Evaluation of the Pretransplantation Workup before Allogeneic Transplantation

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A B S T R A C T

An extensive workup is generally performed before allogeneic transplantation. The extent of this workup varies substantially between centers because of a lack of guidelines. We analyzed 157 consecutive allogeneic transplant candidates to understand the significance of components of the pretransplant evaluation. Workup consisted of chest computed tomography (CT); magnetic resonance imaging of the head; dental, ears-nose-throat (ENT), ophthalmology, and gynecology evaluations; pulmonary function tests; echocardiography; cytomegalovirus PCR; urine culture; clinical evaluation; and disease staging. Results were categorized as "normal or minor finding" or "major finding" (having significant consequences such as further testing or therapy). Major findings were classified as incidental or related to history and symptoms. Components of the pretransplant workup with the highest rate of major findings were CT (22%), dental evaluation (13%), and ENT (12%, mostly symptomatic). All other components had a low rate of major findings. Although 126 transplants were performed as scheduled, 24 were delayed and 7 canceled at short notice. The main reasons for delaying or canceling transplantation were active infection and unexpected disease progression. A prospective evaluation of a more restricted, symptom-guided pretransplant evaluation appears to be warranted.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is standard of care for a number of hematologic diseases. The procedure is associated with a substantial risk of morbidity and mortality. Efforts to make transplantation safer include an optimal selection of transplant candidates and an extensive pretransplant workup. The aims of this workup are to ensure sufficient organ function, rule out infections, evaluate disease status, and generally exclude any contraindications to allogeneic transplantation. Although recommendations concerning the pretransplant evaluation have been published [1], the extent and logistics of the pretransplant workup vary substantially among centers.

Numerous studies have shown a correlation between pretransplant abnormalities and transplant outcome, either for individual parameters such as pulmonary function tests [2] and echocardiography [3] or in the form of comorbidity scores, such as the hematopoietic cell transplantation-specific comorbidity index [4]. However, only a few studies have analyzed whether performing an extensive pretransplant evaluation reduces transplant-related mortality by detecting latent infections or unapparent organ dysfunction. In an attempt to understand the significance of the different components of our pretransplant workup as well as reasons for delaying or canceling a transplant, we evaluated the workup of 157 consecutive patients scheduled for allogeneic HSCT at our center.

METHODS

Patients

Between May 2010 and October 2012, allogeneic transplants were planned in 100 men and 57 women with a median age of 51 years (range, 19 to 70). Patient characteristics are shown in Table 1.

Study Design and Definitions

We performed a retrospective chart review of the results of our pretransplant workup. Data were collected from electronic and paper charts and from the institutional database. All patients gave written consent to the analysis of outcome data at the time of treatment, and the study was approved by the institutional board of ethics.

At the time of analysis, the pretransplant workup consisted of magnetic resonance imaging (MRI) of the head; computed tomography (CT) of the chest and upper abdomen; gynecology, ophthalmology, ears-nose-throat (ENT), and dental evaluations; pulmonary function tests (PFTs) and echocardiography; and quantitative PCR for cytomegalovirus (CMV) in whole blood and urine cultures. All patients received a history and thorough physical examination and disease staging by bone marrow aspirate and biopsy. Patients with extramedullary disease (mainly those with lymphoproliferative disorders) additionally received staging by fluorodeoxyglucose positron emission tomography-CT imaging. Some examinations were canceled in selected patients because of scheduling issues.

We assessed the results of the pretransplant workup, categorizing results as "normal or minor finding" if no abnormalities were found or if abnormalities were detected that did not lead to further diagnostic or therapeutic interventions or "major finding" if results had significant consequences such as further testing or therapy. Among major findings, we distinguished between those that did not interfere with the transplant schedule, those that led to delay of the transplant, and those that led to cancellation of the transplant. In case of a major finding, we also considered whether this was incidental or whether the patient had clinical symptoms or a previous history indicating the patient was at risk for the given finding.

Statistical Analysis

Nonrelapse mortality was defined as death without previous relapse or progression. The incidence of nonrelapse mortality was calculated using the cumulative incidence method, and Gray's test was used to compare among groups.

RESULTS

One hundred twenty-six transplants were performed as scheduled, whereas 31 transplants were either delayed once (n = 22) or twice (n = 2) for a median of 21 days (range, 4 to 146) or were canceled altogether (n = 7). The number of major findings including those leading to delay or cancellation of transplant are summarized in Table 2 for the respective examinations. Examinations in which major findings led to delaying or canceling a transplant are depicted in Figure 1A. The distribution of incidental and symptomatic diagnoses among major findings is depicted in

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Table 1
Patient Characteristics (N = 157)

Characteristics	Value
Median age at transplant, yr (range)	51 (19-70)
Male	100
Female	57
Diagnosis	
Acute myeloid leukemia	54
Acute lymphoblastic leukemia	26
Myelodysplastic syndrome	19
Lymphoproliferative disorder	25
Myeloproliferative disease	14
Multiple myeloma	15
Aplastic anemia	4
Planned conditioning intensity	
Myeloablative	112
Reduced intensity	45
Donor	
Related	70
Unrelated	86
Cord blood	1
Patient origin	
Transplant center	54
External center	103

Figure 1B. The number of major findings did not differ between patients referred from other centers and our own patients (data not shown). None of the patients whose transplant was delayed for reasons unrelated to the underlying disease experienced relapse or progression before being able to proceed to transplant. The nonreapse mortality at day 100 for all patients that proceeded to transplant was 11.3%, with 7.7% versus 14.1% for patients with no versus at least one major finding, respectively ($P = .13$).

MRI of the Head

Five patients had major findings in the MRI, 1 of which resulted in delay of transplant. There were 2 cases of clinically relevant sinusitis, 1 of which was symptomatic; 1 unclear lesion in the thalamus; 1 case of perineural effusion of both optic nerves, both of which led to further testing but did not need specific therapy; and 1 case of progressive subdural hematoma, which required surgery and led to a delay of the transplant. The hematoma was asymptomatic at the time of the workup but was previously known and had been symptomatic at the time of first manifestation several weeks before transplant and was therefore not classified as incidental.

CT of the Chest and Upper Abdomen

Over 20% of CT scans revealed major findings, of which almost half were incidental. Most of these were pulmonary infiltrates or nodules (n = 29), whereas new liver lesions were found in 4 cases and pleural effusions in another 2. All pulmonary infiltrates not previously documented were investigated by bronchoalveolar lavage, and antifungal or antibacterial therapy was initiated if appropriate (n = 21). Transplant was delayed because of previously undocumented liver lesions (n = 2) or cavitary lesions of the lung (n = 2).

Dental Evaluation

Dental evaluation revealed a major finding in 13% of patients, with most of these being incidental. Most of these were severe caries or periodontitis. Of note is the fact that sanitation of dental foci before transplant was recommended in 3 patients but not performed because of time constraints. None of these 3 patients developed active dental infection post-transplant.

Table 2
Major Findings

Exam (no. patients evaluated)	Major Finding		
	No Delay in Transplant (n = 126)	Transplant Delayed (n = 26)*	Transplant Canceled (n = 7)
MRI (n = 150)	4 (3%)	1 (1%)	0 (0%)
CT scan (n = 156)	31 (20%)	4 (3%)	0 (0%)
ENT (n = 153)	18 (12%)	0 (0%)	0 (0%)
Dental evaluation (n = 145)	17 (12%)	2 (1%)	0 (0%)
Gynecology (n = 52)	2 (4%)	0 (0%)	0 (0%)
Ophthalmology (n = 154)	1 (1%)	0 (0%)	0 (0%)
Echocardiography (n = 153)	1 (1%)	0 (0%)	0 (0%)
PFT (n = 153)	5 (3%)	0 (0%)	0 (0%)
CMV PCR (n = 145)	3 (2%)	1 (1%)	0 (0%)
Urine cultures (n = 143)	3 (2%)	0 (0%)	0 (0%)
Clinical evaluation (n = 157)	24 (15%)	7 (4%)	0 (0%)
Disease staging (n = 157)	Not applicable	7 (4%)	6 (4%)
Other	Not applicable	4 (3%)	1 (1%)
Donor issues		3	
Toxicity		1	
Revision of diagnosis			1

* Transplant was delayed once in 22 patients and twice in 2 patients.

ENT Evaluation

A major finding was diagnosed in 12% of ENT evaluations, almost all of these being sinus or upper respiratory tract infections (n = 16); however, only 1 finding was incidental. In 1 case pretransplant sanitation of chronic sinusitis was recommended but was not performed because of scheduling issues. This patient developed a severe fungal sinus infection 3 months post-transplant that required surgical revision.

Gynecology and Ophthalmology Evaluation

Gynecology and ophthalmology evaluation revealed major findings in only 4% and 1% of patients, respectively. Gynecology findings were bacterial vaginosis treated with metronidazole in 2 patients, 1 of which was asymptomatic. The major ophthalmologic finding was idiopathic asymptomatic bilateral papilledema, which led to further testing but did not require treatment.

Echocardiography and PFTs

Echocardiography showed only 1 major finding, which was a case of previously unknown heart failure, for which treatment was initiated. Not classified as major findings were 2 other patients with known heart failure where the echocardiography showed a stable ejection fraction, and therapy was not adjusted. PFTs showed mild to moderate obstruction for which inhalation therapy was initiated in 5 patients (3%), 1 of whom had a previous diagnosis of chronic obstructive lung disease. Abnormal PFTs that did not lead to further testing or treatment were not classified as major findings.

CMV PCR and Urine Culture

Three patients were found by PCR to replicate CMV and were treated, but transplant was performed as planned. One patient had a very high CMV load of 586,472 copies/mL and was symptomatic with CMV colitis with severe diarrhea, and transplant was delayed for CMV treatment. One further patient had a low positive CMV PCR that resolved without treatment and was not classified as a major finding. Three patients received treatment for bacterial urinary tract infection, which was asymptomatic in 1 patient. Urine culture was positive in another 9 patients who were not treated, but these were not considered as major findings.

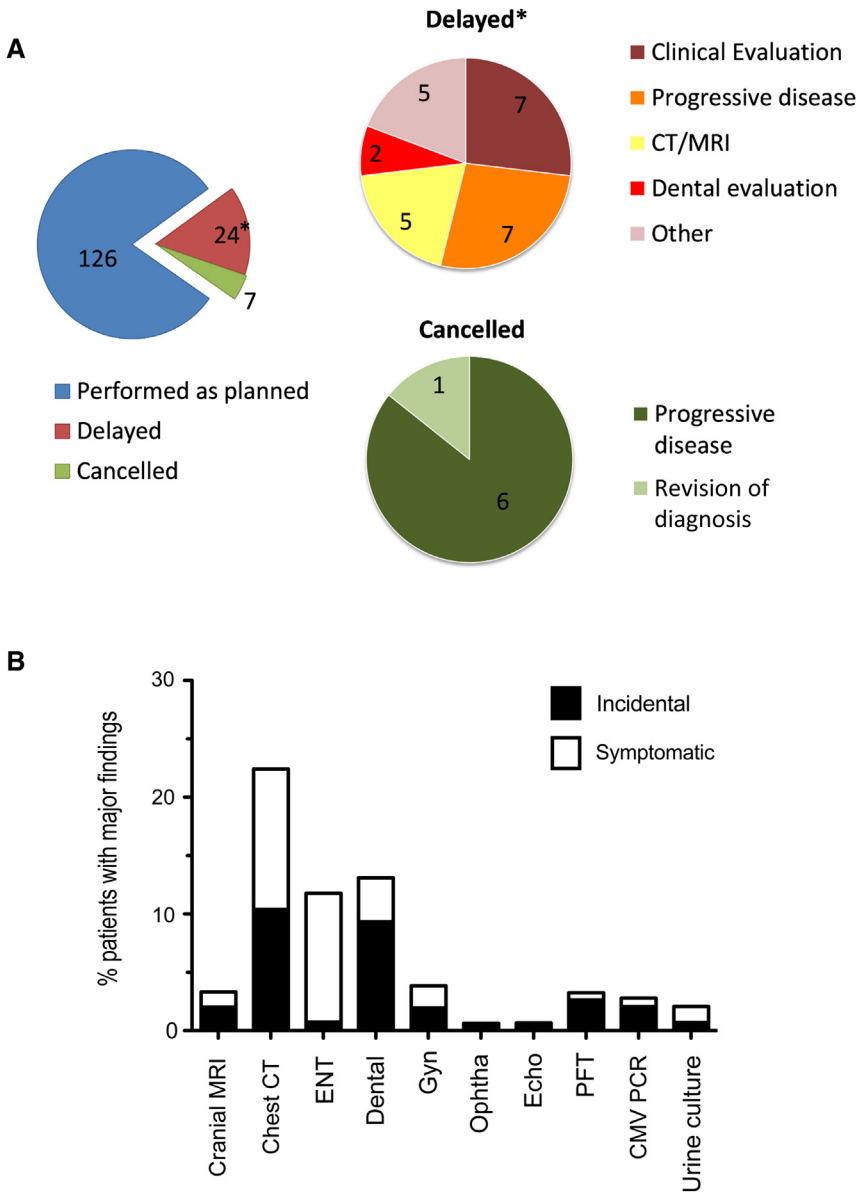

Figure 1. (A) Reasons for delaying or canceling transplant. *Transplant was delayed twice in 2 patients, so there are 26 reasons for delay in 24 transplants. (B) Frequency and distribution of incidental and symptomatic diagnoses among major findings in pretransplant evaluation.

Clinical Evaluation

History and clinical examination (full physical exam) showed signs of infection that led to delay of transplant in 4% of patients. In another 24 patients (16%), clinical evaluation revealed major findings that did not result in postponement of transplant. Although most of these were signs of infection, mainly upper respiratory tract or gastrointestinal, in 2 of these 24, conditioning intensity was reduced because of poor general health.

Disease Staging

In 6 patients, unexpected progressive disease led to postponement of transplant for reinduction therapy (with 1 patient postponed twice). Transplant was canceled due to progressive disease in further 6 patients, for a total of 13 postponed or canceled procedures.

Other Events

Transplant was delayed at short notice because of unforeseen unavailability of the donor in 3 patients and unexpected toxicity of the conditioning regimen in 1 patient. In1 patient, transplant was canceled because of spontaneous recovery of prolonged aplasia after autologous transplantation, so that the initially planned allogeneic transplant was no longer justified.

DISCUSSION

We present here an analysis of the results of examinations performed as part of the pretransplant workup before allogeneic transplantation at our center. The highest rate of major findings was revealed by chest CT and dental and ENT evaluations, with high rates of incidental major findings detected by CT and dental evaluation. All other examinations revealed only a very low number of major findings. The most common reasons for delaying a transplant at short notice were clinical signs of infection or unexpected progressive disease. Progressive disease was also the most common reason for canceling a transplant.

Although it is common practice to perform an extensive workup before allogeneic transplantation, very little evidence is available to support the choice of examinations performed. It seems intuitive to rule out active infection and ensure sufficient organ function. However, few studies have assessed the utility of this widely practiced extensive screening of asymptomatic patients.

Several authors have analyzed the usefulness of ENT evaluation as well as CT of the sinuses that is practiced in some centers. Although 1 study in children found pathological findings in sinus CT in 67% of patients [5], other studies uniformly found that significant findings in ENT evaluations were rare and only found in symptomatic patients [6,7]. There is also conflicting data on the possible association of pretransplant sinus CT and post-transplant development of sinusitis, with Thompson et al. [8] finding no correlation in 100 adults, and Billings et al. [9] finding a significant correlation in children. However, these differences might in part be due to a higher frequency of infections in children.

The question of necessity of dental evaluation pretransplant has also been the subject of several analyses. Although relatively high rates of pretransplant dental foci ranging up to 44% have been described [6,10], several authors have compared outcomes of patients with dental foci that were treated before transplant versus those left untreated and found no difference in post-transplant infections or mortality [11,12]. Similar data come from a study in heart transplant patients [13], keeping in mind that significant differences between organ and stem cell transplant limit extrapolation of results. One study prospectively evaluated a protocol emphasizing minimal dental treatment before intensive chemotherapy or transplant and showed that of 22 patients with severe dental pathology, only 2 developed infections during chemotherapy, which promptly resolved with antibiotic treatment [10].

Concerning other pretransplant evaluations, even less data are available. Only 1 study analyzed the utility of chest CT in children pretransplant and found a high rate of abnormal CTs (44%), but only 2% of patients received a new therapy due to a finding in chest CT [5]. Another study evaluated pretransplant MRI of the head in children and concluded that significant findings requiring therapy in 4.3% of patients justified screening MRI [14]. No data have been published on the value of gynecology or ophthalmology screening before transplant or on CMV antigenemia screening or urine culture.

For evaluations assessing organ function such as echocardiography and PFTs, many studies have analyzed correlations of pretransplant values with post-transplant complications [3,15], but none has assessed if screening improved outcome. However, baseline measurements of organ function can be crucial to establish reference points for post-transplant measurements; this is especially true for PFTs [16,17].

In summary, published data on the pretransplant workup are scarce and ambiguous. When deciding on which components to include in the pretransplant workup, many factors need to be taken into account. Apart from the number of significant findings, other factors include potential consequences of a missed incidental finding, burden for the patient, costs, and value as a baseline measurement. Based on our analysis of the number of major findings and incidental, potentially life-threatening findings in particular, it seems that CT of the chest and dental evaluation are justified irrespective of symptoms. Other components of our extensive workup, including MRI of the head and gynecology and ophthalmology evaluations, showed a very low rate of major findings, suggesting they may be omitted in asymptomatic patients. However, careful history and clinical examination are crucial to identify symptomatic or at-risk patients. The same is true for ENT evaluation, which showed a moderate rate of major findings; however, almost all patients were symptomatic. PFTs, echocardiography, CMV PCR, and urine culture all yielded no or very few major findings. Although PFTs and echocardiography are useful to establish a baseline for post-transplant assessment, the value of CMV PCR and urine culture is less clear.

Another aspect of our analysis is information on delayed or canceled transplants. In addition to several transplants delayed because of acute infection, progressive disease was the most common reason for not continuing with transplant as planned. Less frequently, transplants were delayed because of findings on CT of the chest or in dental evaluation. Because of logistic reasons, the pretransplant workup in our center is performed immediately before start of conditioning. This circumstance most likely had a significant influence, particularly on the number of delayed transplants, because a workup performed several weeks before transplant would leave sufficient time to perform any necessary interventions without delaying the transplant. Although our practice has certain advantages, rescheduling a transplant at short notice has significant consequences for transplant coordination and the donor. Our results suggest that sufficient time between the workup and planned start of conditioning is crucial to deal with unexpected findings. Furthermore, in light of the fact that dental and ENT sanitation was recommended in several patients but not performed because of time constraints, dental and ENT evaluations in particular should be performed with sufficient lead time.

Our study has several limitations. Because of the retrospective nature, we could not account for patients who might have had an informal workup and were not referred for transplant because of eligibility concerns. Furthermore, we could only assess the number of major symptomatic and incidental findings and could not correlate major findings with outcome or determine how pretransplant findings might have influenced post-transplant decisions. Most importantly, we can only speculate on potential consequences of omitting certain components of the workup. Prospective studies are necessary to study whether such an approach is safe. Although our results seem to encourage a more restrictive workup, a single missed major finding could potentially have fatal consequences. Keeping that in mind, unwarranted large-scale screening also harbors potential risks, including complications of diagnostic procedures and unnecessary delay of transplant. However, our data clearly indicate that prospective evaluation of a less-extensive and symptom-guided workup is warranted.

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Conflict of Interest Statement: There are no conflicts of interest to report.

REFERENCES

1. Hamadani M, Craig M, Awan FT, Devine SM. How we approach patient evaluation for hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2010;45:1259-1268.
2. Savani BN, Montero A, Srinivasan R, et al. Chronic GVHD and pretransplantation abnormalities in pulmonary function are the main determinants predicting worsening pulmonary function in long-term survivors after stem cell transplantation. *Biol Blood Marrow Transplant*. 2006;12:1261-1269.

3. Fujimaki K, Maruta A, Yoshida M, et al. Severe cardiac toxicity in hematological stem cell transplantation: predictive value of reduced left ventricular ejection fraction. *Bone Marrow Transplant*. 2001;27:307-310.
4. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912-2919.
5. Kasow KA, Krueger J, Srivastava DK, et al. Clinical utility of computed tomography screening of chest, abdomen, and sinuses before hematopoietic stem cell transplantation: the St. Jude experience. *Biol Blood Marrow Transplant*. 2009;15:490-495.
6. Nieboer P, Roodenburg JL, van der Laan BF, et al. Screening for infectious foci in breast cancer patients prior to high-dose chemotherapy and stem cell transplantation. *Anticancer Res*. 2003;23:1779-1783.
7. Moeller CW, Martin J, Welch KC. Sinonasal evaluation preceding hematopoietic transplantation. *Otolaryngol Head Neck Surg*. 2011;144:796-801.
8. Thompson AM, Couch M, Zahurak ML, et al. Risk factors for post-stem cell transplant sinusitis. *Bone Marrow Transplant*. 2002;29:257-261.
9. Billings KR, Lowe LH, Aquino VM, Biavati MJ. Screening sinus CT scans in pediatric bone marrow transplant patients. *Int J Pediatr Otorhinolaryngol*. 2000;52:253-260.
10. Toljanic JA, Bedard JF, Larson RA, Fox JP. A prospective pilot study to evaluate a new dental assessment and treatment paradigm for patients scheduled to undergo intensive chemotherapy for cancer. *Cancer*. 1999;85:1843-1848.
11. Melkos AB, Massenkeil G, Arnold R, Reichart PA. Dental treatment prior to stem cell transplantation and its influence on the post-transplantation outcome. *Clin Oral Invest*. 2003;7:113-115.
12. Peters E, Monopoli M, Woo SB, Sonis S. Assessment of the need for treatment of postendodontic asymptomatic periapical radiolucencies in bone marrow transplant recipients. *Oral Surg Oral Med Oral Pathol*. 1993;76:45-48.
13. Niederhagen B, Wolff M, Appel T, et al. Location and sanitation of dental foci in liver transplantation. *Transplant Int*. 2003;16:173-178.
14. Zimmermann U, Mentzel HJ, Wolf J, et al. MRI screening before stem cell transplantation—necessary? *Fortschr Geb Rontgenstr Nuklearmed*. 2008;180:30-34.
15. Crawford SW, Fisher L. Predictive value of pulmonary function tests before marrow transplantation. *Chest*. 1992;101:1257-1264.
16. Chien JW, Madtes DK, Clark JG. Pulmonary function testing prior to hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005;35:429-435.
17. Hildebrandt GC, Fazekas T, Lawitschka A, et al. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. *Bone Marrow Transplant*. 2011;46:1283-1295.

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.

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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