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Bacterial Foodborne Infections after Hematopoietic Cell Transplantation

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A B S T R A C T

Diarrhea, abdominal pain, and fever are common among patients undergoing hematopoietic cell transplantation (HCT), but such symptoms are also typical with foodborne infections. The burden of disease caused by foodborne infections in patients undergoing HCT is unknown. We sought to describe bacterial foodborne infection incidence after transplantation within a single-center population of HCT recipients. All HCT recipients who underwent transplantation from 2001 through 2011 at the Fred Hutchinson Cancer Research Center in Seattle, Washington were followed for 1 year after transplantation. Data were collected retrospectively using center databases, which include information from transplantation, on-site examinations, outside records, and collected laboratory data. Patients were considered to have a bacterial foodborne infection if *Campylobacter jejuni/coli*, *Listeria monocytogenes*, *E. coli* O157:H7, *Salmonella* species, *Shigella* species, *Vibrio* species, or *Yersinia* species were isolated in culture within 1 year after transplantation. Non-foodborne infections with these agents and patients with pre-existing bacterial foodborne infection (within 30 days of transplantation) were excluded from analyses. A total of 12 of 4069 (.3%) patients developed a bacterial foodborne infection within 1 year after transplantation. Patients with infections had a median age at transplantation of 50.5 years (interquartile range [IQR], 35 to 57), and the majority were adults ≥18 years of age (9 of 12 [75%]), male gender (8 of 12 [67%]) and had allogeneic transplantation (8 of 12 [67%]). Infectious episodes occurred at an incidence rate of 1.0 per 100,000 patient-days (95% confidence interval, .5 to 1.7) and at a median of 50.5 days after transplantation (IQR, 26 to 58.5). The most frequent pathogen detected was *C. jejuni/coli* (5 of 12 [42%]) followed by *Yersinia* (3 of 12 [25%]), although *Salmonella* (2 of 12 [17%]) and *Listeria* (2 of 12 [17%]) showed equal frequencies; no cases of *Shigella*, *Vibrio*, or *E. coli* O157:H7 were detected. Most patients were diagnosed via stool (8 of 12 [67%]), fewer through blood (2 of 12 [17%]), 1 via both stool and blood simultaneously, and 1 through urine. Mortality due to bacterial foodborne infection was not observed during follow-up. Our large single-center study indicates that common bacterial foodborne infections were a rare complication after HCT, and the few cases that did occur resolved without complications. These data provide important baseline incidence for future studies evaluating dietary interventions for HCT patients.
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INTRODUCTION

Immunocompromised patients are known to be vulnerable to foodborne pathogens [1-6]. Hematopoietic cell transplantation (HCT) recipients have multiple factors that increase risk for foodborne infections, including profound deficits in innate and adaptive immunity and disruption of gastrointestinal mucosa from transplantation-associated

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radiation therapy, chemotherapy, and graft-versus-host disease (GVHD). Although such alterations provide the ideal milieu for microbial invasion/dissemination, many patients have additional risk factors for bacterial infections, such as transfusion-associated iron overload, enteric acid suppression, and gastrointestinal microbiota perturbations from antibiotic use [7-10]. Furthermore, diagnosis and treatment may be delayed, as symptoms of foodborne infections, notably diarrhea and fever, are nearly universal amongst HCT recipients [11,12].

Most transplantation centers follow guidelines and implement specific dietary strategies to reduce the risk of exposure to foodborne pathogens. Particular emphasis has been placed on restricting the consumption of foods more likely to harbor high-risk bacteria by using various low-microbial diets [13]. However, these commonly applied guidelines have not been evaluated in randomized prospective clinical trials [13,14]. Credence for such recommendations is further stunted by a lack of studies addressing the burden of bacterial foodborne infections in HCT recipients [3,15]. More recent data suggest that restrictive nutritional strategies intended to prevent the consumption of pathogenic organisms may, in fact, increase the risk of infection [16].

We set out to determine the burden of common bacterial foodborne infections in a large comprehensive HCT center. Through retrospective chart review, we aimed to describe the incidence of bacterial foodborne pathogens within our HCT patient population during the first year after transplantation and to assess associated morbidity and mortality. These data are important for determining incidence of bacterial foodborne infections and providing a baseline for future studies evaluating nutritional strategies in this high-risk population.

MATERIALS AND METHODS

Study Design/Participant Eligibility

All HCT recipients who underwent an autologous or allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Washington between January 1, 2001 and December 31, 2011 were eligible for inclusion in this retrospective cohort. Patients with evidence of bacterial foodborne infection 30 days before transplantation were excluded. All study activities were approved by the FHCRC institutional review board, and all participants provided written informed consent according to the principles of the Declaration of Helsinki.

Data Collection

Retrospective data were retrieved from a prospectively collected database of patients undergoing HCT at the FHCRC. Pre- and post-transplantation demographic and outcome data were available from clinical databases and medical records. Clinical and laboratory data after discharge from the center were also available in long-term follow-up databases.

Nutrition, Transplantation Procedures, and Infection Prophylaxis

Patients undergoing transplantation were encouraged to follow an "immunosuppressed patient" diet [13] until 3 months after transplantation (autologous recipients) or until cessation of immunosuppressive drugs (allogeneic recipients). Before transplantation, all patients and caregivers participated in a food safety training course that educated patients not only on what foods to avoid, but also on proper preparation, cleaning, and storage of foods and food products. Nutritional services were available for all patients to assist with questions regarding recommendations, to address post-transplantation dietary issues, and to assure and promote adequate nutrition.

HCT conditioning and GVHD prophylaxis/treatment were performed according to current standardization within the center [17]. Patients who were neutropenic received prophylactic antibacterial therapy with either oral levofloxacin or intravenous ceftazidime. Post-transplantation patients received antiviral prophylaxis with low-dose acyclovir [18] and all patients underwent cytomegalovirus screening and preemptive therapy [19,20]; fungal and *Pneumocystis jirovercii* prophylaxes were also routine. To prevent late encapsulated bacterial infections in patients who developed chronic GVHD, long-term prophylaxis with trimethoprim-sulfamethoxazole, either daily or 3 times weekly, along with daily penicillin VK, was administered to those with previous splenectomies.

Bacterial cultures from blood, stool, and other sites were conducted at the discretion of the primary team, as center-based standard practice documents did not recommend routine testing for foodborne pathogens during initial episodes of diarrhea. All specimens submitted for stool culture were screened for the presence of *Salmonella species (spp)*, *Shigella spp*, *Campylobacter jejuni/coli*, *Yersinia spp*, *Escherichia coli* O157:H7, *Vibrio spp*, *Aeromonas spp* and *Plesiomonas*. The following culture media were used: Hektoen Enteric (HE), blood (Trypticase soy agar with 5% sheep blood), MacConkey, MacConkey-Sorbitol, Yersinia selective and Campy CVA (cefoperazone, vancomycin, and amphotericin B) agars. All specimens were also inoculated into selenite broth and subcultured to HE agar after 12 to 18 hours of incubation. Microbial identification of potential stool pathogens present was performed using a combination of microbiological methods, including biochemical identification methods (eg, VITEK 2 GN ID [Gram-negative identification] card [bioMérieux, Durham, NC]), as well as agglutinating sera for *Salmonella* and *Shigella spp*.

Definitions and Statistical Analysis

All patient events were reviewed up to 1 year after transplantation for bacterial foodborne infections. An infectious event was defined as detection of *C. jejuni/coli, Listeria monocytogenes*, *E. coli* O157:H7, *Salmonella spp*, *Shigella spp, Vibrio spp*, or *Yersinia spp* from any clinical site (excluding the lung) from day 1 to day 365 after transplantation. Site of detection for all bacterial foodborne infections was defined as the site of first positive culture. Cultures epidemiologically linked to a non-foodborne exposure (eg, zoonotic) and *Campylobacter spp* whose primary transmission is not epidemiologically established as foodborne, such as *C. curvus* and *C. ureolyticus*, were excluded from analyses [21]; nonspeciated cases were included and noted as such.

In this study, an attributable cause of death was defined when death was documented as a direct result of the bacterial foodborne infection. Infections in patients who survived beyond 30 days, without recurrence, were considered resolved. All bacterial, viral, and fungal infections were identified as concomitant if they were documented within ± 7 days of foodborne event. The timing and severity of GVHD were reviewed and all episodes were graded according to standard criteria [22]. Neutropenia during bacterial foodborne infection was defined as an absolute neutrophil count of <500 mm cells/mm^3 within ± 2 days of infectious event.

Time at risk for bacterial foodborne infection was considered from the first day after transplantation until the bacterial foodborne event or occurrence of any of the following censoring events: lost to follow-up, death, retransplantation, or 365 days. For patients with multiple transplantation events, the at-risk period was considered only after the first transplantation; the at-risk period of patients who underwent a planned tandem transplantation began after the second transplantation.

Incidence rates of bacterial foodborne infection were estimated by dividing the number of incident cases developed in cohort subjects by the number of post-transplantation at risk patient-days contributed by the overall cohort; 95% confidence intervals (CI) were estimated based on a Poisson distribution. Incidence rates were also stratified by age (pediatric/adult), with those <18 years of age considered pediatric HCT recipients.

RESULTS

Of the 4074 patients who underwent HCT at the FHCRC during the 2001 to 2011 study period, 5 were excluded from the primary analysis because of a pre-existing foodborne event (3 *Yersinia spp*, 1 *C. jejuni*, and 1 *Salmonella spp*). Among the remaining HCT recipients, a total of 12 of 4069 (.3%) of patients developed a post-transplantation bacterial foodborne infection; none experienced multiple events. Patients with these infections had a median age at transplantation of 50.5 years (interquartile range [IQR], 35 to 57) and were primarily adults (9 of 12 [75%]) and male gender (8 of 12 [67%]) (Table 1). The majority of infections also occurred after allogeneic (8 of 12 [67%]) rather than autologous transplantation, although cumulative incidence estimates were similar between the 2 transplantation types (8 of 2540 [.3%] among allogeneic versus 4 of 1529 [.3%] among autologous). Clinical circumstances surrounding the foodborne infectious event can be found in Table 1.

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