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Neutropenic Dietary Restrictions for Hematopoietic Stem Cell Patients: Time for a Change

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In the 1960s and 1970s, eradication of host bacteria was thought to be achievable and beneficial for avoiding infection in the immunocompromised host. At that time, patients were fed autoclaved, sterile foods and kept in totally protected environments [1]. Over time, there became an obvious need to liberalize dietary options in these patients, because the sterile foods were not palatable and did not provide enough variety [1]. The neutropenic diet was developed to meet this need and essentially eliminates certain food groups, most commonly raw fruits and vegetables, which contain bacteria, in an effort to decrease bacterial content and potential pathogens from colonizing the gastrointestinal tract. This reduction in gastrointestinal flora and potential pathogens is hypothesized to reduce risk of bacterial translocation and subsequent bacteremia [2]. Notably, the theoretical basis of this practice has never been proven in a clinical trial. Despite a lack of clinically relevant data, the neutropenic diet remains a very common recommendation among HSCT clinicians, justified by claims of "prudent practice" and "should not cause any harm" [3]. However, several factors have led to a reevaluation of this practice, including increased interest by families and physicians in nutrition and its impact on medical and quality of life-related outcomes, substantial improvements in supportive care and anti-infection strategies, and emerging data on the role of the microbiome in health and disease [4].

Renewed interest in the rationale for use of the neutropenic diet has resulted in publication of survey data regarding practice patterns that show great variability within and across institutions and countries regarding the content and timing of the neutropenic diet recommendations [5]. These studies also show that the neutropenic diet is most often used in the hematopoietic stem cell transplantation (HSCT) setting [6]. Observational studies have also emerged showing no differences in infection rates between patients following a neutropenic diet versus those on a regular hospital diet [7]. Finally, randomized controlled trials in neutropenic cancer patients confirmed that the neutropenic diet does not confer protection against infection or gut colonization [4,8,9].

Concurrently, in 2000, the Centers for Disease Control and Prevention, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation cosponsored official guidelines for food safety among HSCT recipients [10]. In these guidelines, HSCT recipients were recommended to follow food safety practices appropriate for all persons to decrease the risk of foodborne infections. These food safety practices were created based on data collected during foodborne infectious disease outbreaks. They include guidance for food shopping, storage, cooking, and handling to reduce risk of foodborne infection (eg, cook meats well done). A low-microbial diet was also included in the recommendations for HSCT recipients; however, raw fruits and vegetables were not totally excluded from the diet. Instead, only fruits deemed difficult to clean due to their rough surface (eg, raspberries) and raw vegetable sprouts were to be avoided. Notably, other washed fruits and vegetables were acceptable. A short list of specific foods were still recommended to be eaten cooked: tofu, nuts, grains, and yeast. This low-microbial diet was only minimally changed in the 2009 published updates [11] (Table 1). The consumption of fast foods is also allowed according to these guidelines with some associated prudent advice, such as "ask that food be freshly prepared." Interestingly, in 2009 the authors reported that "concern arising from the detection of potential pathogens in food has not been supported by documented evidence of such organisms as the source of opportunistic infections in immunocompromised persons. The potential benefit of food safety recommendations directed specifically toward HSCT recipients must be weighed against the uncertain value of such recommendations. . .and their potential to adversely affect patients' nutritional intake and/or quality of life."

Another concern relevant to this discussion is the emerging science regarding the role of the human microbiome in transplantation-related complications, including infection, graft-versus-host disease (GVHD), and mortality. Interventions that restore a healthy and biodiverse microbiome may lead to

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Table 1
HSCT Recipient Low-Microbial Diet Endorsed by the Centers for Disease Control and Prevention, Infectious Disease Society of America, and American Society of Blood and Marrow Transplantation [11]

Do Not Eat	May Eat
Raw and undercooked eggs and foods containing them (eg, French toast, omelets, salad dressings, eggnog, puddings)	Pasteurized or hard-boiled eggs
Unpasteurized dairy products (eg, milk, cheese, cream, butter, and yogurt)	Pasteurized dairy products
Fresh-squeezed, unpasteurized fruit and vegetable juices	Pasteurized juices
Unpasteurized cheeses or cheeses containing molds	Pasteurized, commercially packaged cheeses; cooked soft cheeses
Undercooked or raw poultry, meats, fish, and seafood	Cooked poultry, well-done meats, cooked fish, and seafood
Raw or lightly cooked vegetable sprouts (eg, alfalfa, bean, other seed sprouts)	Sprouts should be washed and well-cooked
Berries, raw	Cooked or canned berries
Unwashed, raw, fruits	Should be washed under running water, peeled, cooked, or dried
Unwashed raw vegetables	Should be washed under running water, peeled, or cooked; avoid fresh salsa and nonpasteurized preprepared items containing raw fruit in the grocery refrigerator (eg, salsa)
Undercooked or raw tofu	Cooked tofu: avoid miso
Raw or unpasteurized honey	Should be avoided; use pasteurized honey for children age >1 yr
Uncooked hot dogs and food from deli slicers	Should be avoided unless further cooked until steaming, or use commercially packaged luncheon meats
Raw, uncooked grain products	Cooked grain products including bread, cooked, and ready-to-eat cold cereal, pretzels, popcorn, potato chips, corn chips, tortilla chips, cooked pasta, and rice
Maté tea	Should be avoided
All moldy and outdated food products	Should be avoided
Unpasteurized beer (eg, homebrews and certain microbrewery brews)	Pasteurized beer (eg, retail bottled or canned, or draft beer that has been pasteurized after fermentation)
Raw, uncooked brewer's yeast	Should be avoided; HSCT recipients should avoid any contact with raw yeast (eg, should not make bread products themselves)
Unroasted raw nuts	Cooked nuts
Roasted nuts in the shell	Canned or bottled roasted nuts or nuts in baked products

improvements in these adverse HSCT outcomes. In fact, some ongoing studies are looking at interventions to support the microbiome in this population including dietary changes (adding back raw fruits and vegetables), prebiotics, probiotics and fecal microbial transplants [12].

So then, why is it, in the face of expert recommendations informed by best evidence, and a lack of relevant rationale, do we clinicians continue to recommend the broad elimination of raw fruits and vegetables, and other foods, in HSCT recipients' diets? Perhaps it can be attributed to habit, coupled with a historical lack of clinical studies in HSCT.

In this issue of *Biology and Bone Marrow Transplant,* Taggart et al [13] contribute to the state of the science, by reporting on a controlled before-and-after study comparing a neutropenic diet with a food safety-based diet in 102 pediatric patients undergoing HSCT. Notably the food safety diet used in this study allows for consumption of all fresh fruits and vegetables, if washed under running water and free from visible damage; it also allows freshly prepared fast food, and packaged lunch meats. Similar to previous studies in neutropenic, non-HSCT populations, they found no difference in bloodstream infections between the 2 groups. Furthermore, Taggert at al [13] found no significant between-group differences in the rates of viral infections, GVHD, total parenteral nutrition use, and death in the first 100 days. That study, the first published study of the neutropenic diet in children undergoing HSCT, provides valuable evidence that the neutropenic diet does not reduce infection rate in this population. This finding is consistent with the studies in adult HSCT recipients [14,15]. Although the evidence in HSCT is limited to nonrandomized studies and a small randomized controlled trial, the findings also match those obtained from every other clinical trial in neutropenic cancer patients, as shown in 3 recent meta-analyses [16–18].

The time has come to stop eliminating raw, washed fruits and vegetables from the diets of HSCT patients and start implementing food safety guidelines to prevent foodborne infection while we aim to further understand the diverse microbiome, how to support it, and how it supports health.

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