Neutropenic diet during high-dose therapy: a risk for patients

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Statement

- of the German Cancer Society, Working Group Prevention and Integrative Oncology (PRIO)
- the German Society for Hematology and Medical Oncology, Working Group Nutrition, Metabolism, Exercise;
- the German Association of Dietitians an the
- Professional Association of Oecotrophologists

Abstract

The neutropenic diet has been a dietary regimen prescribed in many centers to patients undergoing intensive chemotherapies and/or hematologic stem cell transplantation for decades. However, evaluation of the scientific data on the low-germ diet shows that this diet has no benefit but considerable risks for patients. Therefore, this form of nutrition is not indicated.

The undersigned professional societies and working groups therefore call on all physicians, nurses, nutrition therapists and dieticians to provide comprehensive nutritional medical advice to patients undergoing and after intensive chemotherapy. This includes detailed information and training of patients and relatives on hygiene measures in the kitchen and when consuming food.

Key words: neutropenic diet, chemotherapy, hematologic stem cell transplantation, immunosuppression, malnutrition, hygiene training, cancer, nutritional medicine, nutritional therapy

Background

In the context of hematologic stem cell transplantation (HSCT), the immune system is severely weakened by chemotherapy [1]. Therefore, for more than three decades, patients undergoing HSCT have been significantly restricted in their food choices by a so-called neutropenic diet [1]. By avoiding numerous foods and special instructions for preparation, the risk of food infection is to be reduced by the immunosuppressed patients [2]. This seems rational at first, as infections are indeed associated with increased morbidity and mortality in affected individuals [3]. Nevertheless, there is a lack of scientific evidence as to whether adherence to a neutropenic diet prevents infections [1]. This is relevant because strict limitation of dietary options may affect quality of life and compromise body weight maintenance.

According to the definition of the Robert Koch Institute (RKI), a neutropenic diet is an "Expli-

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Professional society, year [reference]	Opinion
German Cancer Society, 2014 [9]	Recommendations are made that can be assigned to a strict neutropenic diet. This involves talking about "bacterial-free" nutrition in the neutropenia phase and "bacterial-reduced" in the leukocyte regeneration phase.
German Society for Nutritional Medicine (DGEM), 2015 [10]	Neutropenic diets are not explicitly mentioned, but "dietary restrictions that limit food intake in patients with (impending) malnutrition can be ... potentially harmful and should be avoided."
German Society for Hematology and Medical Oncology (DGHO), 2017 [11].	The diet of patients with a weakened immune system should be decided on a more individual basis. In addition, evidence-based education programs are recommended by all stakeholders.
European Society for Clinical Nutrition and Metabolism (ESPEN), 2021 [12]	A neutropenic diet is not recommended due to the lack of evidence.
Robert Koch Institute, 2021 [4]	The strict implementation of a neutropenic diet is explicitly rejected "because its benefits are unproven and such a diet significantly impairs patients' quality of life."

Tab. 1: **Opinions by several professional societies and the Robert Koch Institute on neutropenic diets**

cit avoidance of any food that may cause infections in immunocompromised patients via contamination with and transmission of facultative pathogenic or opportunistic microorganisms." [4]
In practice, this is done in different ways. In 2006, Moody et al [5] defined a diet as "low-bacterial" (neutropenic diet) if it excluded raw fruits that cannot be peeled and if it did not include raw vegetables, aged cheese, cold cuts, fast food, or food prepared away from home. In their study published in 2018 [6], nuts and yogurt were additionally excluded for this dietary pattern. Van Thiel et al [7], in a clinical trial published in 2007, investigated a "low bacterial diet" without raw vegetables, lettuce, soft cheeses, raw meats, fresh fruits, tap water, and spices that were not heated. In 2012, Trifilio et al [8] reported a "low bacterial" diet (neutropenic diet) that did not include fresh fruits or vegetables, black pepper, raw or undercooked meat, undercooked cheese products, cold-smoked fish, non-pasteurized dairy products, raw miso products, raw cereal products, or brewer's yeast.
Due to the restricted selection of foods and the intensive preparation, the dietary form of a neutropenic diet can promote malnutrition [13]. In addition, food prepared according to the regulations is not very appetizing and is visually and tastily inadequate, so that food intake is additionally restricted as a result. These factors can exacerbate malnutrition. Malnutrition is associated with a significantly reduced survival prognosis of patients [14].
This is particularly critical as 35% of patients suffer from malnutrition after autologous HSCT [15] and up to 60% after allogeneic HSCT [16]. This is due to the side effects of the therapy such as nausea, vomiting, diarrhea, and mucositis, which can also lead to reduced food intake and thus to malnutrition and anorexia [13, 17, 18]. Another relevant aspect is that the changes in the intestinal microbiome (dysbiosis) triggered by chemotherapy already impair the functionality of the intestinal mucosa as a defense barrier [19, 20] and that drastic restrictions induce further disturbances in the microbiome [21, 22]. A critical examination of the evidence on a neutropenic diet and a clear definition of the patients for whom this is necessary is essential in order to minimize the risk of malnutrition.

While the use of such a low-germ diet has been largely maintained in many transplant centers, the opinions of relevant professional societies have changed over the past decade and have recently come out against the strict implementation of a neutropenic diet (◆ Table 1). In contrast, decisive importance is attached to reliable adherence to basic hygiene measures in the purchase, storage, and preparation of food (safe food handling). Foods with a high risk of bacterial contamination by pathogens should be furthermore avoided [4].

Neutropenic diet in criticism

As early as 2002, there were critical discussions about the neutropenic diet [23]. Subsequent studies found that it was even associated with a worse disease prognosis.

This was confirmed in 2008 by a randomized controlled trial (RCT) (n = 153) in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome (10% to 19% blasts in bone marrow or peripheral blood). Patients consumed either only fresh (but prepared or washed according to Food and Drug Administration (FDA)-compliant food hygiene) or only adequately cooked fruits and vegetables according to the neutropenic diet (ND). In the ND group 29% and in the comparison group 35% of the participants suffered an infection (major infection), accompanied by pneumonia, bacteremia and/or fungemia. This difference was not significant (p = 0.60). In addition, 51% of participants in the ND group showed fever of unclear origin compared to 36% in the comparison group (p = 0.07) [24].

In 2012, a retrospective study (n = 726) examined the impact of ND after HSCT. This showed that 37.2% of ND patients and 29.2% with a standardized diet (SD) according to the Academy of Nutrition and Dietetics, had a microbiologically confirmed infection (p < 0.0272) [25].

In 2014, a pilot RCT (n = 46) examined the difference between a ND versus an unrestricted diet in patients undergoing allogeneic HSCT. Both groups received an FDA recommendation in safe food handling, preparation, and storage. There were 28% confirmed infections in the ND group and 30% in the comparison group (p = 0.99) [26].

An analysis of the pediatric AML-BFM 2004 study published in 2016 showed that dietary restriction in the form of ND did not significantly reduce fever of unclear origin, pneumonia, gastroenteritis, and bacteremia in 339 children in 37 German hematology centers [27].

In 2018, ND was studied in a pediatric multicenter RCT (n = 150) with various cancers. Again, it showed no advantage over FDA food safety guidelines in cancer patients [28]. Only 8.3% of participants who followed the FDA guidelines and 10.4% of those who additionally followed a ND had developed a microbiologically confirmed infection (p = 0.67). Due to the more difficult implementation, adherence to ND was significantly lower at 92.6 (± 15.3) % compared to FDA at 99.3 (± 4.8) % (p < 0.001) [6].

The key message of the individual studies could be corroborated in meta-analyses. A 2015 meta-analysis examined three RCTs and one observational study with a total of 918 participants with various malignancies. Both ND and SD patients had a comparable number of major infections (relative risk [RR] = 1.08, confidence interval [CI] 0.72–1.61, I2 = 39%) [29].

Nevertheless, in a 2018 survey of 90 centers (6 from Germany) of the European Society for Blood and Marrow Transplantation in 23 countries, 93% of participants reported that they recommend ND to patients during the neutropenia phase in HSCT. This is often administered standardized or fortified with high-calorie ingredients and nutritional supplements [30].

Increasing evidence against the use of neutropenic diet

Another meta-analysis published in 2019 from five RCTs with 388 patients undergoing intensive chemotherapy for acute leukemia or childhood sarcoma confirmed the uniqueness of the presented study results. Here, 53.7% of ND participants (different definition, but exclusion of raw fruits and vegetables) and 50% in the comparison group (standard hospital diet or diet according to FDA food safety guidelines) suffered an infection, usually defined as pneumonia, bacteremia, and fungemia (p = 0.10) [31]. A 2019 meta-analysis of five RCTs from six included studies also examined ND in 1116 patients. Within the 69.1% HSCT patients, an increased risk of infection was found with adherence to ND (p = 0.03; RR 1.25; 95% CI 1.02–1.54) [32].

> **Based on these data, it seems reasonable that ND after HSCT should not be offered as standard, but solely in the context of studies to clarify possible efficacy.**

The advancing evidence base is now also reflected in the RKI's 2021 recommendation: The RKI announcement "Requirements for infection prevention in the medical care of immunocompromised patients" [4] emphasizes the importance of patient safety and their quality of life. It is intended to support all medical professional groups to improve the care of immunocompromised patients. This includes training of staff, patients and their relatives, as well as basic hygiene measures in the facility and out-of-hospital settings.

These must also be observed during nutrition. In order to ensure adequate nutritional care during the inpatient stay, individualized nutrition may be necessary, especially during intensive therapy. This is to counteract complications such as cachexia. Here, the Commission for Hospital Hygiene and Infection Prevention of the Robert Koch-Institute emphasizes that a strict neutropenia diet is not suitable.

- Basic hygiene measures in the purchase, storage and preparation of food are essential in order to maintain a low risk of bacterial contamination even in the out-of-hospital context [4].
- Intensive education of patients is intended to sustain compliance with appropriate food hygiene and preparation.

- Accordingly, all-inclusive education begins with purchasing and ends with consumption [33, 34]. Patients should learn the proper selection of intact foods, their refrigeration, transportation, and storage. They should be aware of sources of infection such as raw foods (e.g. minced meat, fish, eggs). In this context, cleaning of hands, surfaces and kitchen utensils should also be taught to avoid cross-contamination.
- For appropriate food preparation, the importance of washing, peeling and blanching, as well as the assessment of adequate heating and cooling, should be explained.

The usefulness of these measures as opposed to extensive heating was confirmed in a laboratory study. In this, the microbiological load of one SD and one ND hospital food was examined. Of 36 samples, two each of the SD and ND were contaminated with B. cereus and one of the ND with coagulase-positive Staphylococcus ($p = 1.00$). Furthermore, this was found in one dish that had undergone a cooking process. This emphasizes the importance of hygiene of food and its preparation [35].

Conclusions

In the context of evidence-based care for patients with intensive chemotherapy regimens, including patients with HSCT, a neutropenic diet is not indicated because it provides no benefit but carries significant risks for patients.

The undersigned associations, professional societies and working groups therefore call on all physicians, nurses, nutrition therapists and dieticians in hospitals and practices to provide comprehensive nutritional advice to patients undergoing and after intensive chemotherapy. This includes detailed information and training for patients and relatives on hygiene measures in the kitchen and when eating food. Any weight loss must be countered by appropriate nutritional medical measures. Qualified nutritional counseling is the first priority here.

Conflict of Interest
Opinions and position papers reflect the viewpoints and assessments – including the interests – of the organization(s) named in the author line. The authors declare that there are no further conflicts of interest in connection with the contents of this publication.

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