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The Efficacy of Neutropenic Diet in Preventing Neutropenia Related Infections among Pediatric Patients Undergoing Chemotherapy: A Meta-Analysis

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Abstract

Background and Aims: Neutropenic diet is still being used among cancer patients despite the lack of evidence of its benefit. Several studies showed lack of effectiveness of this regimen. However, most of these studies were done among adult patients. This meta-analysis analyzes the available data involving pediatric cancer patients who were placed on a neutropenic diet during chemotherapy.

Methods: A systematic search was conducted from April 2020 to October 2020 for randomized controlled trials investigating the effect of neutropenic diet versus regular diet among pediatric patients undergoing chemotherapy was done. Outcomes of interest were incidence of febrile neutropenia and bacteremia. A fixed-effects meta-analysis was done to pool the effect of intervention.

Results: A total of 269 patients were included. There was no statistically significant difference in the incidence of febrile neutropenia (RR 1.16, 95% CI 0.78 to 1.71) and bacteremia (RR 1.57, 95% CI 0.62 to 3.96) between the neutropenic diet and regular diet groups.

Conclusion: This meta-analysis showed that there is no evidence supporting the use of neutropenic diet in preventing febrile neutropenia and bacteremia among pediatric patients undergoing chemotherapy. Clinicians should be aware of the possible implications of applying this dietary regimen to pediatric cancer patients.

Keywords: Neutropenia; Pediatric patients; Neutropenic Diet; Cancer; Chemotherapy

Introduction

The prognosis of pediatric cancer patients has significantly improved with risk-directed chemotherapy. Currently with the advent of multimodality therapy and supportive care, five-year cancer survival of children exceeds 80% in most European and North American countries. However, reliable population-based cancer registry data are limited or entirely lacking in many low and middle-income countries. Estimates suggest that survival is substantially lower compared to high-income settings. Generally, though, survival varies widely by childhood cancer type, irrespective of the country's public health care system [1].

Pediatric cancer patients are often at risk of infection due to intensive treatment regimens which may cause chemotherapy-associated neutropenia. One of the earlier studies in chemotherapy-associated neutropenia was done in 1966 and found that the risk for infection is inversely proportional with the number of neutrophils. Specifically, it noted that as the number of circulating neutrophils decreases below 500 x 10^9/L, the risk for infection is significantly increased [2].

As a part of infection prevention in chemotherapy-associated neutropenia, special precautions have been applied. Studies were done during the 1960s and 1970s to investigate the effects of placing patients with leukemia in relatively germ-free environments called "total protective environments" (TPEs). This involved isolation tents with laminar air flow and high-efficiency particle air (HEPA) filters. Reverse isolation precautions were strictly implemented. Patients were given topical, orifical, and oral non-absorbable antibiotics, and were provided a sterile diet which consisted of food and water that was steam- or gas-autoclaved or food cultured for low bacterial content. The study showed that with the use of TPE, patients had lesser adverse effects from chemotherapy [3].

With the evolution of chemotherapy from a solely in-patient basis to out-patient therapy, TPE had several modifications. Most of the components of TPE have been discarded, but neutropenic diet which evolved from a sterile diet, has been maintained in an effort to decrease the exposure to potential harmful bacteria and decrease the risk of infection in immunosuppressed cancer patients. It typically involves avoiding intake of fresh produce and undercooked meats and fish.

Studies have been done to provide evidence for employing neutropenic diet. However, most of the studies have failed to show a significant benefit from this regimen. A study done in 2007 by van Tiel et al involved adult patients with leukemia who were randomized to receive either a regular diet or a neutropenic diet. The study did not find a statistically significant difference between the two groups in terms of infection rate [4].

A similar study by DeMille et al evaluated the employment of neutropenic diet among twenty-eight adult cancer patients who underwent chemotherapy as an out-patient basis. It was found that there was no significant difference in the rate of admissions due to febrile neutropenia between patients who were compliant with neutropenic diet and those who were not [5].

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Despite the lack of evidence, neutropenic diet remains to be one of the strategies routinely done among chemotherapy patients. In a 2010 study done in Korea, a survey was conducted involving 65 hospitals to examine dietary restriction practices for neutropenic patients. It was found that 80 % (41) of the hospitals placed patients with neutropenia of restricted diets. The most restricted foods were raw fish or fresh meat, uncooked intestine, raw eggs, and fresh fruits and vegetables [6].

In a study by Braun et al, it was found that the implementation of the neutropenic diet by pediatric oncologists remains quite variable even among those at the same institution. The study involved a survey of 1,639 pediatric oncologists at 198 institutions who are members of Children's Oncology Group. Providers at the same institution were not consistent with implementation of the diet, patient populations placed on the neutropenic diet and parameters for initiation, discontinuation of the diet and specific food restrictions [7].

Use of the neutropenic diet remains controversial and standardized guidelines for this diet have not been universally implemented. The application of neutropenic diet contradicting with evidence could be due to the lack of statistical power among the current studies. Given the findings of existing studies, we hypothesize that neutropenic diet has no significant advantage over regular diet in terms of preventing infection among pediatric chemotherapy patients.

Study objectives

The general objective of this study was to determine the efficacy of employing neutropenic diet among pediatric cancer patients undergoing chemotherapy in terms of preventing occurrences of infection. The specific objectives were:

1) To compare the incidence of febrile neutropenia between those given neutropenic diet and regular diet

2) To compare the incidence of culture proven bacteremia between patients given neutropenic diet and regular diet.

Methods

Literature search strategy and study identification

A systematic literature search of PubMed, Herdin, Cochrane databases and the clinical trials registry were conducted from database inception (April 1, 2020) to October 31, 2020. The search strategy utilized the following search terms: "neutropenic diet," low bacterial diet," "low bacteria diet," and "low microbial diet." Mesh search was done with the term "febrile neutropenia". Manual search for studies from local institutions was done. Hand-searching through the references of the selected studies was done. The abstracts of the resulting studies were reviewed. The systematic search and review of abstracts were accomplished independently by two authors. Any conflicts regarding the search were decided by a third author.

Study selection and outcome measures

Included studies were limited to those involving pediatric population undergoing chemotherapy regardless of the treatment phase. Studies that investigated the effect of neutropenic diet versus regular diet among patients undergoing chemotherapy were reviewed. The primary outcome to be analyzed is the occurrence of febrile neutropenia defined as fever and absolute neutrophil count of $<1000/mm^3$. Secondary outcomes are mortality rate, bacteremia, and compliance to the prescribed regimen. Only randomized controlled trials were included. No language restriction was used. Figure 1 shows the flow chart for the systematic search and study selection. **T**able 1 shows the description of appraisal rating.

Data extraction

The names of authors, year of publication, sample population, baseline characteristics, outcome measured, and diet prescribed will be obtained from the selected studies. Two independent reviewers conducted the data extraction. Conflicts were resolved by a third reviewer. Outcomes, if possible, were based on intention-to-treat principle.

Quality evaluation

Critical appraisal using the Cochrane Risk of Bias Tool 2 of each included studies was done by two reviewers independently. Any conflicts are decided by a third appraiser. The following are the five criteria used in the appraisal:

Generation of allocation sequence

This ensures randomization or randomized assignment to the intervention or control group.

- *Adequate:* if the study clearly stated the method of randomization
- *Unclear:* if the study indicated that randomization was done but without specifying the method by which the sequences were generated.
- *Inadequate:* if no randomization was done or there was no

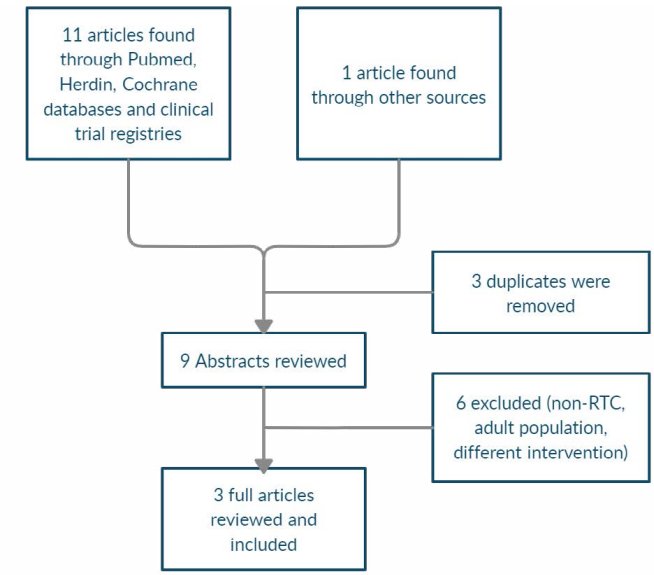

Figure 1: Flow chart showing the systematic search and study selection.

Table 1: Description of appraisal rating.

Rating	Description
A	All primary and secondary criteria were met
B	At least 1 secondary criterion was not met
C	At least 1 primary criterion was not met but drop-out rate was less than or equal to 20%
D	At least 1 primary criterion was not met but drop-out rate was greater than 20%

mention of randomization.

Allocation concealment

This refers to the concealment of the random sequences generated from the researchers responsible for allocating the participants into their respective groups.

- *Adequate:* if allocation concealment was done in such a way that the researchers have no influence on the randomization
- *Unclear:* if the study did not state the process of concealment.
- *Inadequate:* if concealment was not made or the sequences were apparent and easily predictable.

Blinding of participants and personnel

Blinding of participants and personnel refers to whether the investigators and participants were ignorant of the assignments of the study subjects into the intervention and placebo groups.

- *Adequate:* if there was double-blinding of participants and personnel
- *Unclear:* if the study stated that blinding was done but did not indicate the method by which blinding was achieved.
- *Inadequate:* if no blinding was done.

Blinding of outcome assessment

This refers to whether the personnel assigned in assessing the outcomes were not knowledgeable of the intervention or control group to which the participant was assigned in order to prevent bias in the assessment of the outcome.

- *Adequate:* if the personnel evaluating the outcome were not knowledgeable of the assigned grouping.
- *Unclear:* if there was no indication whether the evaluators were aware of the assigned grouping or not.
- *Inadequate:* if the evaluators were aware of who were assigned to the treatment and control groups.

Completeness of outcome data

Completeness of the outcome data was classified as to whether the initial participants were all followed up until the termination of the study.

- *Adequate:* if all the participants were accounted for at the end of the study. Those studies with incomplete follow up but with more than 80% are considered adequate.
- *Unclear:* if the number of participants initially recruited in the study and the final number of participants whose outcomes were adequately measured were not specified.
- *Inadequate:* if less than 80% of the participants were accounted for at the end of the study.

Summarizing the appraisal

The appraisal was categorized based on Table 3 and given a specific rating. The primary criteria were *Generation of allocation sequence* and *Incomplete outcome data*. The secondary criteria were *Allocation concealment, Blinding of participants and personnel,* and *Blinding of outcome assessment*.

Statistical analysis

Review Manager Version 5.4 for Windows was used for the meta-analysis. 2x2 contingency tables were formulated using the abstracted data. Relative risk was computed. Fixed effects analysis was conducted with confidence interval of 95%. The p-value threshold for statistical significance was set at 0.05. I^2 statistic was used to assess for heterogeneity across the studies. No subgroup analysis was done. Significant heterogeneity can be addressed by random effects analysis.

Results

At total of 11 articles were found in online databases using the specified search terms. Another article was obtained through local institutions. Among these 12 studies, 3 duplicates were removed. In the remaining 9 articles, abstracts were reviewed. After excluding non-randomized controlled trials, adult populations and different interventions, only 3 articles remained eligible.

Included studies

The 3 included studies have a combined total of 269 patients [8, 9, 10]. A total of 136 (50.56%) patients were randomized to neutropenic diet while the remaining 133 (49.44%) patients were randomized to regular diet. Majority of the population were diagnosed with hematologic malignancies while the minority with solid tumors. In all the three studies, neutropenic diet restricted raw vegetables and fruits, fast food and improperly cooked meat. This was in addition to minor

Table 2: Baseline characteristics of included studies.

Study ID	Diet	Patients	Age (Median years)	Disease	Intervention	Outcome*
Moody 2006	ND	9	4.4	ALL (5), Sarcoma (2), Medulloblastoma (2)	Avoidance of eating raw fruits, raw vegetables, aged cheese, cold meat cuts, fast food and take-out food	Incidence of Febrile neutropenia and culture proven bacteremia
	RD	10	4.1	ALL (5), Sarcoma (3), Medulloblastoma (2)	Regular diet prescribed by Food and Safety Guidelines	
Moody 2017	ND	77	12	ALL (23), AML (2), Neuroblastoma (2) Sarcoma (25) HL (9) Others (9) Brain tumors (7)	Avoidance of raw fruits and vegetables, cold meat cuts, takeout and fast food, aged cheese, raw nuts and yogurt	Incidence of Febrile neutropenia and culture proven bacteremia
	RD	73	11	ALL (25), AML (3), Neuroblastoma (4) Sarcoma (23) HL (5) Others (6) Brain tumors (6)	Regular diet prescribed by Food and Safety Guidelines	
Serrano 2013	ND	50	7	ALL (48) AML (2)	Avoidance of raw fruits and vegetables, fast food and improperly cooked meat	Incidence of Febrile neutropenia and culture proven bacteremia
	RD	50	6.5	ALL (47) AML (3)	Regular diet prescribed by Food and Safety Guidelines	

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; ND, neutropenic diet; RD, regular diet
*Occurrence of outcome was observed until the resolution of neutropenia

differences such as restrictions of yogurts and aged cheese in the study by Moody et al. 2017. In all of the studies, regular diet is defined in accordance to the FDA prescribed Food and Safety Guidelines. **(Table 2)**

Quality of evidence

Each of the included studies were critically appraised using the criteria stated above. Table 3 shows the summary of the appraisal. Only one of the included studies was classified under quality grade B while the remaining 2 were classified under quality grade A. The study done by Serrano was classified as quality grade B since the participants and personnel were not blinded to with regards to randomization. However, this is considered as a minor inadequacy since the measured outcome is objectively determined (occurrence of fever 38 degCel, complete blood count diagnostics, and blood culture growth). All outcomes of interests could not possibly be affected by this lack of blinding. **(Table 3)**

Febrile Neutropenia

In all the studies, incidence of febrile neutropenia was the main outcome measured. In 2 of the three studies, febrile neutropenia was defined as 1) axillary temperature of 38.3 degCel or oral temperature of 38 degCel, AND

2) Absolute neutrophil count (ANC) of <1000/mm^3 [9, 10]. In the remaining study, febrile neutropenia was defined as 1) oral temperature of 38C and ANC of <1000/mm^5 [8]. There was no statistically significant difference between the neutropenic diet groups and regular diet group in terms of incidence of febrile neutropenia (RR 1.16, 95% CI 0.78 to 1.71) (Figure 2). With an I^2 of 0%, there was no significant heterogeneity noted under fixed effects analysis. At 95% confidence interval, the pooled results of 0.78 to 1.71 are precise.

Culture Proven Bacteremia

All three studies determined the incidence of culture proven bacteremia through blood culture sampling. There was no statistically significant difference between the neutropenic diet groups and regular diet group in terms of incidence of culture proven bacteremia (RR 1.57, 95% CI 0.62 to 3.96). **(Figure 3)**

Discussion

The results of the literature search have failed to provide evidence to support the use of neutropenic diet among pediatric cancer patients undergoing chemotherapy. The analyses showed no significant decrease in the incidence of both febrile neutropenia and culture proven bacteremia. These results are in congruence to the results of a systematic review done by Sonbol et al. involving 1116 adult patients undergoing chemotherapy or hematopoietic cell transplantation. In the study, there was no significant difference between regular diet and neutropenic diet in terms of incidence of major infection, bacteremia, and mortality [11].

Another meta-analysis involving five randomized controlled trials involving a total of 388 adult patients with neutropenia was conducted by Ball et al. Their study also failed to show a significant difference in the incidence of febrile neutropenia between those receiving neutropenic diet and unrestricted diet [12].

A randomized controlled trial done last 2006 showed that neutropenic diet is significantly more difficult to adhere to compared to regular diet. The study also conducted a comparison of quality of life between the neutropenic group and regular diet using the Peds QL Quality of Life Inventory Core Module and Cancer Module. Results showed that there was significantly decreased quality of life among the neutropenic diet group [8].

Diet restrictions such as neutropenic diet may further aggravate the decreased caloric intake often found in pediatric cancer patients.

Table 3: Quality of evidence of the included studies.

Study ID	Generation of Allocation Sequence	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Completeness of Outcome Data	Quality Grade
Moody 2006	Adequate	Adequate	Adequate	Adequate	Adequate	A
Moody 2017	Adequate	Adequate	Adequate	Adequate	Adequate	A
Serrano 2013	Adequate	Adequate	Inadequate	Adequate	Adequate	B

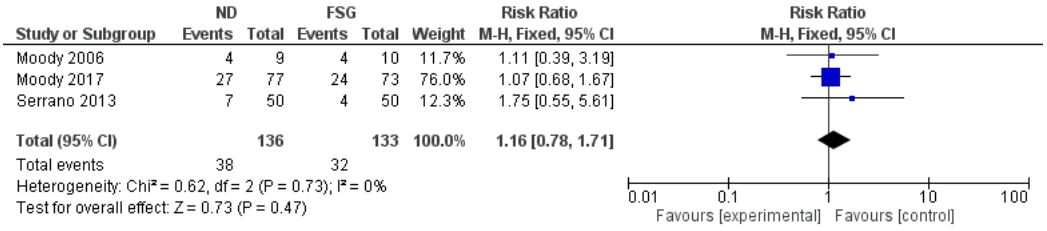

Figure 2: Summary of risk ratio of febrile neutropenia among patients under neutropenic diet versus regular diet.

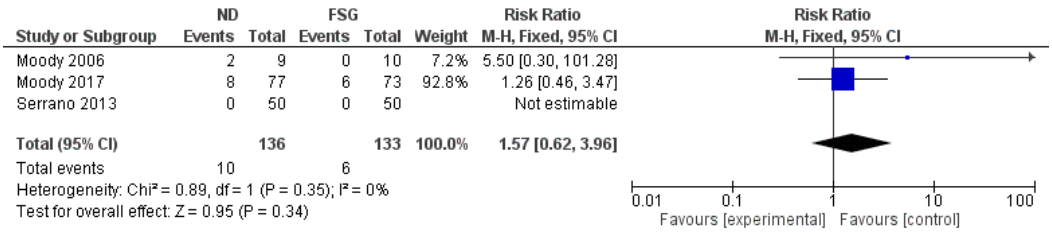

Figure 3: Summary of risk ratio of culture proven bacteremia among patients under neutropenic diet versus regular diet.

Furthermore, according to Esbenshade et al, there is evidence that there is an imbalance in the nutritional intake of pediatric patients diagnosed with leukemia and central nervous system tumors (the most common pediatric cancers). As caloric intake decreases during therapy, fat intake increases. Therefore, the nutritional value of foods should be prioritized over total caloric intake in planning a dietary regimen for these patients [13].

This study is the first meta-analysis on the efficacy of neutropenic diet exclusively among pediatric cancer patients undergoing chemotherapy. The results are in congruence to the studies done among adult patients. Results from this study can further advise against the continued application of neutropenic diet.

One major limitation of this study is the lack of information regarding varied prophylactic measures within the included studies such as antibiotic use and administration of granulocyte colony-stimulating factor. Information regarding adherence to the prescribed diet regimen is also lacking.

Conclusion

This meta-analysis shows that there is not enough evidence to support the use of neutropenic diet among pediatric patients undergoing chemotherapy. There are a number of studies that show the negative impact of its use, resulting in a significant decrease in the quality of life of patients. Clinicians should be aware of the possible implications of applying this dietary regimen to pediatric cancer patients.

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