 OR 2.4 (1.4–4.1). | 100 |
| 10 | Corapcioglu, 2004, Turkey | Retrospective | Febrile Neutropenic patients < 18 years with linphproliferative disease or solid tumor (136) | Evaluate efficacy of empirical treatment and its costs | Bacteremia without significant difference between type of tumor and Absolute Neutrophil Count (P>0,05). Type of tumor and use of G-CSF without difference in neutropenia duration, fever or hospitalization (p< 0,05). Multivariate analysis: neutropenia duration was the most determinant factor for the duration of fever, hospitalization and antibiotics (p=0.015) | 90 |

80.
81.

| Ref | First autor, year, local | Type of study | Population (n) | Objectives | Outcome | CASP (%) |
|---|---|---|---|---|---|---|
| **11** | Peralta, 2004, Spain | Retrospective | Febrile Neutropenia in children (62) | Describe incidence of bacteremia incidence and criteria of low risk for bacteremia Febrile Neutropenia | The presence of more than three high risk factors has a higher relation with bacteremia (p<0.05) and an incidence of 32,6% | 58 |
| **12** | Lausen, 2006, Dinamark | Prospective | Febrile Neutropenia in children with non-B Acute Lymphoblastic Leukemia (135) | Associate genotype of Manose Binding Lectin (MBL) deficiency with infection in the first 50 days of chemotherapy induction in Acute Lymphoblastic Leukemia | No statistical difference between the three groups (p < 0.05) | 75 |
| **13** | Rondinelli, 2006, Brasil | Retrospective | Febrile Neutropenia < 18 years (283) | Identify the risks of severe infectious complications | Six factors identified as risk for severe infectious complication: < 5 years OR 1,8 (95% CI 1,0-3,4) p 0.049; Hb < 7 OR 2,0 (95% CI 1,2-3,6) p 0.021; Tax > 38,5 OR 1,9 (95% CI 1,0-3,6) p 0.033; presence of CVC OR 2,8 (95% IC 1,5-5,5) p 0.001; lack of upper respiratory tract infection OR 5,1 (95% CI 1,7-15,0) p 0.001; focus of infection on admission OR 16,6 (95% CI 7,0-39,5) p 0.001. Score of 2,5 - 12 points. 3 groups: low risk, intermediate risk 13 x the risk for severe infectious complication (4.4 - 38.3) and high risk with 50 x (16.4 to 149.2) | 100 |
| **14** | El-Maghraby, 2007, Egypt | Prospective | Febrile Neutropenia leukemia and lymphoma < 18 years (85) | Determine the value of C Reactive Protein, IL8 e MCP1 as predictive markers to define risk stratification for severe bacterial infection | Reactive C Protein >90mg/L had association with bacteremia (P=0.038). The sensibility, specificity, negative predictive value and positive predictive value of CRP, MCP-1, e IL-8 were (70%, 73%, 51%, e 85%), (64%, 92%, 53%, e 95%), and (71%, 77%, 54%, e 88%), respectively | 83 |
| **15** | El-Mahallawy, 2005, Egypt | Retrospective | Febrile Neutropenia in patients < 18 years (1135) | Identify risk factors for severe bloodstream infection | Risk factors related to severe Bloodsteam Infection: Febrile Neutropenia in the hospital p= 0.014 OR 2.142 (95% CI 1.170- 3.921); intense chemotherapy p <0.001 OR 3.153 (95% CI 1.737-5.725); polimicrobian episode p <0.001 OR 7.614 (95% CI 3.307-17.532); Lower Respiratory Tract Infection p <0.001 OR 4.261 (95% IC 2.307 7.869); ANC > 500 > 7 days p=0.002 OR 0.367 (95% CI 0.192 0.701) | 83 |
| **16** | Santolaya, 2008, Chile | Prospective | Febrile Neutropenia in patients < 18 years (601) | Evaluate 6 biomarkers: BUN, blood glucose, LDH, C Reactive Protein, IL-8 and procalcitonin as severe sepsis preditors | The risk factors for severe sepsis were: age > 12 years (OR: 3.85; 95% CI: 2.41– 6.15); C Reactive Protein in admission >= 90 mg/L (OR: 2.03; 95% CI: 1.32–3.14), IL-8 in admission > 200 pg/mL (OR: 2.39; 95% CI: 1.51–3.78); C Reactive Protein in admission after 24 hours > 100 mg/L (OR: 3.06; 95% CI: 1.94–4.85) and IL8 after 24 hours > 300 pg/mL (OR: 3.13; 95% CI 1.92–5.08) | 100 |
| **17** | Bakhshi,2008, Índia | Retrospective | Febrile Neutropenia Acute Lymphoblastic Leukemia < 15 years (222) | Describe the frequence, focus of infection and outcomes between the phases of chemotherapy | Urinary tract infection, gastroenteritis and sepsis are more common in the induction and in intensification (p<0.001). Fungal infection is more common in the induction (p0.001) | 66 |
| **18** | Wicki, 2008, Switzerland | Retrospective | Febrile Neutropenia in patients < 17 years (629) | Develop a model based in clinical variables to predict risk of developing Febrile Neutropenia and Febrile Neutropenia with bacteremia. | Variables associated with Febrile Neutropenia with bacteremia: intensity of chemotherapy OR 7.41 (95% CI 2.41–22.8) p<0.001; blood marrow involvement OR 3.77 (95% CI 2.38–5.99) p<0.001; CVC OR 2.48 (95% CI 1.61–3.82) p<0.001; short time since diagnosis OR 0.10 (95% CI 0.04–0.21) p<0.001 and previous FN with bacteremia OR 2.95 (95% CI 1.79–4.87) p<0.001 | 100 |
| **19** | Yilmaz, 2008, Turkey | Retrospective | Febrile Neutropenia in patients < 18 years with leukemia (239) | Evaluate clinical evolution, type of treatment, use of G-CSF and outcome of patients treated with BFM protocol | Patients who used G-CSF had a Febrile Neutropenia resolution in a smaller amount of time than those who did not used (p<0.05). There was a positive relation between neutropenia duration, resolution time of fever and duration of antibiotics (p<0.001 para todos) | 70 |

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| **20** | Diepold, 2008, Germany | Prospective | Febrile Neutropenia in patients in children (141) | Determine the value of IL6, IL8 and C Reactive Protein to predict sepsis risk | IL6 > 42pg/ml on the 1º day has sensibility =90%, specificity = 85% positive predictive value =94% e negative predictive value = 77% to develop sepsis or prolonged neutropenia | 83 |

82.

| Ref | First autor, year, local | Type of study | Population (n) | Objectives | Outcome | CASP (%) |
|---|---|---|---|---|---|---|
| **21** | Sonabend, 2008, USA | Prospective | Febrile Neutropenia in children (135) | Evaluate if children with hyperglycemia in the 1° month of treatment (induction) will present more severe infections and hospitalizations during the 1° year of chemotherapy | Patients with moderate or severe hyperglycemia had 2,5 0R (95% CI 1.0–6.2) 2.1 OR (95% CI 1.0–4.6) more chance of document infection,respectively. Patients with severe hyperglycemia had 4.2 OR (95% CI 1.5–12) more chance of bacteremia/fungemia, 3.8 OR (95% CI 1.2–11.6) more chance of cellulitis and 4.0 OR (95% CI 1.7–9.3) more chance of NF than the group with normal blood glucose | 83 |
| **22** | Hakim,2009, USA | Retrospective | Febrile Neutropenia in patients < 22 years (337) | Describe the etiology and the clinical course of fever in neutropenic children in the USA | Fever of Unknow Origen has the smallest duration of fever (0.5 vs. 2.0 dias; p<0.0001) and hospitalization (3 vs. 6 days; p<0.0001), the bigger average duration since chemotherapy (6.0 vs. 4.0 days; p=0.01) and the smallest probability of acute myeloid leukemia diagnosis (11% vs 22%; p=0.009) or developing clinical complications (5.1% vs 24.4%; p<0.0001) | 100 |
| **23** | Kassam, 2009, Canada | Prospective | Febrile Neutropenia in children (73) | Determine the association between low levels of C protein and bacteremia, prolonged fever and documented infection | Low C reative protein did not had statistical relation with bacteremia in Febrile Neutropenia -OR 0.18 (95% CI 0.00 - 8.33) p= 0.38. Low C protein did not had statistical relation with prolonged fever and documented infection - OR 2.30 (95% IC0.18, 30.12) p=0.53 | 100 |
| **24** | Schlapbach, 2010, Switzerland | Retrospective | Febrile Neutropenia in children < 17 years (177) | Determine if concentrations of H-ficolin have association with Febrile Neutropenia | H-ficolin in low concentrations was associated to bigger risk of FN during chemotherapy (OR 2·24; 95% CI, 1·38–3·65; p = 0·004). Patients with low H-ficolin had bacteremia episodes three times more frequently than those with normal levels (OR 2·82; 95% CI, 1·02–7·76; p = 0·045). | 58 |
| **25** | Asturias,2010, Guatemala | Prospective | Febrile Neutropenia in children < 18 years (102) | Evaluate the association between 6 risk factors and bacteremia | None of the factors had association with the presence of bacteremia.(p>0.05 for all) | 100 |
| **26** | Ammann, 2010, Switzerland Germany | Prospective | Febrile Neutropenia < 18 years (423) | Define a prediction of risk for adverse events in episodes of Febrile Neutropenia | Variables associated with adverse events: Chemotherapy more intense than the ALL maintenance phase OR 8,8 (CI 95% 2,0-39,8); Hb >9 OR 10,0 (CI 95%4,8-20,8); Leukocytes < 300 OR 5,2 (CI 95%2,7-10,1); Platelets <50.000 OR 4,7 (CI 95%2,3-9,5). Score >= 9 had sensibility = 92% and specificity =51% | 100 |
| **27** | Macher, 2010, France | Retrospective | Febrile Neutropenia in patients < 18 years (377) | Evaluate the reproducibility of 6 clinical scores and compare their ability of predict an adverse infectious outcome | None of the scores fulfilled 3 established criteria and none had 100% of sensibility | 91 |
| **28** | Hodge, 2011, USA | Prospective | Febrile Neutropenia in children (26) | Evaluate if Th1 cytokines are reduced and regulatory T cells are elevated in FN with comproved infection | Raise in the percentages of CD25, CD127, CD8 and CD3 (p=0.005) and reduction of Th1 cytokines in patients with bacteremia compared with patients with negative cultures | 75 |

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| **29** | Agyeman, 2011, Switzerland | Retrospective | Febrile Neutropenia in patients < 18 years (423) | Develop a risk score for bacteremia using predictors of adverse events and determine if the performance improves with the analysis of the data after inicial management | Variables used for the risk score of bacteremia evaluated after 24-48 hours: Hb> 90 g/L OR 5.3 (95% CI 2.5-11.0) p= 0.001, minus 3 points; platelets < 50 G/L OR 4.6 (95% CI 2.1-10.3) p= 0.001, minus 3 points; pirogenia OR 10.3 (95% CI 4.1-25.6) p= 0.001, minus 5 points; another reason for hospitalization OR 4.1 (95% CI 2.1-8.1) p= 0.001, minus 3 points (AR >=3). Sensibility = 93% (IQR, 91%–97%); Specificity = 41% (IQR, 22%–45%); Negative predictive value = 97% (IQR, 96%–97%); Positive predictive value = 23% (IQR, 19%–24%). | 100 |
| **30** | Miedema, 2011, Holand | Prospective | Febrile Neutropenia in children (210) | Apply the model of risk stratification for bacteremia proposed by Ammann et al | Capacity of predicting bacteremia: specificity =57% (95% CI 50 – 64%), sensibility =82% (95% CI 77-87%), negative predictive value=91% (95% IC 87-95%) and positive predictive value = 23% (95% CI 17-30%) with a performance worse than original study | 100 |

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| Ref | First autor, year, local | Type of study | Population (n) | Objectives | Outcome | CASP (%) |
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| **31** | Gupta, 2011, El Salvador | Prospective | Febrile Neutropenia in patients < 16 years (106) | Describe the microbiology and the outcome of Febrile Neutropenia in children and determine predictors of adverse outcomes | Bigger age reduces risk of MDI [odds ratio (OR) per year=0.87, 95% (CI), 0.75-0.99; P=0.04] and bigger interval time between chemotherapy and FN tempo maior de interval entre QT e NF aumenta o risco (OR=1.03 per day, 95% CI, 1.01-1.04; P=0.002). | 100 |
| **32** | Badurdeen, 2012, Australia | Retrospective | Febrile Neutropenia in children (55) | Investigate the use of cytokines to predict bacteremia in Febrile Neutropenia | IL8 (p<0.02), IL10 (p<0.001), IL6 (p<0.006) and C reactive protein >90 (p<0.01) were discriminatory between the bacteremia group and the one without positive blood culure. Positive predictive value=96% | 58 |
| **33** | Urbonas, 2012, Lituanie | Prospective | Febrile Neutropenia in patients < 17years (62) | Investigate the clinical value of IL-10 as a early marker of bacterial infection | Sensibility = 73% (95% CI 39-94%), specificity =92% (95% CI 74-99%), negative predictive value = 83%. Might be used to exclude bacteremia/sepsis in admission | 100 |
| **34** | Urbonas, 2012, Lituanie | Prospective | Febrile Neutropenia in patients < 17 years (36) | Evaluate the predictive value of IL-6 and IL-8 for bacteremia and sepsis in the first days of Febrile Neutropenia | Might be useful in the exclusion of bacteremia or sepsis in 1º day of Febrile Neutropenia: IL-6 negative predictive value = 89% com AUC 0.69 (95% CI 0.92-0.83) p <0.0001; IL-8 negative predictive value =82% com AUC 0.67 (95% CI 0.89 -0.80) p <0.0001. | 100 |
| **35** | Reitman, 2012, EUA | Prospective | Febrile Neutropenia in patients < 18 years (89) | Test the diagnostic performance of serial measures of procalcitonin to predict bacteremia | Elevated procalcitonin levels are predictive of bacteremia in serial measures (7.84: positive cultures and 0.63: negative cultures), p<.0001). Serial Procalcitonin sensibility = 78%, specificity =76% , positive predictive value =45% and negative predictive value=83% | 100 |
| **36** | Dix, 2012, Canada | Retrospective | Febrile Neutropenia in patients in Acute Myeloid Leukemia (342) | Identify associated factors with infection, sepsis and mortality in children with recent diagnosis of acute myeloid leukemia | Risk factors associated with microbiological infection: cytarabine dosage RR 1.04 (95% CI 1.02, 1.05) <0.0001; duration of corticotherapy RR 1.04 (95% CI 1.03, 1.05) p<0.0001; clinical infection: duration of corticotherapy RR 1.02 (95% CI 1.01, 1.03) p =0.002; prophylaxis with fluconazole RR 1.46 (95% CI 1.06, 2.02) p=0.022; Fever of Unknow Origin: obesity 1.44 (1.03, 1.99) 0.031, cytarabine dosage 1.02 (1.00, 1.04) 0.019; Bacteremia: cytarabine dosage OR 1.05 (95% CI 1.02, 1.07) p<0.0001, neutropenia > 15 dias 1.92 (1.35, 2.73) 0.0003, duration of corticotherapy (1.04, 1.09) <0.0001; Sepsis: neutropenia > 15 dias 1.97 (1.04, 3.76) 0.039, duration of corticotherapy OR 1.07 ( 1.04, 1.10) p<0.0001. | 100 |
| **37** | Madsen, 2012, USA | Retrospective | Febrile Neutropenia in children (157) | Evaluate the reproducibility of a model of Rackoff for prediction of bacteremia using retrospective electronic data | New prediction model: high risk = Absolute Monocyte Count < 10 e temperature. > 39,5; intermediate risk = Absolute Monocyte Count < 10 e temp. < 39,5; low risk = Absolute Monocyte Count > 10 e temp. < 39,5. OR of high risk vs | 58 |

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| | | | | | intermediate risk 11.8 (95% CI 1.7–81.8), and OR of intermediate risk vs low risk 10.2 (95% CI 1.2–83.4). | |
| **38** | Luthi, 2012, Switzerland Germany | Prospective | Febrile Neutropenia in patients < 18 years (443) | Describe severe medical complications in children with Febrile Neutropenia and correlate variables | Four variables with independent and meaningful association: acute myeloid leukemia, time since chemotherapy > 7 days, severe general state and hemoglobin > 9.0 g/dl in admission | 100 |
| **39** | Binz,2013, Switzerland | Retrospective | Febrile Neutropenia in patients < 17 years (783) | Evaluate the association between temperature limits for fever and different rates of Febrile Neutropenia and Febrile Neutropenia with bacteremia | Higher limit of body temperature was not associated with the rate of Febrile Neutropenia with bacteremia (OR 1.39; 95% CI, 0.53–3.62; p < 0.50) | 100 |
| **40** | Ammann,2013, USA | Retrospective | Febrile Neutropenia in patients < 18 years (278) | Determine association of concentrations of Mannan-Binding Lectin and MBL-associated serine protease (MASP2) with risk of an adverse event | Mannan-Binding Lectin < 100 OR 1,0 (CI 95% 0,3-3,37) and MASP2 < 200 OR 0,62 (CI 95% 0,31-1,63), did not had association with bacteremia risk | 100 |

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| Ref | First autor, year, local | Type of study | Population (n) | Objectives | Outcome | CASP (%) |
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| **41** | Johannsen,2013, Dinamarca | Retrospective | Febrile Neutropenia in patients < 14 years with Acute Myeloid Leukemia (268) | Evaluate the infections in children treated with the NOPHO-AML-2004 protocol | Without significant correlation between S. viridans, bacteremia and high doses of cytarabine (p=1.00). High frequency of the pathogen might have relation with intensity and not only with cytarabine | 100 |
| **42** | Urbonas, 2013, Lituânia | Prospective | Febrile Neutropenia in patients < 17 years (62) | Measure of the predictive value of procalcitonin IL-2, CD45 and HLA-G in the identification of bacteremia and sepsis in the beginning of the episode | IL2 sensibility = 83%, specificity = 50%, positive predictive value 54%, negative predictive value = 81% (AUC 0,79 95% CI 0,66-0,88 p<0.0001) and PCT sensibility = 85%, specificity = 67%, positive predictive value = 62%, negative predictive value = 84% (AUC 0,73 95% CI 0,57-0,86). Might be useful in the differentiation between bacteremia/sepsis and Fever of Unknow Origin. | 83 |
| **43** | Reyes, 2013, México | Prospective | Febrile Neutropenia in patients in children with cancer (271) | Identify risk factors for bacteremia and its prevalence | Variables associated with bacteremia: monocitopenia OR 6.8 (95% CI 0.85 - 55.6 p= 0.07); plaquethopenia OR 2.3 (95% CI 1.02 - 5.4 p = 0.04); central venous catheter OR 2.6 (95% CI 1.16 - 5.9 p=0.02); vincristine useOR 2.8 (95% CI 1.22 - 6.4, p = 0.01) | 90 |
| **44** | Rosenblum,2013, EUA | Prospective | Febrile Neutropenia in children (457) | Examine the rate of bacteremia detection in the subsequente blood cultures when the first is negative | The risk factors to a positive blood culture after the first being negative: previous bacteremia OR 2,77 (95% CI 1,04 - 7,37), hospitalization for over 48 hours OR 3,38 (95% CI 1,45-7,87) | 91 |
| **45** | Bothra, 2013, Índia | Prospective | Febrile Neutropenia between 1 - 18 years (155) | Explore risk factors for severe adverse events in Febrile Neutropenia of high and low risk | Risk factors for severe adverse outcomes: history of Febrile Neutropenia (OR adjusted of 4.83 95 % CI 1.65–14.10), patient already in use of antibiotics (OR adjusted of 2.88 . 95 % CI 1.28– 6.48) and thorax radiography alteration (OR adjusted of 3.26, 95 % CI of 1.44–7.37) | 100 |
| **46** | Zapata-Tarres, 2013, México | Prospective | Febrile Neutropenia in patients < 18 years (57) | Describe the association between homozygous and heterozygous of IL1RN in children with Acute Lymphoblastic Leukemia and septic shock | The risk of septic shock is higher in homozygous L1RN*2/IL1RN*2 and heterozygous ILRN *1/ILRN*2 (Odds ratio, 45; p = 0.001) | 100 |
| **47** | Hazan,2014, Israel e Romênia | Prospective | Febrile Neutropenia in patients < 18 years (195) | Determine the association between clinical and laboratorial parameters of bloodstream infection (BSI) | Average duration of fever was higher in the BSI group (5d) compared to the group without BSI (2d, p=0.01) . Average monocyte count in admission was smaller in the BSI group compared to the group without BSI (0.06±0.1 vs. 0.14±0.33cells/mm3, respectively p =0.05). C-reative protein average in the days 5 to 8 of hospitalization was bigger in the BSI group (p < 0.001). Raise in the monocytes and platelets and reduction of C-reative protein were noted in the BSI group, but not in the group without BSI infection (P<0.01). | 100 |
| **48** | Kitanovski, 2014, Eslovênia | Prospective | Febrile Neutropenia in patients < 20 years (90) | Determine the diagnostic accuracy of lipopolysaccharide-binding protein (LBP) to predict bacteremia/sepsis and compare it to procalcitonin, IL-6 and C-reative protein | LBP accuracy: sensibility = 61.1, specificity = 76.8, positive predictive value =40.7 and negative predictive value = 88.3; LBP had smaller accuracy to predict bacteremia/ sepsis than C-reactive protein (p=0.04) e procalcitonin (p=0.01). | 66 |
| **49** | Aviles-Robles, 2014, México | Prospective | Febrile Neutropenia in patients < 18 years (217) | Evaluate the association between bloodstream infection and days of hospitalization | Average of 11 days of hospitalization (bacteremia group 19 days vs 10 days of the group without bacteremia (OR 2,0 95% CI 1,6-2,6). | 100 |

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| Ref | First autor, year, local | Type of study | Population (n) | Objectives | Outcome | CASP (%) |
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| **50** | Ducasse, 2014, Chile | Prospective | Febrile Neutropenia in patients < 18 years (506) | Describe infectious agents, focus and evolution of Febrile Neutropenia in the Acute Myeloid Leukemia and Acute Lymphoid Leukemia | Smaller chemotherapy interval, higher C-reactive protein, lower Absolute Neutrophil Count, more days of fever, more cases of hypotension, prolonged hospitalization time and higher necessity of Intensive Care Unity were statitically associated to acute myeloid leukemia patients (p<0,001) | 100 |
| **51** | Tran, 2014, Canadá | Retrospective | Febrile Neutropenia in Acute Myeloid Leukemia in patients with bacteremia (290) | Describe the prevalence of second bacteremia and identify risk factors in children with Acute Myeloid Leukemia | Associated risk factors with second bacteremia in Acute Myeloid Leukemia were: days of corticotherapy (OR, 1.09; 95% CI, 1.07–1.12; p <.0001), corticotherapy dose (OR, 1.04; 95% CI, 1.00–1.08; p =.035), and days of neutropenia (OR, 1.07; 95% CI, 1.02– 1.12; p =.007) | 91 |
| **52** | Prasad, 2014, Índia | Prospective | Febrile Neutropenia in children < 15 years (250) | Identify clinical and laboratorial parameters to predict adverse outcomes in children with FN | Five independent factors for adverse outcomes: previous documented infection in the last 6 months OR 2.869 (95% CI 1.277-6.448) p=0.011; focus of infection OR 18.364 (95% CI 7.984-42.240) p<0.001; AFC <100/mm³ OR 2.618 (95% CI 1.195-5.733) p=0.016; body temperature > 39ºC OR 2.953 (95% CI 1.349-6.462) p = 0.007 and fever duration > 5 days OR 2.953 (95% CI 1.349-6.462) p = 0.007 | 91 |
| **53** | Delebarre,2015, França | Retrospective | Febrile Neutropenia in children < 18 years (372) | Identify variables capable of predicting severe infection | Variables associated with severe infection: prolonged neutropenia (ORa 2,5 95% CI 1,3-5,0), hematological cancer (ORa 1,9 95% CI 1,3-5,0), fever > 38,5 (ORa 3,7 95% CI 1,8-7,7), C-reactive protein > 90 (ORa 4,5 95% CI 1,6-2,3). | 100 |
| **54** | DeLaMasa, 2015, Chile | Prospective | Febrile Neutropenia in children < 18 years (388) | Determine time of antibiotics administration since admission and determine the association with clinical outcomes | Univariate analysis: patients that received the first dose of antibiotics ≤ 60 minutes had higher duration of hospitalization (in days, p = 0.012) and bigger frequency of sepsis (p = 0.022; Table 2). No statistical difference between hospitalization time and frequency of sepsis | 91 |
| **55** | Demirkaya, 2015, Turquia | Prospective | Febrile Neutropenia in children < 18 years (50) | Evaluate levels of adrenomedullin in the Febrile Neutropenia episodes and compare to C-reative protein and protein levels | In the group with microbiologically documented infection, the levels of adrenomedullin on day 3 were significantly bigger than the groups with clinical infections and fever with no focus. PCT was significantly bigger in the group with sepsis than in the group with clinical infection in the admission, day 3 and days 7-10. CRP did not had statistical significance between groups. Between adrenomedullin, CRP and PCT, PCT demonstrated the bigger correlation with the gravity of infection | 91 |
| **56** | Salstrom, 2015, EUA | Retrospective | Febrile Neutropenia in children | Relate a scheme of quality improvement to reduce the time for the first antibiotic administration dose and associate with the clinical outcomes in Febrile Neutropenia | No significantly difference in the frequency of bacteremia. The intervention improved the first antibiotics administration time for next to 100% < 60 minutes. Necessity of Intensive Care Unity was significantly reduced (p = 0.003) | 75 |
| **57** | Miedema, 2016, Holanda | Prospective | Febrile Neutropenia in children (233) | Examine the security and reproducibility of a stratification of Febrile Netropenia risk from a multicentric study | Failure of the low risk stratificação = 12,8% (CI 95% 4,8-25,7%). Model of stratification sensibility = 92%, specificity = 48%, positive predictive value = 26% and negative predictive value = 97% | 100 |

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| Ref | First autor, year, local | Type of study | Population (n) | Objectives | Outcome |
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| **58** | Fekete, 2016, Hungria | Retrospective | Febrile Neutropenia in children (54) | Evaluate the effect of polymorphism of promoter (X/Y) and exon 1 (A/0) from the gene related to MBL2 in the blood level of MBL (manose binding lectine) in children with FN | No significantly difference in the freque control groups |
| **59** | Villanueva, 2016, EUA | Retrospective | Febrile Neutropenia in children < 21 years (299) | Evaluate the rate of readmission and subsequent infection in discharged neutropenic patients with no fever | Acute Lymphoid Leukemia had a relatio (95% CI 1,24-10,87) |
| **60** | Chaudhuri, 2016, Índia | Prospective | Febrile Neutropenia in children from 1 to 12 years (162) | Evaluate the effect of malnutrition for adverse events in neutropenia | Association with malnutrition and death severe complications with moderate sign P=0.084) |
| **61** | Kesik, 2016, Turquia | Retrospective | Febrile Neutropenia in children (34) | Evaluate the part of adrenomedullin in the risk prediction in Febrile Neutropenia | Adrenomedullin could predict the prese 0,85 p = 0.303) and patients with high ri |
| **62** | Baraka,2017, Egito | Prospective | Febrile Neutropenia under 16 years(60) | Evaluate presepsin significance for diagnosing bacteremia | Presepsin had a significantly raise in the correlation with CRP and PCT p < 0,001 point of 1014) |
| **63** | Whittle, 2017, EUA | Retrospective | Febrile Neutropenia in neuroblastoma (76) | Describe the etiology of infections in patients with high risk neuroblastoma in the induction phase and identify risk factors for infection and Febrile Neutropenia patients | Risk factors as feminine sex - RR 1,7 (9 RR 1,4 (95% CI 0,01-2,76) p 0.05; healt p 0.016 were associated with bigger infe |