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Infectious Disease

Limited Utility of Outpatient Surveillance Blood Cultures in Hematopoietic Cell Transplant Recipients on High-Dose Steroids for Treatment of Acute Graft-versus-Host-Disease

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A B S T R A C T

Steroids used to treat acute graft-versus-host-disease (GVHD) are believed to blunt clinical symptoms of infection. We aimed to assess the value of weekly surveillance blood cultures (SBCs) drawn in an outpatient setting from hematopoietic cell transplant (HCT) patients receiving high-dose steroids. We hypothesized that most positive outpatient surveillance cultures would be low-pathogenicity, gram-positive organisms and would lead to excess vancomycin therapy. We conducted a retrospective review of blood cultures collected from a cohort of adult HCT patients enrolled in a clinical trial of acute GVHD therapy with high-dose steroids (prednisone-equivalent doses ≥ .5 mg/kg/day) between April 2009 and May 2013. SBCs were defined as those collected weekly from central venous catheters in the outpatient setting while patients were receiving high-dose steroids. Cultures obtained as part of a symptom workup or as follow-up for documented bacteremia were excluded. Clinical data were collected using center databases supplemented by medical record review. One hundred twenty-seven HCT recipients were eligible for inclusion in the study. A total of 1015 SBCs were obtained, with a median of 8 cultures (interquartile range, 5 to 10) per patient. Forty-two organisms were isolated from 36 of 1015 cultures (3.5%) in 30 unique patients, or 1 positive culture per 28 blood cultures drawn. The most frequently detected organisms were coagulase-negative *Staphylococci* (25/1015 [2.5%]). Gram-negative organisms were rare (4/1015 [.4%]. Antibiotics were administered to most patients with positive surveillance cultures (33/36 [92%]). Six were admitted to the hospital for treatment; none needed intensive care or died from their bacteremia. Vancomycin was the most frequently administered antibiotic, comprising 256 of 376 total days (68%) of antibiotic received by the cohort with a median duration of 10 days ((interquartile range, 7 to 14). Weekly outpatient SBCs obtained from asymptomatic patients on high-dose glucocorticoids for treatment of acute GVHD after allogeneic HCT were infrequently positive, and most organisms were low-pathogenicity organisms. SBCs also led to excess antibiotic exposure and costs, suggesting benefits of such ambulatory screening may be of limited value in this setting.

INTRODUCTION

Bloodstream infections are a frequent cause of morbidity and mortality in patients undergoing hematopoietic cell transplantation (HCT) [1]. HCT recipients are at high risk for bacterial infections caused by gram-negative organisms due to underlying neutropenia, immunosuppressive therapy, and mucosal disruption from chemotherapy and acute graft-versus-host-disease (GVHD) [1,2]. Although most cancer/transplant centers use antibiotic prophylaxis during neutropenia to prevent gram-negative bacteremia and associated mortality in these patients, acute GVHD primarily occurs outside the window of typical neutropenic prophylaxis. Glucocorticoids, which are used during the treatment of GVHD, are known to inhibit the synthesis and function of certain cytokines, thereby limiting classic responses to infection such as tachycardia, flushing, and fever [3,4]. The limited

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symptoms while on steroid therapy are believed to potentially delay diagnosis of bacteremia, which is associated with serious complications such as septic shock, intensive care unit (ICU) admission, organ dysfunction, and death [5].

Concern over missed and/or delayed detection of these life-threatening infections has led some centers to collect blood cultures over periodic intervals in an attempt to identify bacteremia events before symptom onset for high-risk HCT patients, such as those on high-dose glucocorticoids [3,4,6], with neutropenia [7,8], and/or those with a central venous catheter [9,10]. Studies of the value of such surveillance blood cultures (SBCs) have produced variable results [2–4,6–10]. Our center has performed weekly outpatient SBCs for HCT patients treated with glucocorticoids for GVHD for over 10 years, but the utility of this policy had not yet been formally evaluated. Here, we quantified and characterized outpatient SBCs, subsequent antibiotic treatment, and patient outcomes in a cohort of HCT recipients from a clinical trial of patients treated with glucocorticoids for active acute GVHD [11]. We hypothesized that most positive cultures from outpatient SBCs would be low-pathogenicity, gram-positive organisms and would lead to excess vancomycin therapy.

METHODS

Study Design, Population, and Data Collection

The study population consisted of a cohort of patients who underwent an allogeneic HCT between April 2009 and May 2013 and were enrolled in a randomized trial comparing efficacy and safety of different doses of glucocorticoids for initial treatment of acute GVHD [11]. As per study protocol, decisions to begin glucocorticoid therapy were at the discretion of the attending physician, and initial therapy varied according to treatment arm (prednisone-equivalent doses, .5 mg/kg/day versus 1 mg/kg/day versus 2 mg/kg/day) based on GVHD grade at symptom onset [11]. In the present study of SBCs, the study period began at the time of initiation of high-dose glucocorticoids.

HCT patients at our center have tunneled, double-lumen, central venous catheters for a minimum of 90 days post-transplant. Patients were excluded from the primary analysis if they were younger than 18 years old or did not have any outpatient surveillance cultures performed. Demographic, laboratory, and clinical outcome data were extracted from prospectively collected institutional databases. Clinical and microbiology data were collected by abstraction from electronic medical records.

Definitions

Per our current center-based guidelines, SBCs were defined as once weekly outpatient blood cultures for allogeneic HCT patients receiving high-dose glucocorticoids (≥.5 mg/kg/day) for GVHD. GVHD was defined as per established international criteria [12]. SBCs were identified by either surveillance labels in microbiology records or as blood cultures collected weekly in the outpatient department while patients were asymptomatic per chart review. Cultures drawn because of other clinical symptoms were considered non-SBCs. Labeled SBCs were excluded if they were obtained as part of a symptom workup (eg, fevers, chills, or rigors) or if obtained within 7 days after a documented bacteremia. Because such cultures were often a single set, positive cultures were defined as positive with the detection of any bacterial species.

Infectious Disease Prophylaxis Post-HCT

HCT recipients were given pre- and post-HCT prophylaxis for *Pneumocystis jirovecii* with trimethoprim-sulfamethoxazole (TMP-S), dapsone, or atovaquone; those not on TMP-S with a known history of a splenectomy were also placed on daily oral penicillin VK after count recovery. All patients with GVHD treated with ≥.5 mg/kg of steroids were placed on posaconazole prophylaxis, unless already on antifungal therapy for a prior or suspected diagnosis of filamentous mold infection or until steroid dose dropped to <.5 mg/kg. All patients were given levofloxacin 750 mg daily for bacterial prophylaxis during periods of post-transplant neutropenia. Antiviral prophylaxis was given as has previously been described [13].

Outcomes of interest were antibiotic days of therapy, hospital admission, ICU admission, and death within 30 days if deemed directly related to a positive culture based on review of the clinical data. Each antibiotic administered specifically for a positive blood culture was documented. If multiple antibiotics were administered on any given day (eg, broad-spectrum antibiotics while speciation and sensitivities were pending), each antibiotic was counted as a separate day regardless of how many doses were administered.

RESULTS

One hundred twenty-seven allogeneic HCT patients were eligible for study inclusion, and Table 1 shows the characteristics of the patient population. Acute leukemias were the most common underlying malignancies at 47%, followed by lymphoma and myelodysplastic syndromes representing 13% and 11%, respectively. The average age of the cohort was 52 years (interquartile range [IQR], 40.5 to 59), with a male predominance (61%). All patients were on high-dose glucocorticoids to

Table 1
Patient Demographics (N = 127)

Characteristic	Value*
Median age, yr (IQR)	52 (41-59)
Gender	
Male	78 (61)
Female	49 (39)
Underlying disease	
Acute leukemia	60 (47)
Lymphoma	16 (13)
Myelodysplastic syndrome	14 (11)
Chronic leukemia	12 (9)
Myelofibrosis	8 (6)
Multiple myeloma	8 (6)
Myeloproliferative disorder	3 (2)
Aplastic anemia	3 (2)
Other	3 (2)
Donor	
Unrelated	88 (69)
Related sibling	31 (24)
Haploidentical	8 (6)
Graft	
PBSCs	110 (87)
Cord blood	9 (7)
Bone marrow	8 (6)
Conditioning	
Myeloablative	79 (62)
Nonmyeloablative	48 (48)
CMV status	
Recipient positive	58 (46)
Recipient negative	69 (54)
GVHD prevention	
Tacrolimus/MTX	55 (43)
Cyclosporine/MMF	41 (32)
Tacrolimus/MMF	8 (6)
Combination with rapamycin	6 (5)
Other combination	17 (13)
Acute GVHD grade II	108 (85)
Grade III	17 (13)
Grade IV	2 (2)
GVHD location	
Skin and gut	68 (54)
Gut only	46 (36)
Skin only	13 (10)
Initial glucocorticoid dose	
2 mg/kg/day	26 (21)
1 mg/kg/day	65 (51)
.5 mg/kg/day	36 (28)

Values are n (%) unless otherwise defined. PBSCs indicates peripheral blood stem cells; IQR, interquartile range; CMV, cytomegalovirus; MTX, methotrexate; MMF, mycophenolate mofetil.

* Percentages may not equal 100% because of rounding.

treat acute GVHD, with 26 of 127 (21%) receiving an initial methylprednisolone-equivalent dose of 2 mg/kg/day, 65 (51%) receiving 1 mg/kg/day, and 36 (28%) receiving .5 mg/kg/day.

Among these 127 patients, 1015 SBCs were obtained in the outpatient department for a median of 8 cultures (IQR, 5 to 10) per patient. Most patients (97 [76%]) had no positive cultures, whereas 26 (20%) had 1 positive culture and 4 (3%) had >1 positive culture. Bacteria were isolated from 36 of 1015 blood cultures (3.5%) from 30 unique patients, or 1 positive culture per 28 blood cultures drawn. Median day for positive surveillance culture was 59 days (IQR, 46 to 89) after HCT and 29 days (IQR, 20 to 50) after the start of steroid therapy for acute GVHD.

More than 1 bacterial organism was isolated in 5 blood cultures; 2 of these isolated >1 species of coagulase-negative *Staphylococcus*. When we compared SBCs with non-SBCs obtained in the same cohort for symptomatic workup, SBCs isolated significantly fewer organisms (36/1015 [3.5%] versus 12/86 [14%], $P < .001$). There were no differences in the number of positive cultures based on glucocorticoid dose: 5 of 201 patients (2.5%) initiated at 2 mg/kg/day prednisone-equivalent, 18 of 542 (3.3%) initiated at 1 mg/kg/day, and 13 of 272 (4.8%) initiated at .5 mg/kg/day ($P = .38$). Mean cumulative prednisone-equivalent doses from day 0 to day 42 after initiation of steroids were similar when comparing patients with those without positive SBCs (Figure 1). Only 1 patient was neutropenic at the time of positive blood culture (4%), and an additional 2 patients had an absolute neutrophil count between 500 and 1000 neutrophils/μL. In addition to steroids, the most frequent immunosuppressive agents used at the time of positive outpatient SBCs were calcineurin inhibitors (27/30 [90%]) and antimetabolites (eg, mycophenolate (12 [40%]). Sixteen patients (53%) were also receiving concomitant oral beclomethasone/budesonide for gastrointestinal GVHD. Two patients (7%) with positive outpatient SBCs had received antithymocyte globulin, 1 alemtuzumab, and another was receiving extracorporeal photopheresis before their positive cultures.

The most frequently detected bacteria were gram-positive organisms, dominated by coagulase-negative *Staphylococcus* species (25/1015 [2.5%] SBCs), which represented 60% of the organisms isolated (Table 2). The median time to report positive cultures for those with coagulase-negative *Staphylococcus* species (at time when gram-positive cocci were first noted) was 26 hours after collection (IQR, 24 to 30). One patient had vancomycin-resistant enterococcus, 1 vancomycin-sensitive enterococcus, and 1 *Staphylococcus aureus* (methicillin-sensitive). Gram-negative rods were rare (4/1015 [.4%]) and included *Serratia marcescens, Klebsiella pneumoniae, Pseudomonas putida*, and *Stenotrophomonas maltophilia*. Case reviews of patients with blood cultures positive for high-pathogenicity organisms including gram-negative rods, *S. aureus*, and enterococci are provided in Table 3. One SBC set was drawn for each of these patients, and average time from blood culture to administration of antibiotics was >24 hours (average 32.9 hours [range, 17.5 to 45] from culture to antibiotic administration; Table 3). Half of these blood cultures were obtained from patients whose steroid dose was below the threshold outlined by our center's standard practice guidelines. Repeat blood cultures among those with high-risk pathogens were drawn before antibiotic administration in only 2 patients (Table 3): 1 culture yielded the same organisms and the other repeat culture was negative.

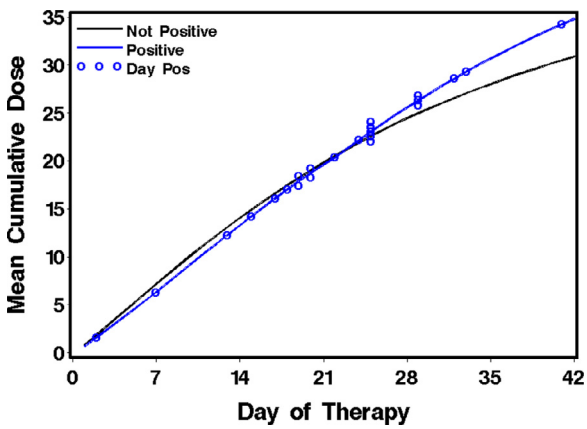

Figure 1. Cumulative prednisone dose (mg/kg) over time in patients with and without positive surveillance cultures. Data demonstrating first 42 days of follow-up after initiating steroid therapy. Blue line indicates patients with bacteremia on surveillance cultures; blue circles, bacteremia episodes; black line, patients without bacteremia. Mean cumulative prednisone-equivalent dose at day 42 after initiating steroids when comparing patients with (23; 31.1 mg/kg [SD = 14.9]) or without (98; 35.5 mg/kg [SD = 15.5]; $P = .24$) positive surveillance cultures.

Table 2
Microbiology Identified from Positive SBCs (n = 42)*

Identified Organisms	No. of Cases (%)
Gram positive	
Coagulase-negative *Staphylococcus*	25 (60)
Bacillus spp.	2 (4.8)
Diphtheroids	2 (4.8)
Enterococcus faecium†	2 (4.8)
α-Hemolytic *Streptococcus*	2 (4.8)
Nonhemolytic *Streptococcus*	1 (2.4)
Rothia mucilaginosa	1 (2.4)
Viridans group *Streptococcus*	1 (2.4)
Methicillin-sensitive *Staphylococcus aureus*	1 (2.4)
Gram-positive cocci (not otherwise specified)	1 (2.4)
Gram negative	
Serratia marcescens	1 (2.4)
Klebsiella pneumonia	1 (2.4)
Pseudomonas putida	1 (2.4)
Stenotrophomonas maltophilia	1 (2.4)

* Among 36/1015 (3.5%) SBCs from 30/127 (28%) total patients in the cohort, which includes patients with polymicrobial infections.
† Includes 1 vancomycin-resistant and 1 vancomycin-sensitive strain.

Figure 2 illustrates days of antibiotic therapy for patients with positive SBCs. Thirty-three of 36 patients with positive SBCs (92%) were treated for a sum total of 376 antibiotic days. Vancomycin comprised a total of 256 days (68% of all antibiotic days); the median duration of vancomycin was 10 days (IQR, 7 to 14). Together, antibiotics targeting gram-positive pathogens (vancomycin, daptomycin, and linezolid) made up 302 or 80% of all antibiotic days. Only 6 patients were admitted to the hospital for treatment (2 gram-negative, 3 gram-positive, and 1 polymicrobial). None required ICU-level care or died from their documented bacteremia within 30 days.

DISCUSSION

Weekly outpatient SBCs in asymptomatic allogeneic HCT patients on high-dose glucocorticoids were infrequently positive (3.5%), and high-pathogenicity organisms accounted for less than 1% of all cultures. Coagulase-negative *Staphylococcus* was the most common organism recovered, which led to excess vancomycin use within this cohort.

Previous studies have evaluated the utility of SBCs in various high-risk populations of oncology and transplant patients

Table 3
Case Review of Surveillance Cultures with High-Pathogenicity Organisms

Patient No.	Days Post-Transplant	Steroid Dose (mg/kg/day)	Organism	Hours from Blood Culture Collection to Positivity	Hours to First Antibiotic after Notification*	Blood Culture Repeated before Antibiotics?	Admit	ICU	30-Day Mortality
1a	53	.8	*Serratia marcescens*	19.5	2.5	No	Yes	No	No
1b	78	.4	*Pseudomonas putida* and *Enterococcus faecium*†	14.5	3	Yes	Yes	No	No
2	265	.34	*Stenotrophomonas maltophilia*	30	N/A (<24)	No	No	No	No
3	55	.4	*Klebsiella pneumoniae*	42	3	Yes	Yes	No	No
4	56	1	*Enterococcus faecium*‡	19	2	No	No	No	No
5	85	.6	MSSA	24	5	No	No	No	No

N/A indicates not available; MSSA, methicillin-susceptible *Staphylococcus aureus.*
* Time at which lab reported positive culture results .
† Vancomycin resistant.
‡ Vancomycin sensitive.

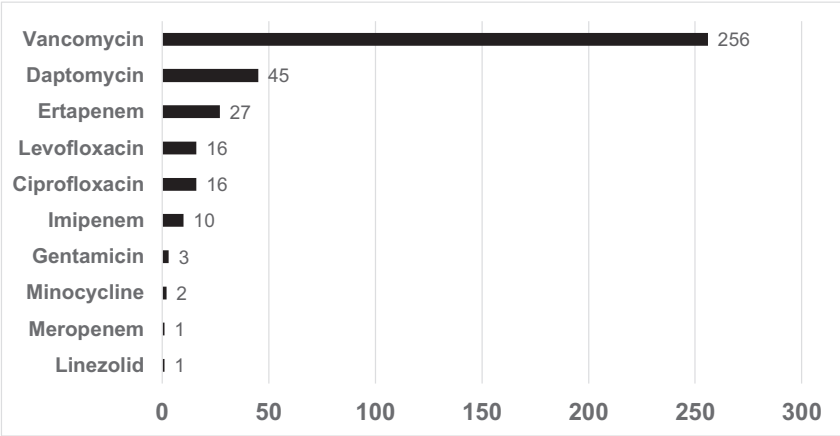

Fig. 2. Antibiotic days received in patients with positive SBCs. Asterisk indicates 37 total antibiotic courses. Individual patients may have received more than 1 agent during the course of their therapy.

with mixed results. The term "surveillance blood cultures" in these studies refers to periodic collection of blood cultures for defined patient populations, but frequency of collection, inpatient versus outpatient setting, and presence of clinical symptoms are variable (Supplemental Table 1). For instance, Chizuka et al. [3] found that weekly blood cultures in 69 afebrile allogeneic HCT patients who were on >.5 mg/kg prednisone equivalent yielded 110 of 968 positive blood cultures in 36 patients and were the only diagnostic clue for occult bloodstream infection; however, patients' courses were not reviewed for other symptoms beyond fever. In contrast, when studies are limited strictly to asymptomatic HCT patients, SBCs appear to provide limited value (Table 4) [2,6,9,10]. The largest study of SBCs to date was performed by Nesher et al. [9] at the University of Texas MD Anderson Cancer Center on a cohort of 776 allogeneic HCT patients who had weekly SBCs drawn from central venous catheters whether or not they were on high-dose glucocorticoids. The general conclusions from studies of asymptomatic HCT patients reflected that SBCs were of limited value, not cost-effective, and had a weak correlation for predicting subsequent septicemia [2,6,9,10]. Ghazal et al. [2] evaluated the utility of weekly SBCs in asymptomatic hospitalized HCT recipients versus those who were symptomatic at the time of blood cultures to detect catheter-related bloodstream infection. In their cohort of 205 HCT patients, SBCs did not identify any bloodstream infections and resulted in overdiagnosis and overtreatment for over 10% of their cohort.

Our results suggest that the practice of obtaining weekly SBCs among asymptomatic patients in the outpatient department may be of limited value because of the low frequency of positive blood cultures. When we compared SBCs with blood cultures obtained in the same cohort for symptomatic workup, SBCs isolated significantly fewer organisms (36/1015 [3.5%] versus 12/86 [14%], $P < .001$).

Furthermore, most positive cultures ultimately grew coagulase-negative *Staphylococcus*, a common skin commensal [14]. Distinguishing true bloodstream infection from contamination may be difficult in this patient population given their medically vulnerable state, the lack of a simultaneously collected peripheral blood culture in most cases, and a provider's sense of urgency to treat when a blood culture returns positive. Adherence to central venous catheter care maintenance practices by nursing staff, patients, and caregivers should be another consideration. Thirty-three of 36 positive SBCs were treated, but only 11 patients (33%) had repeat blood cultures before starting antibiotics. Although documentation of blood culture clearance for non-*S. aureus* bacteremia may not always be necessary, particularly for gram-negative rods [15,16], in this cohort with largely gram-positive organisms from single positive blood cultures obtained from central venous catheters, repeat cultures may help to distinguish contamination from true infections.

Table 4
Review of Previous Studies Examining the Utility of SBCs from Asymptomatic HCT Patients

Study	No. of patients	Median age (yr)	Study year	Proportion of Positive SBCs	Proportion of SBCs with High Pathogenicity Organisms*	Conclusions/Comments
Colombier et al.	82	52	2013	103/1450 (7%) accounting for 73 infectious episodes† in 33 patients	22/73 (30%) episodes	Daily SBCs rarely identified BSI. Clear benefit could not be demonstrated.
Ghazal et al.	205	49	2010-2011	NA/2474 SBCs accounting for 55 episodes†	13/55 (24%) episodes	SBCs did not identify BSI. Twenty-two of 55 episodes were treated with antibiotics for at least 10 days/episode.
Nesher et al.	776	53	2010-2011	211/6801 (3%) in 187 patients	21/211 (10%)	Frequency of clinically significant SBCs is very low and leads to unnecessary medical interventions and added costs.
Rigby et al.	43	7	1999-2005	NA/316 accounting for 3 episodes in 3 patients	2/3 (66%)	SBCs is low yield and significant cost. Unclear whether SBCs contribute to improved patient outcomes.
This study	127	52	2009-2013	36/1015 (3.5%) in 30 patients	10/36 (27%)	—

BSI indicates bloodstream infection.
* High-pathogenicity organisms included any gram-negative rod, *S. aureus*, enterococci, *Streptococcus* sp., and *Candida* sp.
† Blood cultures growing the same organism over a 7-day period were considered as part of a single episode.
‡ Episode defined as a set or group of successive positive culture sets done within 1 week, irrespective of their number or whether the patient was classified as infected or not.

The practice of SBCs led to vancomycin use in 27 of 36 positive blood cultures (75%), with a median therapy duration of 10 days, mainly for low-risk pathogens (eg, coagulase-negative *Staphylococcus*) or for pathogens almost universally considered contaminants (eg, diptheroids). Although it is difficult to ascertain whether these courses are warranted in a retrospective study, chart review revealed sparse documentation regarding rationale for vancomycin duration, oversight in dosing, and drug-level monitoring. As programs begin to focus on antimicrobial stewardship among immunocompromised patients, this study reinforces the importance of monitoring antibiotic use in the ambulatory setting. Since this study was completed a number of changes have been made at our center. An antimicrobial stewardship pharmacist performs prospective audit and feedback on vancomycin administered among outpatients and assesses appropriateness of dosing, indication, and duration and identifies opportunities for de-escalation.

Given the association of gram-negative bacteremia with mortality in highly immunocompromised patients [17–19], early detection and treatment of gram-negative bacteremia may arguably be the most important target of SBCs. In our cohort, occult gram-negative bacteremia was rare; SBCs identified 4 gram-negative rods in 3 unique patients. The number of weekly cultures needed to identify 1 occult gram-negative bacteremia in this cohort was 254. For 3 of these bacteremia events the patient was admitted; none required ICU care, and there were no deaths. Because glucocorticoids for GVHD are gradually tapered, prednisone doses in these cases were reviewed, and interestingly only 1 patient was still on high-dose glucocorticoids when cultures were drawn. Therefore, strict adherence to our center's standard practice guidelines for SBCs would have identified only 1 occult gram-negative bacteremia, suggesting less benefit from these efforts. Because limiting morbidity and mortality among these high-risk patients remains crucial, each center must rely on its own observational data on SBCs until additional randomized controlled trials can document the utility of this approach.

Costs of weekly blood cultures, microbiology workup, i.v. antibiotic administration, and days of hospitalization should be considered potential burdens of such policies. Additionally, the effect of antibiotics, particularly how they may lead to other adverse side effects, is important to consider. Furthermore, antibiotic effects on the microbiome in allogeneic HCT patients with GVHD are highly dynamic [20] and may potentially worsen GVHD outcomes [21]. Low microbiome diversity from antibiotic exposure has been associated with multidrug-resistant pathogen colonization/disease [22] and progression to lower respiratory tract disease in allogeneic HCT patients [23].

Our study is limited by the retrospective observational design at a single cancer center. However, our focus on the practice of SBCs for patients on high-dose glucocorticoids in the outpatient setting is unique. Additionally, clinical information, decision-making, and lab monitoring for outpatient antibiotics were infrequently documented in the outpatient setting. The risk profile of hospitalized patients receiving glucocorticoid treatment for acute GVHD may be different and was not evaluated in the present study. Finally, we cannot assess the role additional antibiotic therapy could have on late GVHD complications. Although these data highlight the need for diagnostic and antimicrobial stewardship, it also precedes implementation of rapid molecular diagnostics, review of all positive blood cultures by our stewardship team, and outpatient vancomycin pharmacy review, which likely have influenced subsequent antibiotic use since the time in which this study was conducted.

In conclusion, our study examined the utility of outpatient ambulatory SBCs to identify occult bacteremia in patients on high-dose glucocorticoids for treatment of acute GVHD after allogeneic HCT. SBCs were infrequently positive (3.5%), and most identified organisms were coagulase-negative *Staphylococcus,* for which vancomycin was administered. Our results do not support the practice of obtaining weekly SBCs in asymptomatic outpatients, although a randomized trial would be needed to confirm this recommendation. Ambulatory

diagnostic stewardship and antibiotic administration are important areas that need renewed focus for future stewardship efforts in high-risk immunocompromised populations.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.01.031.

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