Rates of Microbiologically Diagnosed Infection and Pathogen Detection in Hematopoietic Stem Cell Transplant Patients

Capt Lauren E. Lee, USAF MC; Maj Alice E. Barsoumian, USAF MC†; MAJ Alexander W. Brown, MC USA‡; LTC Michael A. Wiggins, MC USA‡; Lt Col John S. Renshaw, USAF MC‡; Col Michael B. Osswald, USAF MC (Ret.)‡; COL Clinton K. Murray, MC USA†*

ABSTRACT Infections remain a significant cause of mortality in hematopoietic stem cell transplant patients. Evaluations of causes of infection are often unrevealing, and at some sites, increasing rates of antimicrobial resistance have been noticed. We performed a retrospective analysis of infection rates and microbiologic testing yield, or percent of tests ordered to diagnose an infection, in the first 100 days of 30 allogeneic and 56 autologous stem cell transplants performed at San Antonio Military Medical Center from July 2011 to April 2014. Blood stream infections were diagnosed in 11.6% with a yield of 6%. Urinary tract infections were diagnosed in 2.3% with a yield of 3%. *Clostridium difficile* infections were diagnosed in 9.3% and testing yield was 6%. Incidence of respiratory viruses was 5.8% with 4 rhinoviruses/enteroviruses and 1 influenza virus identified. One *Proteus mirabilis* urinary isolate was an extended spectrum beta-lactamase producer. Five patients, 13% of allogeneic and 4% of autologous patients, died within the first 100 days post-transplantation. History of bacteremia was present in 60% of patients who died; however, only one died due to a microbiologically diagnosed infection. Improved diagnostic tests and methods are needed to increase yield of detection of infection in hematopoietic stem cell transplant patients.

INTRODUCTION

The number of hematopoietic stem cell transplants (HSCT) continues to increase. Despite advances in antimicrobial prophylaxis and treatment, infections remain a major contributor to morbidity and mortality in HSCT recipients. Recent data show that infection is the cause of death in 7% of autologous stem cell transplant (ASCT) recipients and 13 to 17% of allogeneic stem cell transplant (AlloSCT) recipients.[1]

Diagnostic evaluation of symptoms, including fever, in the peritransplant period often leads to extensive testing. Evaluation of causes of fevers yields pathogen identification in 25 to 38.9% of cases post-HSCT and 51% of cases remain undiagnosed.[2,3] Whether undiagnosed cases are because of noninfectious causes or occult infections is undetermined. The clinical impact and yield of standard microbiologic testing can be low, and efforts have been made to improve resource utilization.[4] Additional concerns are increasing rates of gram-negative bacterial infection and antimicrobial resistant organisms, which have been observed since the widespread introduction of fluoroquinolones for neutropenic fever prophylaxis.[5–8]

San Antonio Military Medical Center (SAMMC) is the only facility within the Department of Defense that performs AlloSCT and one of just two that perform ASCT. Established in 1983, the Fisher Bone Marrow Transplant Program moved from Wilford Hall Medical Center to SAMMC because of Base Realignment and Closure in 2011. The first HSCT was performed at SAMMC in July 2011. Retirees, dependents, and active duty service members from all services are referred to SAMMC from around the world to undergo HSCT. As both patterns of infections and clinical practice vary among institutions, we decided to characterize our rates and sources of infections and the yield of microbiologic testing in the early post-transplant period. The primary goal was to identify areas for intervention in the diagnostic approach in this population. A secondary goal was to identify the rate of antimicrobial resistance which, if high, could change empirical antimicrobial selection.

METHODS

Design

We performed a single-site retrospective medical records review performance improvement project of HSCT patients who underwent AlloSCT or ASCT at SAMMC from July 2011 to April 2014 with a minimum of 100 days of post-transplant follow-up. HSCT recipient data were tracked at our institution for quality assurance. From this system, all patient demographic information, including diagnosis, transplant type, mortality, cause of death by clinical death summary, and presence of acute or chronic graft versus host

*Department of Medicine, San Antonio Military Medical Center, 3551 Roger Brooke Drive, JBSA Fort Sam Houston, TX 78234.

†Infectious Disease Service, San Antonio Military Medical Center, 3551 Roger Brooke Drive, JBSA Fort Sam Houston, TX 78234.

‡Hematology/Oncology Service, San Antonio Military Medical Center, 3551 Roger Brooke Drive, JBSA Fort Sam Houston, TX 78234.

doi: 10.7205/MILMED-D-15-00553

disease (GVHD) was obtained. Data on antimicrobial prophylaxis were not available; however, it is our usual practice to place all patients on recommended prophylaxis regimens according to recognized risk factors.[9]

The yield of microbiologic diagnostic testing was determined by analyzing testing obtained during the first 100 days following transplant. Multiples of the same diagnostic tests ordered within a 24-hour period were treated as one assessment. Diagnostic testing was directed by the treating physician based on clinical judgment; no protocolled approach was used to guide testing. Data were analyzed for types and rates of infection during day 0 to day 30 and day 31 to day 100 post-transplant, to represent the pre- and early postengraftment periods, respectively. The absolute neutrophil count (ANC, cells/μL) was determined for patients with microbiologically diagnosed infections at the time of positive test result and time of death, if applicable. The project was approved by the performance improvement/research advisory panel at our institution.

Microbiological Procedures

Blood stream infections (BSI) were diagnosed by recovery of any organism in a blood culture, with the exception of common skin contaminants. Common contaminants, such as coagulase negative staphylococci, required recovery from more than one site, continued recovery, or recovery from an intravenous catheter to be considered a BSI. *Streptococcus viridans* was not considered to be a common skin contaminant as it is well described as a known pathogen in this population.[9] Repeated isolation of the same organism was considered a single BSI unless a negative blood culture was obtained between episodes. Aerobic and anaerobic blood cultures were processed according to routine methods. Urinary tract infection (UTI) was diagnosed if $\geq 10^5$ colony forming units per milliliter of urine were recovered in a monomicrobial sample or when an organism was simultaneously recovered with co-occurring bacteremia. BK virus was assessed via real-time polymerase chain reaction (PCR) (Quest Diagnostics, Irving, Texas) testing of blood or urine. *Clostridium difficile* infection (CDI) was diagnosed with either a positive cytotoxin assay or PCR assay. The *C. difficile* PCR assay replaced the cytotoxin assay as the first-line test at SAMMC in May 2012. Bacterial stool cultures were assessed for common bacterial causes of diarrhea. Herpes simplex virus assays were performed via direct antigen testing or PCR. Respiratory viruses were investigated through the FilmArray Respiratory Panel multiplex PCR (BioFire Diagnostics LLC, Salt Lake City, Utah), direct fluorescent antigen assays (respiratory syncytial virus), or lateral flow antigen assays (influenza A/B) obtained from nasopharyngeal swabs, washings, or bronchoalveolar lavage (BAL). Endemic fungal infection antigen testing was noted. The Platelia *Aspergillus* Galactomannan enzyme immunoassay (EIA) (Bio-Rad Laboratories, Hercules, California) and the Fungitell (1,3)-ß-D glucan assay (Associates of Cape Cod, East Falmouth, Massachusetts) were interpreted as positive or negative according to manufacturer's instructions. Antimicrobial susceptibility was recorded for all culture-positive specimens. Our institution employs a pre-emptive strategy for cytomegalovirus disease prevention, and utilization rates were not included in this evaluation.

Statistical Analysis

Pearson's χ^2 or Fisher's exact test compared differences for categorical values, and the Mann–Whitney U test was performed on continuous variables. Kaplan–Meier estimates were used to analyze the time to test positivity. All statistical analyses were performed using SPSS (version 22.0; IBM Corporation, Armonk, New York), and two-tailed p values of ≤ 0.05 were considered significant.

RESULTS

Patient Characteristics

A total of 86 patients, 30 AlloSCT (67% males) and 56 ASCT (63% males), met inclusion criteria. The median age was 35 (range 20–66) and 55 (range 19–72) years for AlloSCT and ASCT patients, respectively ($p = 0.01$). Oncologic diagnoses varied (Table I).

Blood

During the period of evaluation, 158 blood culture assessments were obtained of 54 (63%) of 86 patients. A total of 10 BSI were identified in 4 AlloSCT and 6 ASCT patients (Table II). Two additional cultures grew coagulase-negative staphylococci, not meeting criteria for infection. Fourteen percent of patients in whom cultures were drawn from day 0 to 30 had positive cultures, and 19% of patients in whom cultures were drawn from day 31 to 100 had positive cultures. The overall yield of blood culture assessments was 6% (10 BSI in 158 sets). The median number of blood culture sets obtained per patient was 2 (min 1, max 9). Eleven patients in the 0- to 30-day period had 4 or more blood culture assessments; none of these patients were diagnosed with BSI. All patients with BSI during day 0 to 30 were diagnosed on the first day cultures obtained. There was no difference in median age, percent male gender, or percent transplant type among those diagnosed with BSI compared to patients in whom blood cultures were negative. A patient was more likely to have negative blood cultures than positive blood cultures in both periods. 30% of patients with a history of microbiologically diagnosed BSI died compared with 4% of patients in whom blood cultures were ordered and were negative ($p = 0.04$).

Of the 10 BSI, 7 occurred within the first 30 days (median day 11, range 7–78). The median time to blood culture positivity was 54 days, 95% confidence interval (CI) (0, 113) for AlloSCT and 8 days, 95% CI (7, 9) for ASCT ($p < 0.01$). 20% of all BSI were caused by monomicrobial

TABLE I. Demographic Information and Indication for Transplant by Transplant Type

	Allogeneic Stem Cell Transplant	Autologous Stem Cell Transplant	*p* Value
Patients	30	56	
Median Age (Min, Max)	35 (20, 66)	55 (19, 72)	0.01
Male Gender	20 (67%)	35 (63%)	0.70
Mortality	4 (13%)	1 (2%)	0.05
Diagnosis	*n*		*n*
Acute Myelogenous Leukemia	8	Multiple Myeloma	36
Acute Lymphocytic Leukemia	5	IgG Only	14
Myelodysplastic Syndrome	4	IgA Only	9
Aplastic Anemia	3	Light Chain Only	9
Chronic Myelogenous Leukemia	2	Unspecified	4
Hodgkin's Lymphoma	2	Non-Hodgkin's Lymphoma	9
Myelofibrosis	2	Mantle Cell Lymphoma	4
Chronic Lymphocytic Leukemia	1	Diffuse Large B Cell Lymphoma	4
Hemophagocytosis	1	Unspecified	1
Non-Hodgkin's Lymphoma	1	Hodgkin's Lymphoma	5
Paroxysmal Nocturnal Hemoglobinuria	1	Testicular Cancer	4
		Ewing Sarcoma	1
		Gray Zone Lymphoma	1

Mortality is expressed as 100-day mortality post-transplant.

gram-negative organisms, 40% by monomicrobial gram-positive organisms, and the remaining 40% were polymicrobial infections (Table III). One *Staphylococcus aureus* was noted to be fluoroquinolone resistant; fluoroquinolone susceptibility was not available in the electronic medical record for the other isolates. Two of the *S. viridans* were nonsusceptible to penicillin, and the *Staphylococcus hominis* isolate was resistant to methicillin. No other drug resistance was noted. There was no statistical significance associated with neutrophil count at time of BSI diagnosis per transplant type.

Urine

Ninety-six urine cultures were obtained in 55 patients. Three UTIs were identified in 2 AlloSCT patients producing a yield of 3%. No isolates were recovered in ASCT patients. One patient had microbiologically diagnosed UTI on day 40 with extended-spectrum beta-lactamase-producing *Proteus mirabilis*. The same patient had a subsequent UTI on day 78 with *Pseudomonas aeruginosa* with concurrent *P. aeruginosa* bacteremia. The second patient demonstrated *Escherichia coli* UTI on day 76 with concurrent *E. coli* bacteremia. Neither patient was neutropenic at the time

TABLE II. Number of Patients With Positive and Negative Blood Cultures

	Positive Blood Cultures	Negative Blood Cultures	*p* Value
Overall (*n* = 54)	10	44	
Median Age (Min, Max)	54 (25, 67)	48 (19,67)	
Male Gender	6 (60%)	28 (64%)	
D0–30 (*n* = 50)	7 (14%)	43 (86%)	<0.01
D31–100 (*n* = 16)	3 (19%)	13 (81%)	0.02
All-Cause Mortality	3 (30%)	2 (4%)	0.04
AlloSCT (*n* = 21)	4	17	
Median Age (Min, Max)	38 (25, 66)	35 (20, 65)	
Male Gender	3 (75%)	10 (59%)	
D0–30 (*n* = 16)	1 (6.25%)	15 (94%)	
D31–100 (*n* = 9)	3 (33%)	6 (67%)	0.01
All-Cause Mortality	2 (50%)	2 (12%)	
ASCT (*n* = 33)	6	27	
Median Age (Min, Max)	59 (31, 67)	55 (19, 67)	
Male Gender	3 (50%)	18 (67%)	
D0–30 (*n* = 31)	6 (19%)	25 (81%)	<0.01
D31–100 (*n* = 7)	0 (0%)	7 (100%)	
All-Cause Mortality	1 (17%)	0 (0%)	

D0–30, day 0 through day 30 post-transplant; D31–100, day 31 through day 100 post-transplant. Patients were counted once for assessment of overall positive and negative blood cultures. When described in the time frames of interest, a patient may be counted once in each time frame. Mortality is expressed as mortality in the first 100 days post-transplant. Only p values ≤ 0.05 are shown.

TABLE III. Positive Blood Culture Data by Patient.

	Transplant Type	Day Post-Transplant	ANC at Time of First Culture Positivity (cells/μL)	Blood Culture Result
Patient 1	ASCT	7	5	*E. coli*
Patient 2	ASCT	8	0	*E. coli, Streptococcus agalactiae*, *Staphylococcus hominis*
Patient 3	ASCT	8	0	Alpha hemolytic *Streptococcus*
Patient 4	ASCT	9	0	*S. viridans*
Patient 5	ASCT	9	7	*S. aureus*
Patient 6	ASCT	13	9,330	*S. viridans*
Patient 7	AlloSCT	16	162	*Bacteroides fragilis*, *Fusobacterium* species, *S. viridans*
Patient 8[a]	AlloSCT	54	2,635	*Klebsiella pneumoniae*, *S. aureus*
		56		*S. aureus*
Patient 9[a]	AlloSCT	76	6,868	*E. coli*
		77		*E. coli*, *Enterobacter cloacae*
Patient 10	AlloSCT	78	112	*P. aeruginosa*

[a]Patients 8 and 9 did not clear their bacteremia between blood culture assessments and are thus recorded as representing the same blood stream infection.

of pathogen isolation. Both patients were diagnosed with acute GVHD.

Stool

During the evaluation period, 152 *C. difficile* studies were obtained in 77 patients with 9 positive tests in 8 patients, a yield of 6%. One was positive by cytotoxin assay; the others were positive by PCR. *C. difficile* was detected in the stool of 3 (11%) of 27 AlloSCT and 5 (10%) of 50 ASCT patients. The median time from transplant to CDI was 5 days (range 2–100). Six (67%) CDIs occurred in the first 30 days after transplant and 3 (33%) occurred between day 31 and 100. The median ANC at the time of CDI was 2,500 (range 352–8,256) for AlloSCT patients and 425 (range 111–2,700) for ASCT patients. One (33%) of 3 AlloSCT and 3 (60%) of 5 ASCT patients were neutropenic at the time of CDI. All 3 AlloSCT patients who developed CDI also experienced acute GVHD and two developed chronic GVHD. Four bacterial stool cultures were ordered, and all were negative.

Other

A total of 9 respiratory viral PCR panels were obtained in 8 patients, 4 (44% of tests) of which revealed rhinovirus/enterovirus. Five influenza antigen assays were ordered, 1 (20%) of which was positive. Two respiratory syncytial virus antigens were obtained, and both were negative. Twenty samples (12 patients) were assessed for BK viruses, 5 (42%) of which were positive. HSV was detected in vesicular fluid of 2 patients via antigen testing; 6 additional PCRs were performed on serum and cerebral spinal fluid and were negative. Twelve expectorated bacterial sputum cultures were obtained with no recovery of organisms. Two BAL cultures were obtained; one recovered both a *Cunninghamella* species and *Candida glabrata*. Seven samples were assessed with the Platelia *Aspergillus* Galactomannan EIA in 3 patients and 8 Fungitell assays were obtained in 6 patients; 2 galactomannan EIAs were positive, 1 in a BAL and 1 in a serum specimen, and 1 Fungitell was positive. These positive Galactomannan and Fungitell assays were detected in the same patient. No endemic fungal antigens were isolated in the 7 samples ordered.

Mortality

Five patients, 4 AlloSCT and 1 ASCT, died within the first 100 days post-transplantation. The overall median time from transplant to death was 89 days (range 80–99). The median time from transplant to death for AlloSCT and ASCT was 86 and 89, respectively. Eighty percent of patients who died within 100 days were AlloSCT recipients ($p = 0.05$) with a relative risk of death in the first 100 days of 7.5, 95% CI (0.87, 63.84) compared to ASCT recipients. There was no statistically significant difference in age or gender with respect to death in first 100 days post-transplant. A history of BSI in the first 100 days post-transplant was present in 60% patients who died compared to 14% of patients who lived ($p = 0.01$). No difference in diagnosis of other infections was observed with respect to mortality (Table IV).

Overall, 3 deaths (60%) were at least partially attributed to infection; 1 AlloSCT patient died of septic shock on day 80, 1 AlloSCT patient died of pneumonia on day 91, and 1 ASCT patient died of mucormycosis and disease-related complications on day 89. The remaining deaths were attributed to disease progression and GVHD. Only 1 of the deaths was attributed to a microbiologically diagnosed infection (Table V).

DISCUSSION

This is the first survey of types of infections and rates of infection detection in our HSCT population. We examined rates of pathogen detection to compare our performance to the performance at other institutions as well as to examine practice patterns for opportunities to modify clinical practice.

TABLE IV. Association of 100-Day Mortality With Patient Demographics and With Microbiologically Diagnosed Infection by Test Utilized

	100-Day Survival (n = 81)	100-Day Mortality (n = 5)	p Value
Male Gender	53 (65%)	2 (40%)	0.35
Median Age (Min, Max)	52 (19, 72)	42 (23, 66)	0.83
Type of Transplant (AlloSCT)	26 (32%)	4 (80%)	0.05
Blood Culture	7 (14%)	3 (60%)	0.01
Urine Culture	1 (2%)	1 (20%)	0.2
C. difficile Assay, Any	7 (11%)	1 (25%)	0.4
Respiratory Viral PCR	4 (5%)	0 (0%)	1.0
Influenza Antigen	1 (1%)	0 (0%)	1.0
Serum Fungitell	0 (0%)	1 (20%)	0.06
Serum Platelia *Aspergillus* Galactomannan EIA	0 (0%)	1 (20%)	0.06
Fungal Respiratory Culture	0 (0%)	1 (20%)	0.06

No difference was noted for microbiologically diagnosed infection by time frame of interest (data not shown).

Our overall yield for blood cultures in detecting BSI was 6%, and a large portion of our patients tested pre-engraftment (22%) had blood cultures obtained on 4 or more days without identifying a BSI. We presume that blood cultures were obtained largely because of febrile neutropenia during this period. We noted detection of BSI from day 0 to 30 in 14% HSCT patients in whom blood cultures were obtained. This is similar to described rates of bacteremia in febrile neutropenic HSCT patients in the era of fluoroquinolone prophylaxis.[4,5] In one study, blood cultures were obtained at the first onset of neutropenic fever, on day 3 of persistent fever, and for any changes in clinical status or escalation of therapy, which decreased cost and patient phlebotomy without an increased incidence of infectious complications.[4] A similar approach in our patients before engraftment may also be useful, as we noted all BSI in this period were diagnosed on the first day cultures were obtained. Volume of collected blood is known to be the most important variable in recovery of bacteria[10]; however, data on blood culture volume were unavailable in this evaluation.

Causes of BSI are varied among institutions. We demonstrated largely gram-positive and polymicrobial bacteremias and did not recover fluoroquinolone-resistant gram negatives. We did not observe any coagulase-negative staphylococci causing BSI as opposed to others describing it as the most commonly cultured bloodstream isolate.[3,11] However, it should be noted that definition of coagulase-negative staphylococci BSI is not uniform in the HSCT literature. Although not statistically significant, we did note that all BSIs identified in ASCT patients were in the pre-engraftment period, and AlloSCT patients continued to experience bacteremia in the postengraftment period, which is consistent with findings by others.[4] Significance is likely limited by small sample size and greater number of ASCT patients than AlloSCT patients at our institution. We noted that 60% of patients with BSI died in the first 100 days compared with

TABLE V. Microbiologically Diagnosed Infections by Positive Tests of Patients Deceased Within 100 Days Post-Transplant

	Age (Year)	Gender	Transplant Type	Day of Death	Cause of Death	Culture History
Patient 1	64	F	ASCT	89	Complications of Multiple Myeloma and Zygomycosis	Blood Cultures *S. viridans*, Day 13 Fungal Respiratory Cultures *Cunninghamella* sp., Days 86, 87 *Candida glabrata*, Day 86 Platelia *Aspergillus* Galactomannan EIA, BAL, and serum, Day 86 Fungitell, Day 86
Patient 2	42	M	AlloSCT	80	GVHD	Blood Cultures *K. pneumoniae*, Day 54 *S. aureus*, Day 56 BK Virus, Day 56
Patient 3	23	F	AlloSCT	80	Sepsis	*Clostridium difficile* Toxin, Day 3
Patient 4	66	M	AlloSCT	91	Pneumonia	Blood Cultures *P. aeruginosa*, Day 78 Urine Cultures *P. aeruginosa*, Day 78
Patient 5	35	F	AlloSCT	99	Disease Progression, Veno-occlusive Disease	N/A

14% of those with negative blood cultures, which is consistent with literature showing that bacteremia is associated with increased mortality in the post-transplant period.[12]

Bacterial UTIs were diagnosed infrequently, with 2 patients showing 3 UTIs. Overall incidence is low at other sites as well, 1 to 2% in modern studies.[3,13] Notably, 2 UTIs were diagnosed with concurrent bacteremia attributed to the same pathogen; we were unable to describe the relationship between BSI and UTI. No discussion on the relationship of UTIs and concurrent BSIs in HSCT patients was found in the literature. Data on indwelling urinary catheterizations and urinary symptoms were not available; however, the number of samples ordered (96 in 55 patients) suggest that they were ordered in the absence of other factors. Other studies reporting UTIs in their HSCT population also do not address these factors,[8,10–12] and we found no studies examining urinary culture testing rates. Guidelines for the evaluation of fevers in neutropenic patients recommend obtaining blood cultures in all patients and reserving testing of other sites if clinically suspected.[14] Reserving urinary cultures only for HSCT patients with urogenital catheterization or with urinary tract symptoms, particularly pre-engraftment, would likely improve yield.

The overall incidence of CDI of 9% noted in this population is consistent with the results of a recent large meta-analysis.[15] CDI is recognized to be more common among AlloSCT patients than ASCT, with rates from 12 to 27% in the first year post-transplant for AlloSCT patients. We did not note a similar pattern, and attribute it to the number of patients in our evaluation. The median time to onset in this population was 5 days, consistent with findings by others.[16] No information was available on pretransplant diagnosis of CDI and whether these instances were relapses of earlier illnesses. The overall yield of our assays was 6%. However, during the study period, our institution introduced the PCR assay to diagnose CDI, which requires fewer tests to make the diagnosis because of increased sensitivity.[10] A recent study assessing all *C. difficile* testing ordered at a tertiary care center describes a similar yield of tests; although the yield of toxin EIA (5%) and PCR (8.2%) varied, no difference in diagnosis of CDI was noted.[17] All of our AlloSCT patients who developed CDI also developed acute GVHD, which is an association observed by some investigators.[18,19] Whether a causative relationship exists or if *C. difficile* detection does not represent CDI in GVHD-associated diarrhea is unclear.[20] However, investigations have previously described objective findings of infection in HSCT with reports of pseudomembrane formation[18] and infection recurrence.[18,21] The clinical impact of *C. difficile* detection in our patients could not be assessed.

A potentially underutilized platform at our institution is respiratory viral PCR testing; 44% of tests ordered detected a pathogen with an overall incidence of 5% of our patients in the first 100 days. This is lower than what is described at other institutions that perform active surveillance. In one study, the incidence of human rhinovirus was 22.3% and human coronavirus was 11.1% at 100 days.[22] Our low rate may be attributed to underutilization of this test, although presence of respiratory symptoms in this cohort is unknown. In addition, we did not analyze incidence for seasonality, which impacts incidence of respiratory viral infections in HSCT.[22] High rates of progression from upper respiratory tract infection to lower respiratory tract infection have been shown, and co-occurrence with more virulent copathogens has been described.[23] More work is being accomplished with respiratory viruses in HSCT as diagnosis has improved. A recent publication examined surveillance of respiratory viruses by PCR and found a pretransplant incidence of 25% for all viruses tested and noted that this was associated with increased mortality at 100 days;[24] the authors advocate for incorporation of respiratory viral testing as part of the pretransplant evaluation. Currently, there is no recommendation for active surveillance or pretransplant assessment of asymptomatic respiratory viruses.[9] We suspect, however, that increased usage of the viral PCR panel may aid in diagnosis, infection control, treatment decisions, and may prompt investigation and prevention of potential copathogens, and we plan to expand its use in our HSCT patients experiencing respiratory symptoms.

The patient who succumbed to zygomycosis with recovery of *Cunninghamella* on BAL had positive serum Platelia Aspergillus Galactomannan EIA and Fungitell assays. Neither test detects zygomycosis and detect invasive aspergillosis (IA) or a select few other invasive fungal infections (IFI). Possibilities explaining these positive results, such as piperacillin-tazobactam exposure or coinfection with an additional IFI, could not be explored based on methods to evaluate data. Interestingly, this patient had a history of BSI with *S. viridans* pre-engraftment. An association between early BSI and IFI has been described.[25] The incidence of invasive aspergillosis is about 5 to 10% in HSCT depending on the length of follow-up, and zygomycosis occurs less frequently.[26]

Limitations of this evaluation include a small sample size, a single location, and the retrospective nature of evaluation. Also, testing for infections other than BSI, UTI, CDI, and respiratory viral testing was performed in low numbers, limiting analysis. The procedure for collecting and evaluating information also limited obtaining clarity on potential false-positive test results as well as detailed inspection of clinical outcome. No information on antibiotic exposure, including prophylactic, empirical regimens, or history of antibiotic usage, was collected, which may have an impact on rates of infection and mortality.

CONCLUSIONS

Overall, the yield of our microbiologically diagnosed infections was low, with a yield of 3 to 6% for the most commonly used diagnosis at SAMMC. Though the optimal yield of diagnostic testing is not defined, this suggests that a more

protocolized approach to microbiologic investigation may be beneficial. Such a protocol may include recommendations to minimize overtesting of low-risk patients, guidance for ways to increase yield of ordered tests, and recommend increased utilization of specialized tests when clinically indicated. Future analysis addressing protocol performance should be performed.

REFERENCES

1. Pasquini MC, Zhu X: Current uses and outcomes of hematopoietic stem cell transplantation: 2014 CIBMTR summary slides. Available at http://www.cibmtr.org; accessed November 16, 2015.
2. Kruger W, Russmann B, Kroger N, et al: Early infections in patients undergoing bone marrow or blood stem cell transplantation—a 7 year single centre investigation of 409 cases. Bone Marrow Transplant 1999; 23(6): 589–97.
3. Gil L, Styczynski J, Komarnicki M: Infectious complication in 314 patients after high-dose therapy and autologous hematopoietic stem cell transplantation: risk factors analysis and outcome. Infection 2007; 35(6): 421–7.
4. Serody JS, Berrey MM, Albritton K, et al: Utility of obtaining blood cultures in febrile neutropenic patients undergoing bone marrow transplantation. Bone Marrow Transplant 2000; 26(5): 533–8.
5. Satlin MJ, Vardhana S, Soave R, et al: Impact of prophylactic levofloxacin on rates of bloodstream infection and fever in neutropenic patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2015; 21(10): 1808–14.
6. Macesic N, Morrissey CO, Cheng AC, Spencer A, Peleg AY: Changing microbial epidemiology in hematopoietic stem cell transplant recipients: increasing resistance over a 9-year period. Transpl Infect Dis 2014; 16(6): 887–96.
7. Mikulska M, Del Bono V, Raiola AM, et al: Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant 2009; 15(1): 47–53.
8. Collin BA, Leather HL, Wingard JR, Ramphal R: Evolution, incidence, and susceptibility of bacterial bloodstream isolates from 519 bone marrow transplant patients. Clin Infect Dis 2001; 33(7): 947–53.
9. Tomblyn M, Chiller T, Einsele H, et al: Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009; 15(10): 1143–238.
10. Baron EJ, Miller JM, Weinstein MP, et al: A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). Clin Infect Dis 2013; 57(4): e22–e121.
11. Ninin E, Milpied N, Moreau P, et al: Longitudinal study of bacterial, viral, and fungal infections in adult recipients of bone marrow transplants. Clin Infect Dis 2001; 33(1): 41–7.
12. Marena C, Zecca M, Carenini ML, et al: Incidence of, and risk factors for, nosocomial infections among hematopoietic stem cell transplantation recipients, with impact on procedure-related mortality. Infect Control Hosp Epidemiol 2001; 22(8): 510–7.
13. Castagnola E, Fontana V, Caviglia I, et al: A prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. Clin Infect Dis 2007; 45(10): 1296–304.
14. Freifeld AG, Bow EJ, Sepkowitz KA, et al: Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52(4): e56–93.
15. Zacharioudakis IM, Ziakas PD, Mylonakis E: *Clostridium difficile* infection in the hematopoietic unit: a meta-analysis of published studies. Biol Blood Marrow Transplant 2014; 20(10): 1650–4.
16. Kamboj M, Xiao K, Kaltsas A, et al: *Clostridium difficile* infection after allogeneic hematopoietic stem cell transplant: strain diversity and outcomes associated with NAP1/027. Biol Blood Marrow Transplant 2014; 20(10): 1626–33.
17. Akbari M, Vodonos A, Silva G, et al: The impact of polymerase chain reaction on *Clostridium difficile* detection and clinical outcomes. J Med Microbiol 2015; 64(9): 1082–6.
18. Alonso CD, Treadway SB, Hanna DB, et al: Epidemiology and outcomes of *Clostridium difficile* infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2012; 54(8): 1053–63.
19. Willems L, Porcher R, Lafaurie M, et al: *Clostridium difficile* infection after allogeneic hematopoietic stem cell transplantation: incidence, risk factors, and outcome. Biol Blood Marrow Transplant 2012; 18(8): 1295–301.
20. Alonso CD, Marr KA: *Clostridium difficile* infection among hematopoietic stem cell transplant recipients: beyond colitis. Curr Opin Infect Dis 2013; 26(4): 326–31.
21. Alonso CD, Dufresne SF, Hanna DB, et al: *Clostridium difficile* infection after adult autologous stem cell transplantation: a multicenter study of epidemiology and risk factors. Biol Blood Marrow Transplant 2013; 19(10): 1502–8.
22. Milano F, Campbell AP, Guthrie KA, et al: Human rhinovirus and coronavirus detection among allogeneic hematopoietic stem cell transplantation recipients. Blood 2010; 115(10): 2088–94.
23. Martino R, Porras RP, Rabella N, et al: Prospective study of the incidence, clinical features, and outcome of symptomatic upper and lower respiratory tract infections by respiratory viruses in adult recipients of hematopoietic stem cell transplants for hematologic malignancies. Biol Blood Marrow Transplant 2005; 11(10): 781–96.
24. Campbell AP, Guthrie KA, Englund JA, et al: Clinical outcomes associated with respiratory virus detection before allogeneic hematopoietic stem cell transplant. Clin Infect Dis 2015; 61(2): 192–202.
25. Sparrelid E, Hagglund H, Remberger M, et al: Bacteraemia during the aplastic phase after allogeneic bone marrow transplantation is associated with early death from invasive fungal infection. Bone Marrow Transplant 1998; 22(8): 795–800.
26. Marr KA: Fungal infections in hematopoietic stem cell transplant recipients. Med Mycol 2008; 46(4): 293–302.