The Oncologist®

Symptom Management and Supportive Care

The Benefit of the Neutropenic Diet: Fact or Fiction?

STEVEN J. JUBELIRER

WVU Charleston Division, CAMC Research Institute, and David Lee Outpatient Center, Charleston, West Virginia, USA

Key Words. Neutropenic diet • Neutropenia • Clinical trials • Food guidelines

Disclosures: Steven J. Jubelirer: None.
The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the author or independent peer reviewers.

ABSTRACT

There really should not be a debate about the use of neutropenic diet for cancer patients. Its usefulness has never been scientifically proven. However, neutropenic diets remain in place in many institutions even though their usefulness is controversial. Neutropenic diets were once thought to be important in protecting patients from having to succumb to infection from neutropenia while undergoing chemotherapy. Although food may contain harmful organisms and research has shown that bacterial translocation is possible, recent studies have been unable to obtain significant differences between placebo and intervention groups. The dietetic challenges neutropenic patients struggle with include decreased quality of life, malnutrition, gastrointestinal side effects, food aversion, and impaired cell-mediated immunity from vitamin deficiency. Unanswered questions in regard to the neutropenic diet include the following: (a) which food should be included; (b) which food preparation techniques improve patient compliance; (c) which patient populations benefit most; and (d) when should such a diet be initiated. Without scientific evidence, the best advice for neutropenic patients is to follow food safety guidelines as indicated by government entities. ***The Oncologist*** 2011;16:704–707

INTRODUCTION

Chemotherapy has had a major impact on the survival rates of patients with cancer, particularly those with hematologic malignancies. Neutropenia due to chemotherapy is the major risk factor for infection [1]. Several studies [2, 3] reported the isolation of gram-negative organisms such as *Pseudomonas aeruginosa, Escherichia coli, Klebsiella*, and *Proteus* from a variety of foods, particularly salads, fresh vegetables, and cold meats. *Aspergillus*, a fungus often lethal to patients with prolonged neutropenia, was found to be isolated from food, water, and ice [4].

The movement of these bacteria from the gastrointestinal tract (GI tract) to other body sites, called bacterial translocation [5], is thought to cause many of the infections in patients with neutropenia. Deitch et al. [6] demonstrated that bacteria in the GI tract can travel through the intestinal mucosa to infect mesenteric lymph nodes and body organs. Bacterial overgrowth, immunosuppression, physical dis-

Correspondence: Steven Jubelirer, M.D., Clinical Professor of Medicine, WVU Charleston Division, Senior Research Scientist, CAMC Research Institute, and via mail at David Lee Outpatient Center, Suite 101, 3100 MacCorkle Avenue SE, Charleston, West Virginia 25304, USA. Telephone: 304-388-8380; Fax: 304-388-8395; e-mail: steven.jubelirer@camc.org; christine.welch@camc.org Received January 3, 2011; accepted for publication February 14, 2011; first published online in ***The Oncologist*** *Express* on April 6, 2011. 1083-7159/2011/$30.00/0 doi: 10.1634/theoncologist.2011-0001

ruption of the gut by chemotherapy or radiotherapy, slowed peristalsis due to narcotics or antidiarrheal agents, trauma, and endotoxins are factors contributing to bacterial translocation [7]. Theoretically, bacterial translocation can be decreased by reducing sources of pathogenic bacteria from food and decreasing the bacterial burden of the gut with oral nonabsorbable antibiotics.

The above studies led to the use of the neutropenic diet. The neutropenic diet is also called a sterile diet, low microbial diet, or a low bacterial diet (LBD). However, a standardized definition of the neutropenic diet has not been established [8, 9]. Variations of the neutropenic diet include an exclusively sterile diet (e.g., all foods that have been made sterile by canning, baking, autoclaving, or irradiation), a LBD (well-cooked foods only), or a modified house diet (i.e., a regular diet omitting fresh fruits and vegetables) [8–11].

The benefit of the neutropenic diet has never been scientifically proven [12]. Despite this, neutropenic diets are used in many institutions. A descriptive telephone survey by Todd et al. [11] looked at the use of LBDs for chemotherapy-induced neutropenia among 21 childrens' hospitals and found that (a) 43% of these hospitals used the neutropenic diet for neutropenic non–bone marrow transplant patients and (b) 86% of these hospitals used the neutropenic diet for bone marrow transplant patients. French et al. [13] surveyed 10 bone marrow transplant centers in Canada and northwestern United States and reported that 5 of the 7 responding hospitals used a neutropenic diet. However, the timing of the start of the diet and the food choices that were allowed varied with each institution. In a national survey, Poe et al. [14] found that 66% of responding transplant units enforced some type of modified microbial diet. Smith and Besser [9] surveyed 400 members of the Association of Community Cancer Centers (ACCC) and reported that 78% of the responding hospitals restricted diets of patients with neutropenia. The most commonly prohibited food items in these institutions were fresh vegetables and fruits, fresh juices, and raw eggs. Criteria for dietary restrictions varied between hospitals. The most common reasons for restricted diets were documentation of neutropenia defined as a white cell count $<1{,}000\ mm^3$ and documentation of risk factors for neutropenia such as recent chemotherapy.

Published Studies on the Neutropenic Diet and Incidence of Infection in Cancer Patients

The current rationale for recommending the neutropenic diet is based on prospective cohort or randomized studies performed in the 1960s and 1970s in which leukemia patients were placed in a total protective environment in the hospital setting [10] (i.e., isolation tents, use of oral nonabsorbable antibiotics, laminar air flow, and sterile diet). In this controlled environment, patients were found to tolerate higher doses of chemotherapy with less toxicity, including infections. Although these early studies suggested that protected environments may offer some protection from infection, the independent effect of the neutropenic diet on infection rates was unclear.

In a more recent study by Moody et al. [15], 19 pediatric patients receiving myelosuppressive chemotherapy were randomized to a neutropenic diet or to the Food and Drug Administration–approved (FDA-approved) food safety guidelines diet [16]. Patients randomized to the neutropenic diet were given dietary restrictions that included not eating raw fruits (except for those that could be peeled by hand), raw vegetables, aged cheeses, cold meat cuts, fast food, and takeout food. For the most part, all patients on the food safety guideline diet adhered to the diet while adherence was 94% for the neutropenic diet. There were no statistically significant differences between the two groups with respect to the degree and duration of neutropenia (absolute neutrophil count $<1{,}000\ mm^{-3}$), median number of cycles of chemotherapy, use of postchemotherapy filgastrim, and comorbidities. Four patients on each diet developed febrile neutropenia, and the authors concluded that infection rates between the groups were similar.

Gardner et al. [17] studied 153 newly diagnosed acute myelocytic leukemia (AML) patients who were admitted to a high-efficiency particulate air-filtered room to receive induction therapy. With use of their early risk of mortality (ERM) score for stratification, patients were randomly assigned to a diet with (uncooked $n = 75$) or without (cooked $n = 78$) fresh fruits and vegetables. Prophylaxis with both antibacterial and antifungal was used for all patients. No differences were found between the groups for age, ERM score, chemotherapy received, or days at risk. The study outcomes showed no significant difference for time to major infection ($p = .44$) or survival ($p = .36$). The proportion of those who developed a major infection was 29% for those in the group without fresh fruits and vegetables and 35% for those allowed to have fresh fruits and vegetables ($p = .60$). Fevers of unknown origin developed in 51% of the cooked group and 36% of the raw group ($p = .07$).

DeMille et al. [8] sought to determine whether the use of the neutropenic diet (no fresh fruits and vegetables) in an outpatient setting influenced the number of febrile admissions and positive blood cultures. Twenty-three patients aged 33–67 years completed a 12-week program in which they were instructed on the neutropenic diet prior to chemotherapy. Study personnel used phone calls to assess adherence at 6 and 12 weeks and reviewed hospital charts at the

end of the study. Sixteen patients were deemed compliant while seven were noncompliant. Four (25%) from the compliant group had a febrile admission, three of whom had gram-negative bacteremia, whereas one (14%) of the noncompliant group had a gram-negative febrile admission.

In a study by van Tiel et al. [18], 20 adult patients with acute leukemia (acute lymphoblastic leukemia [ALL] and AML) receiving remission-induction chemotherapy were randomized into two groups: one group to receive antimicrobial prophylaxis (Cipro) and a LBD, and the other group to receive the same antibacterial prophylaxis and a normal hospital diet. During chemotherapy cycles, fecal samples were collected daily to detect gram-negative bacilli or Candida species. There were no differences in the two groups with respect to mean age, mean weight, total number of chemotherapy cycles, and total number of days within chemotherapy cycles. There were no statistically significant differences between the treatment groups regarding the incidence of stool colonization by yeasts and gram-negative bacilli, confirmed and unconfirmed infections, and number of days of antibiotic use.

There are major limitations of most of these studies. These include the following: (a) small sample size; (b) the absence of documentation and/or measurement of other variables that determine the incidence of neutropenic infection including the degree and duration of neutropenia, exposure to viruses, use of granulocyte colony-stimulating factors, hematologic versus solid tumors, and extent of mucositis; and (c) potential study bias due to awareness of the neutropenic diet by patients assigned to the regular diet arm, resulting in their reluctance to eat fresh fruits or vegetables. Larger randomized studies powered adequately to compare infection rates between a normal diet and neutropenic diet are needed. Such a study has been initiated by Moody [19] (Montefiore Hospital, New York) to compare the FDA-approved food safety diet to the neutropenic diet with respect to rate of infection during neutropenia in patients aged 1–21 years receiving chemotherapy for ALL, AML, sarcoma, and neuroblastoma. The neutropenic diet in this study emphasizes the avoidance of the following: raw vegetables and fruits except oranges and bananas; takeout food and fast foods; aged cheese (blue, Roquefort, and Brie); deli meats; raw nuts or nuts roasted in shell; well water; and yogurt. An estimated 900 patients will be enrolled.

Are There Published Guidelines on the Use of the Neutropenic Diet?

Because there is an absence of evidenced-based studies supporting the use of the neutropenic diet, there are no official published guidelines on its use. The National Comprehensive Cancer Network (NCCN) 2009 guidelines [20] on prevention and treatment of infectious complications do not mention the use of the neutropenic diet. The Oncology Nursing Society (ONS) Cancer Chemotherapy guidelines and Recommendations for Practice [21] state that "no recent studies have linked dietary restrictions with a lower risk of infection for neutropenic patients with cancer; however, basic principles, such as avoiding uncooked meats, seafood, eggs, and unwashed fruits and vegetables, may be prudent." The United States Department of Agriculture (USDA) recommendations for food safety for people with cancer [22] include the following: (a) consumption only of pasteurized juices and dairy products; (b) washing hands in warm soapy water before handling, preparing, and eating food; (b) consuming food that has not passed the expiration date; and (d) storing raw meat, fish, and chicken carefully in wrapped containers to avoid spillage of juice onto other foods. Notably there is no recommendation for the restriction of fresh fruits and vegetables.

Conclusion

Further research needs to be conducted to better evaluate the use of neutropenic diet. Research questions to consider might include the following: (a) Which food choices and food-preparation techniques would best improve patient compliance? (b) Is there a specific oncology population who benefits most from the use of neutropenic diet? (c) Is there a role for the neutropenic diet in neutropenic chemotherapy patients independent of other interventions (i.e., antibiotics, growth factors, and use of private room) used to prevent infection? (d) Should the neutropenic diet be initiated at the start of chemotherapy or only when neutropenia develops?

Until this research is completed, the available evidence does not support use of the neutropenic diet. In addition, neutropenic diets are not standardized. Several studies have emphasized the importance of food in patients' quality of life [10, 15]. Patients receiving chemotherapy undergo many stressors including body image changes and an uncertain future [8]. Many patients identify appetite and weight as variables within their control, and food is seen as a nurturing and comforting area of life [8].

References

1 Bodey GP, Buckley M, Sathe YS. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 1966;64:328–340.

2 Casewell M, Phillips I. Food as a source of *Klebsiella* species for colonization and infection of intensive care patients. J Clin Path 1978;31:845–849.

3 Pizzo PA, Purvis DS, Waters C. Microbiologic evaluation of food items. J Am Diet Assoc 1982;81:272–279.

4 Thio CL, Smith D, Merz WG et al. Refinements of environmental assessment during an outbreak investigation of invasive aspergillosis in a leukemia and bone marrow transplant unit. Infect Control Hosp Epidemiol 2000; 21:18–23.

5 Berg RD. Bacterial translocation from the gastrointestinal tract. Adv Exp Med Biol 1999;473:11–30.

6 Deitch E, Winterton J, Li M et al. The gut as a portal of entry for bacteremia. Ann Surg 1987;205:681–692.

7 Carter LW. Bacterial translocation: nursing implications in the care of patients with neutropenia. Oncol Nurs Forum 1993;20:1241–1250.

8 DeMille D, Deming P, Lupinacci P et al. The effect of the neutropenic diet in the outpatient setting: a pilot study. Oncol Nurs Forum 2006;33:337–343.

9 Smith LH, Besser SG. Dietary restrictions for patients with neutropenia: a survey of institutional practices. Oncol Nurs Forum 2000;27:515–520.

10 Moody K, Charlson ME, Finlay J. The neutropenic diet: what's the evidence? J Pediatr Hematol Oncol 2002;24:717–721.

11 Todd J, Schoride M, Christain J et al. The low bacteria diet for immunocompromised patients: reasonable prudence or clinical superstition? Cancer Pract 1979;7:205–207.

12 Wilson BJ. Dietary recommendations for neutropenic patients. Semin Oncol Nurs 2002;18:44–49.

13 French MR, Levy-Milane R, Zibrik D. A survey of the use of low microbial diets in pediatric bone marrow transplant programs. J Am Diet Assoc 2001; 101:1194–1198.

14 Poe SS, Larson E, McGuire D et al. A national survey of infection prevention practices on bone marrow transplant units. Oncol Nurs Forum 1994; 21:1687–1694.

15 Moody K, Finlay J, Mancuso C et al. Feasibility and safety of a pilot randomized trial of infection rate: neutropenic diet versus standard food safety guidelines. J Pediatr Hematol Oncol 2006;28:126–133.

16 Gateway to Government food safety information, advice for consumers. 2005. Available at http://www.foodsafety.gov.

17 Gardner A, Mattiuzzi G, Faderl S et al. Randomized comparison of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukemia. J Clin Oncol 2008;26:5684–5688.

18 van Tiel FH, Harbers MM, Terporten PHW et al. Normal hospital and low bacterial diet in patients with cytopenia after intensive chemotherapy for hematological malignancy: a study of safety. Ann Oncol 2007;18:1080–1084.

19 Moody K. The effectiveness of the neutropenic diet in pediatric cancer patients. Available athttp://ClinicalTrials.gov.

20 National Comprehensive Cancer Network (NCCN) guidelines on prevention and treatment of infectious complications. 2009. Available at http://www.nccn.com. Accessed October 13, 2009.

21 Oncology Nursing Society. Prevention of infection. What interventions are effective in preventing infection in people with cancer? ONS Putting Evidence into Practice (PEP). 2005;1–8.

22 U.S. Department of Agriculture. Food safety of people with cancer. Available at http://www.fsis.usda.gov/PDF/Food_Safety_for_People_with_Cancer.pdf. September 2006. Accessed May 19, 2009.