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REVIEW

Bacterial bloodstream infections in the allogeneic hematopoietic cell transplant patient: new considerations for a persistent nemesis

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Bacterial bloodstream infections (BSI) cause significant transplant-related morbidity and mortality following allogeneic hematopoietic cell transplantation (allo-HCT). This manuscript reviews the risk factors for and the bacterial pathogens causing BSIs in allo-HCT recipients in the contemporary transplant period. In addition, it offers insight into emerging resistant pathogens and reviews clinical management considerations to treat and strategies to prevent BSIs in allo-HCT patients.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is the definitive therapy for many malignancies, marrow failure syndromes and immune deficiencies in children, adolescents and adults.[1,2] Transplant strategies and supportive care have evolved over the past few decades, resulting in improved overall survival (OS).[3] Despite these advances, infection remains a primary cause of death following allo-HCT. Allo-HCT patients are at increased risk of developing bacterial bloodstream infections (BSIs), which are among the most serious infectious complications, leading to prolonged hospitalization and exposure to antimicrobial therapy, increasing nosocomial infection risk. In addition, BSI often results in the need for intensive care and increases non-relapse mortality (NRM).[4–6] Central line-associated bloodstream infections (CLABSIs) are serious complications in HCT recipients and lead to prolonged hospitalization, and intensive care admissions.[4–7] According to National Healthcare Safety Network (NHSN) data, CLABSI incidence continues to be highest in the HCT population, wherein rates are higher than in any other high-risk population, including solid organ transplant and burn patients, or care setting (that is, intensive care units).[8] This paper will review the impact of bacterial BSI in the current transplant period as measured by resource utilization and associated morbidity and mortality in allo-HCT patients. The manuscript will also offer insight into emerging resistant pathogens responsible for causing bacterial BSI and novel antimicrobial therapies and approaches implemented to reduce BSI-related morbidity and mortality in allo-HCT patients.

DEFINITIONS

An important challenge in interpreting data is ensuring accurate definitions. BSIs in the healthcare setting are classified as either primary BSI, related to either a central venous catheter (CVC) or other hospital-acquired source, or secondary BSI, a bacteremia related to another site of infection (for example, abscess or pneumonia).[9] Thus, unless an alternative source is identified, all BSIs in patients with a CVC are considered CLABSIs. Some patients with CVCs experience BSIs that do not arise from the catheter, but rather originate from translocation of bacteria through non-intact oral and gut mucosa.[9,10] To address this type of BSI, the Centers for Disease Control and Prevention defined a specific CLABSI type known as 'mucosal barrier injury laboratory-confirmed bloodstream infection' (MBI-LCBI) based on literature review and expert opinion. In 2013, the MBI-LCBI definition was integrated into NHSN methods for primary BSI surveillance to identify a subset of BSIs reported as CLABSIs that were likely related to mucosal barrier injury in the mouth and gut and not the presence of the CVC itself.[9] (Figure 1) Currently, the NHSN defines primary BSIs in patients with a CVC as 'laboratory-confirmed bloodstream infection (LCBI)' and subcategorized as 'CLABSI' or 'MBI-LCBI'.[11] Inherent to this distinction is emerging evidence showing that improved CVC maintenance is effective at reducing CLABSI rates,[12–14] but not in preventing MBI-LCBIs.[15]

CLABSI and MBI-LCBI are terms utilized by the NHSN for BSI surveillance. To augment this the Infectious Disease Society of America (IDSA) produced guidelines for the detection of bacteremia in patients with CVCs utilizing the term 'catheter-related bloodstream infection' (CRBSI).[16] CRBSI is a clinical definition used to determine if the presence of bacteremia originates from the CVC, or from another source. Confirming a CRBSI diagnosis includes calculating the differential time-to-positivity between equal volume blood cultures drawn concomitantly from the CVC and a peripheral site or a second CVC lumen.[16] In pediatric oncology patients, blood cultures drawn from the central CVC site that grow $\geqslant$150 min before blood cultures from a peripheral site predict that the CLABSI is from a colonized CVC with 89% sensitivity and 100% specificity.[16,17] If peripheral blood cultures are not obtained, but blood cultures are obtained from both lumens of a double lumen CVC,

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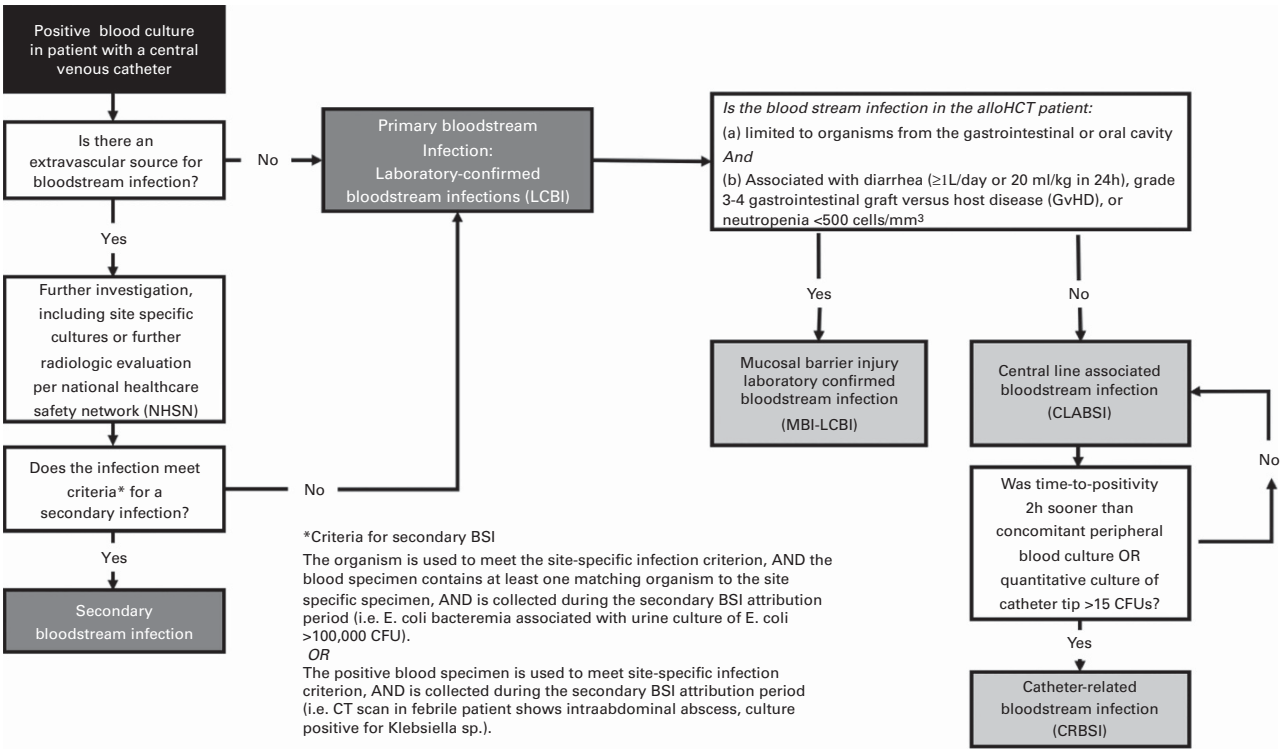

Figure 1. Classification of primary and secondary bloodstream infections (BSI) per 2016 National Healthcare Safety Network (NHSN). Primary BSIs are caused by a common commensal organism, isolated from a blood culture on two occasions, or a recognized pathogen isolated from one blood culture. Specific criteria must be met for secondary BSI or mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI) designations. Otherwise, BSIs are classified as a central line-associated bloodstream infection (CLABSI).

a differential time-to-positivity of $\geqslant 180$ min can be used to diagnose a CLABSI with 61% sensitivity and 94% specificity. However, this comparison has a poor negative predictive value.[18]

EPIDEMIOLOGY

The incidence of BSI and associated bacteria types vary widely by geographic location, patient population, and study design. BSI is the most common infectious complication following adult (Table 1) and pediatric (Table 2) allo-HCT.

Mikulska *et al.*[19] showed 60% of all BSIs occurred in the pre-engraftment period. Kikuchi *et al.*[20] showed similar results in their retrospective review, noting that BSIs were more common in the pre- (39% of patients) vs post-engraftment (17% of patients) periods. During the pre-engraftment period, important risk factors for BSI are neutropenia, presence of a CVC and severe mucositis.[21] In multivariate analysis, pre-engraftment BSI has been associated with engraftment failure and high-risk disease status at the time of HCT.[20]

Post-engraftment BSIs are more commonly found in patients who undergo allo-HCT and have a history of acute (aGvHD) or chronic GvHD (cGvHD). Patients with post-engraftment BSI received more antibacterial prophylaxis, previous antibiotic therapy and immunosuppression (corticosteroids and cyclosporine) than patients without BSI.[20,21] In addition, patients with post-engraftment BSIs traditionally have poorer outcomes, with higher early and all-cause fatality rates.[21]

RISK FACTORS

Risk factors for BSI include age greater than 18 years, use of unrelated graft source and myeloablative conditioning regimen, acute GvHD, mucositis, transplant-associated thrombotic microangiopathy (TA-TMA), high-risk malignant disease and steroid use[5,22] (Figure 2).

Graft source

Ballen *et al.*[23] compared the incidence of bacterial, viral and fungal infections in 1781 adults with acute leukemia who received alternative donor HCT between 2008 and 2011. Over 50% of patients developed bacterial infections by 1 year post HCT. In multivariable analysis, bacterial infections were more common after mismatched unrelated donor (MMUD) than matched unrelated donor (MUD) grafts ($P = 0.0295$) and most common after umbilical cord blood (UCB) vs MUD ($P < 0.001$) or MMUD grafts ($P = 0.0009$), likely due to the slower engraftment and delayed immune recovery associated with UCB.[23] Although UCB are associated with increased BSI rates, Sanz *et al.*[24] reported that higher $CD8^+$ cell doses in UCB grafts independently associated with reduced risk of BSI.

Young *et al.*[25] conducted a phase three, multicenter, randomized trial comparing HCT outcomes using unrelated bone marrow (BM) and peripheral blood (PB). Although 2-year OS was similar between the two graft sources, BSIs at 100 days and two years post HCT were higher in patients receiving BM grafts. The cumulative incidence of BSI during the first 100 days was 44.8% (95% confidence interval (CI), 38.5–51.1) for BM vs 35.0% (95% CI, 28.9–41.1) for PB ($P = 0.027$); and the two-year cumulative incidence of BSI was 72.1% and 62.9% in BM vs PB recipients, respectively ($P = 0.003$).[25]

Haploidentical HCT is emerging as a comparable alternative to MUD transplantation with respect to disease control and complications. Despite a notable increase risk for viral-related morbidity and mortality, haploidentical HCT currently does not appear to be associated with increased BSI risk.[26]

Table 1. Contemporary era literature review of bacterial BSI in adult HCT recipients

Ref	Design	Years	No. of patients	Antibiotic prophylaxis	No. BSI	BSI incidence	Predominant pathogens				Resistance trends	Mortality rates
							GPB	*LF GNB*	*NLF GNB*	*Other*		
83	P	2013–2015	*N* = 360 Adult HCT Allo = 62 Auto = 281	FQ	135	Pre = 38%	Pre = 35% Most common: CoNS	Pre = 44%	PRE = 21% Most common: *Pseud*, *Acineto*	NA	*Kleb* CRE = 20% ESBL = 50% *E.coli* CRE = 0% ESBL = 25% NLF CR = 80%	30d Crude mortality = 31% ↑Mortality: CRE NLF BSI and inadequate empiric Rx
20	R	2006–2013	*N* = 209 Adult HCT	FQ	136	Pre = 39% Post = 17%	Pre = 67% Post = 84%	Pre = 13% Post = 7%	Pre = 15% Post-4.6%	Pre-4.5% Fungal	GNB FQ = 24% CRE = 52% AG = 29%	Pre-Attributable mortality = 6.8% D180 OS BSI = 70% No BSI = 83%
24	R	1997–2012	*N* = 241 Adult UCB, HCT	FQ	189	D30 = 34% D100 = 43%	D30 = 47% CoNS 28% *Entero*13% VSG 8% SA 6%	D30 = 21% *E.coli* = 19%	D30 = 19% *Pseud* = 8% *Steno* = 5% *Acineto* = 6%	11%	Pre-D100 MDR = 83% CRE = 30% Post-D100 MDR = 33% CRE = 9%	7d Mortality CRE = 39% CSE = 12% 30d Mortality CRE = 61% CSE = 18%
21	R	2006–2013	*N* = 400 Adult HCT Allo = 161 Auto = 239	FQ	189	Allo 75% Auto 29%	PRE = 64% CoNS 39% VGS 8% *Entero* 6% SA 6% POST = 57%	PPRE = 25% *E. coli* 19% Kleb 5% POST = 29% *S.pneumo* = 13.5%	PRE = 5% Pseud = 5% POST = 6%		FQ = 45-54% MDR = 7%	30d Mortality = 14% ↑ Risk of death: VGS BSI and ICU admission Mortality ↑ for Late vs Early BSI
38	P	2004–2008	*N* = 382 Adult HCT	FQ	149	39%	54% *Staph* 19% *Entero* 24% VGS 9%	20%	13%	12% Fungal/ Other	GNB: FQ = 73% ESBL = 35%	7d Mortality All = 15.4% GPB = 10% GNB = 22% 30d Mortality All = 27% GP = 22% GNR = 31% *Pseud* mortality = 67% *Pseud* MDR Mortality = 100%
28	R	2001–2008 Pre-	*N* = 521 Adult HCT	FQ	120	21%	80% VGS 34% CoNS 26% *Entero*14%	9% *E.coli* 7%	4%	2.3% Fungal	*E.coli*: FQ = 78% ESBL = 56% CRE = 0%	120d Mortality = 21% Attributable mortality = 3.3% VSG mortality = 27%
147	R	2001–2010	*N* = 528 Adult HCT Allo = 285 Auto = 243	FQ	380	NA	54% CoNS 24% *Entero*12% SA 9% VGS 9%	28% *E coli* 11% *Kleb* 9% *Enterobac* 5%	8% *Pseud* 3% *Acin* 3% *Steno* 2%	14% Fungal/ Other	2007-10: FQ = 28% ESBL = 36% CRE = 8% *Pseud & Acin* CP res = 44% After FQ ppx: ↓ GNR BSI, ↑ FQ resistance ↑ VRE	28d Mortality = 25% Predictors of mortality: Active disease, Grade 4 GvHD, and MDR BSI
97	R	1999–2006	*N* = 246 Adult HCT	FQ	77	25%	36%	All GNB 54%		10% Fungal	FQ = 30%	BSI: ↑ Mortality despite FQ ppx
148	R	2001–2009	*N* = 269 Adult HCT	FQ	30	12%	56% CoNS 50%	26% *E.coli* 23%	13%	6.2% Fungal	FQ = 50%	Crude and attributable mortality = 3%

Table 1. (Continued)

Ref	Design	Years	No. of patients	Antibiotic prophylaxis	No. BSI	BSI incidence	Predominant pathogens				Resistance trends	Mortality rates
							GPB	*LF GNB*	*NLF GNB*	*Other*		
149	R	2002–2012	*N* = 134 Adult HCT Allo = 59 Auto = 75	FQ	36	45%	35%	35%	18%		MDR = 50%	Attributable mortality: = 33% Allo = 7% Auto
150	P	1997–2011	*N* = 800 Adult HCT	NA	NA	VRE only = 10%	NA	NA	NA	NA	NA	↓ OS: VRE BSI (HR 4.3) Majority treated with daptomycin
39	R	2004–2008	*N* = 752 Adult &Peds HCT	NA		*Entero* only VRE = 6.6% VSE = 5.7%	VRE/VSE ratio (%) Adult = 66/ 23 Ped = 30/60	NA	NA	NA	NA	30d Crude mortality: Adult: VRE = 38% VSE = 38% Ped: VRE = 20% VSE = 4.5%
52	P	2010–2011	*N* = 794 Adult HCT	FQ	20	*Pseud* only = 2.5%	NA	NA	NA	NA	MDR Pseud colonization* = 1.5% Overall Pseud colonization = 7.3% *by rectal swab	
151	P	2000–2005 2006-2011	*N* = 1052 Adult HCT	FQ+Vanc	159 203	Before FQ +Vanc = 32.7% After FQ+Vanc = 24.4%	49% Entero17% CoNS 17%	36%	11%	NA	LF FQ = 30% ESBL = 10% MDR = 5-10% NLF FQ = 30-45% MDR = 20-38%	NA
84	P	2005–10	*N* = 834 Adult HCT Allo = 555 Auto = 279	FQ	631	Allo 51% Auto 24%	88%	Total GNB 12%		2009-2010 *Pseud*: FQ = 40% CAZ = 30% AG = 30% *Kleb*: FQ = 25% CAZ = 25%	NA	
25	+ P Multi-center	2004–2009	*N* = 499 Adult HCT	FQ	413	At D100 BM = 45% PB = 35%	Most common: CoNS, *Entero*	Most common: *E.coli*, Enterobac, *Kleb, Pseud, Steno*	NA	NA	NA	
30	R	2000–2005	*N* = 218 Adult HCT	FQ	96	39%	NA GPB more common	NA	NA	NA	NA	NA

Abbreviations: Acineto = acinetobacter spp; AG = aminoglycoside; Auto: autologous HCT; Allo: allogeneic HCT; BM = bone marrow; BSI = bloodstream infection; CAZ = ceftazidime; CoNS = coagulase-negative *Staphylococcus*; CP-resistance = carbapenem resistance; CRE = carbapenem-resistant *Enterobacteriaceae*; CSE = carbapenem-sensitive *Enterobacteriaceae*; D = days post HCT; Entero = *Enterococcus* spp.; Enterobac = Enterobacter spp.; ESBL = extended spectrum beta-lactamase; FQ = fluoroquinolone; GNB = gram negative bacteria; GPB = gram positive bacteria; HCT = hematopoietic cell transplantation; HR = hazard ratio; *Kleb* = *Klebsiella pneumoniae*; LF = lactose fermenting; MDR = multidrug resistant; NA = not available; NLF = non-lactose fermenting; OS = overall survival; P = prospective study; *Pseud* = *Pseudomonas aeruginosa*; PB = peripheral blood; Ped = pediatric; Pip/taz = piperacillin/tazobactam; Ppx = prophylaxis; Pre = pre-engraftment; Post = post-engraftment; R = retrospective study; Ref = reference; Rx = antibiotic therapy; SA = *Staphyloccocus aureus*; Steno = *Stenotrophomonas* spp.; VGS = viridans group *Streptococcus*; Vanc = vancomycin; VRE = vancomycin-resistant *Enterococcus*; VSE = vancomycin-sensitive *Enterococcus*. All studies are observational, single center unless noted (+). Prospective design refers to prospective data collection with retrospective analyses. Lactose-fermenting gram negative bacteria (GNB) include *Enterobacteriaceae* (*E coli*, Klebsiella spp., *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp.). Non-lactose fermenting (GNB) include *Pseudomonas* spp., *Stenotrophomonas* spp. and *Acinetobacter* spp.

Table 2. Contemporary era literature review of bacterial BSI in pediatric HCT recipients

Ref	Design	Years	No. of patients	Antibiotic prophylaxis	BSI rates or incidences	Predominant pathogens			Resistance trends	Mortality rates
						GPB, Number (%)	GNB, Number (%)	Other, Number (%)		
35	R	1988–2009	*N* = 277 Ped HCT	Oral polymixin	ND Incidence = 8.7%	17 (75%)	6 (21%)	1 (4%)	ND	ND
152	R	2000–2011	*N* = 351 Ped HCT for AA	ND	ND Incidence = 11.1%	25 (64%)	11 (28%)	3 (8%)	ND	5 year 35% in those with BSI
28	R	2001–2008	*N* = 365 A HCT *N* = 156 Ped HCT	Ciprofloxacin	Incidence 1 BSI = 21%	100 (80%)	17 (13%)	9 (7%)	FQ-resistant GNB	D120 Attributable 3.3%, Crude 21%
39	R	2004–2008	*N* = 752 A & Ped HCT	ND	ND Incidence = 12.3% (VRE+VSE)	93	n/a	n/a	66% VRE adults, 31% VRE ped	4.5–20% ped
19	R	2004–2008	*N* = 382 A & Ped HCT	FQ	ND	80 (54%)	49 (33%)	20 (13%)	ND	15% if BSI within D20
88	R	2004–2012	*N* = 126 Ped HCT	Pip/tazo with fever	0.9–6.32/100 person-months	150 (44%)	152 (45%)	ND	↑ VRE	ND
29	R	2004–2012	*N* = 264 Ped HCT with GVHD	Pip/tazo with fever	0.95–2.7 enteric infections/person-year	16 (13%)	105 (86%)	ND	ND	33.9% in those with enteric BSI at 1 year
89	P	2005–2011	*N* = 70 Ped HCT	ND	Onc + HCT rates of 1.61–3.59 CLABSI/ 1,000 CVC days	55 (79%)	12 (17%)	3	ND	ND
86	R	2006–2008	*N* = 90 Ped HCT	ND	3–10 CLABSI/1,000 CVC days	55 (40%)	74 (54%)	8 (6%)	ND	ND
153	R	2007–2009	*N* = 54, Ped Onc + HCT	ND	2.8/1,000 CVC days in HCT	34 (58%)	19 (32%)	6 (10%)	VRE most frequent	ND
154	R	2008–2014	*N* = 85, A & Ped HCT	ND	ND	29 (27%)	76 (70%)	3 (3%)	↑ MDR GNB, including CPE	D90 13.1%
155	R	2009–2011	*N* = 73, A & Ped HCT	ND	ND CLABSI: 23/73 (32% pts) MBI CLABSI: 8/73 (11%)	27 (57%)	14 (30%)	6 (13%)	GPB	D100 26% infection-related
156	P, epi	2009–2011	36 hospitals, including 18 HCT centers	19% of centers	576 CLABSIs	250 (54%)	181 (39%)	33 (7%)	ND	ND
12	P, epi	2009	32 Onc & HCT units	24% of centers	2–2.85 CLABSI/1,000 CVC days	ND	ND	ND	ND	ND
157	S	2012–2013	*N* = 3,248, 15 Onc & HCT hospitals	ND	0.16–0.67/1,000 hospital days	ND	ND	ND	CRE bacteremia only	D90 15.9%

Abbreviations: A = adult; AA = aplastic anemia; BSI = bloodstream infection; CLABSI = catheter line-associated BSI; CRE = carbapenem-resistant *Enterobacteriaceae*; CVC = central venous catheter; D = days post HCT; Epi = epidemiology study; FQ = fluoroquinolone; GNB = gram negative bacteria; GPB = gram positive bacteria; HCT = hematopoietic cell transplantation; MBI = mucosal barrier injury/insult; MDR = multidrug resistant; ND = not determined/ specified; Onc = oncology patients; P = prospective study; Ped = pediatric; Pip/taz = piperacillin/tazobactam; R = retrospective study; Ref = reference; S = single center; VRE = vancomycin-resistant *Enterococcus*; VSE = vancomycin-sensitive *Enterococcus*.

Conditioning regimen

Reduced-intensity conditioning (RIC) is associated with less regimen-related toxicity than myeloablative conditioning (MAC) regimens.[27] As such, patients receiving RIC conditioning regimens typically have lower rates of BSI, likely due to decreased mucositis and shorter durations of neutropenia.[27,28] However, pediatric patients undergoing RIC transplant for non-malignant disease have been noted to have an increased BSI risk,[5] which may reflect the added risk for BSI associated with the underlying diagnosis itself (for example, primary immunodeficiency).

Acute GvHD

Damage to the gastrointestinal epithelium caused by aGvHD may facilitate bacterial translocation across the gastrointestinal mucosal barrier. BSI rates secondary to enteric bacteria in the first 120 days following allo-HCT are three times higher following rather than preceding aGvHD.[29] Also contributing to increased BSI risk following aGvHD is its associated intensive immunosuppressive therapy.[30] In murine allo-HCT models, aGvHD causes a shift toward predominance of gram negative organisms, which, in turn, increases the risk for sepsis-related morbidity and mortality.[31] In addition, Paneth cells which selectively kill noncommensals through secretion of α-defensins are targeted by aGvHD.[32,33]

Transplant-associated thrombotic microangiopathy

TA-TMA causes generalized endothelial dysfunction that can progress to multi-organ injury and poor transplant outcome.[34]

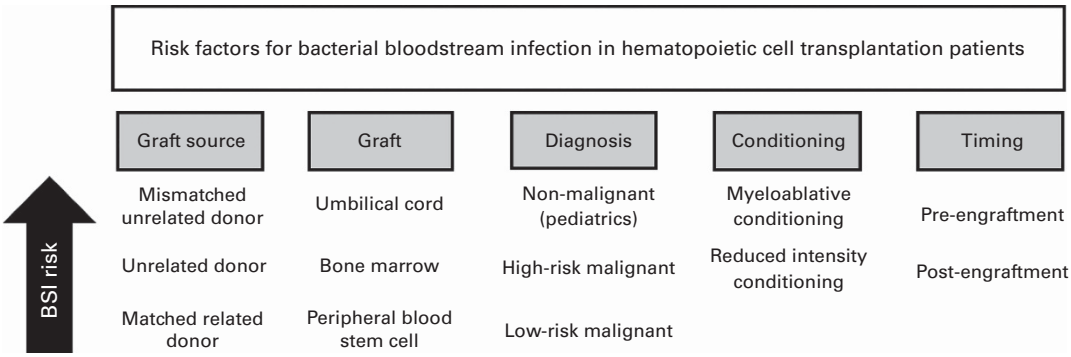

Figure 2. Risk factors for bacterial bloodstream infection (BSI) in hematopoietic cell transplant patients. Risk factors for bloodstream infections within each listed patient- and transplant-related demographic are listed from lowest to highest bloodstream infection risk.

TA-TMA is frequent after HCT, occurring in about one-third of patients if monitored carefully and leads to systemic vascular injury and widespread tissue injury. The intestine can also be a target of TA-MA, potentially leading to bacterial translocation and interestingly, TA-TMA is strongly associated with MBI-LCBI.[5] Patients with TA-TMA might benefit from preventative strategies to reduce MBI-LCBI.

Other risk factors

High-risk malignant disease such as acute myelogenous leukemia not in remission at the time of HCT is associated with increased risk of post-HCT BSI.[20] In pediatric populations, non-malignant diseases are associated with higher BSI risk than malignant diseases.[5,35]

EMERGING RESISTANCE IN BLOODSTREAM INFECTION PATHOGENS IN THE CONTEMPORARY TRANSPLANT PERIOD

Few studies address etiology and resistance patterns for bacterial pathogens responsible for BSI in HCT recipients. Although several single-center, retrospective analyses have been published in the last 10 years, many refer to data obtained prior to the current contemporary transplant period (2010–2015). As the etiology of infections in these reporting hospitals may have changed, reflecting different infection prevention and management strategies, many of the published resistance rates in these studies are likely obsolete. General trends in contemporary studies include an overall decreased incidence of BSI compared to earlier studies.[22,36,37] While the overall incidence of BSI by gram negative bacteria has decreased, the proportion of BSI caused by fluoroquinolone-resistant bacteria has increased compared with prior studies (Table 1). Similarly, contemporary microbial epidemiology data in pediatric HCT over the last 5 years demonstrates a decrease in CLABSI rates with a suggestive trend toward less predominance of gram positive bacteria and selection of multidrug resistant (MDR) pathogens (Table 2).

Center-specific infection control and antibiotic stewardship practices are seldom reported in published studies, but likely contribute to observed BSI heterogeneity across centers. In 2014, Mikulska *et al.*[38] distributed a questionnaire to assess bacterial resistance and empiric antibiotic use to institutions across 18 countries. Thirty-nine[39] centers completed and evaluated changes in pathogen resistance patterns over 5 years (2005–2011). The individual centers reported reduction in gram positive to gram negative bacteria ratios (55:45 vs 60:40%), increased rates in *Enterococcus* spp. (8 vs 5%) and *Enterobacteriaceae* spp. (30 vs 24%), and decreased rates in *Pseudomonas aeruginosa* (5 vs 10%) from earlier to more recent time periods. However, rates of extended spectrum beta-lactamase (ESBL)-producing organisms, aminoglycoside-resistant gram negative bacteria and carbapenem-resistant *P. aeruginosa* were substantially increased,[38] reflecting emergence of these resistant pathogens.

Vancomycin-resistant *Enterococcus*

BSI with vancomycin-resistant *Enterococcus* (VRE) is emerging in pediatric and adult HCT recipients.[39] In a single-center report, the rate of VRE was substantially higher for adult patients than pediatric patients; and VRE BSI resulted in inferior one-year OS post-HCT.[39] In addition, patients with VRE BSI have significantly longer duration of (attributable difference 2.1 days longer) and costs in hospitalization.[40]

Enterococcus faecium has emerged as a leading cause of MDR enterococcal infection in the United States;[41] as VRE is responsible for nearly 18% of all invasive enterococcal infections in North America, with an incidence nearly doubling in recent years.[41] Importantly, *E faecium* is intrinsically more antibiotic-resistant than *E faecalis* with more than half of its pathogenic isolates expressing resistance to vancomycin and ampicillin. As a result, treating infections caused by this species can be difficult.[42] The primary mode of spread of VRE from patient-to-patient occurs through the hands of healthcare workers. *Enterococci* can persist for as long as 60 min after inoculation onto hands and up to 4 months on inanimate surfaces, where they can serve as a reservoir for ongoing transmission in the absence of regular decontamination.[43,44]

Antibiotic therapy leading to VRE gastrointestinal overgrowth may lead to a unique pathogenesis and predisposition to gut translocation and bacteremia.[45,46] Specifically, perturbation of normal commensal intestinal microbiota by antibiotics and domination by VRE were shown to precede VRE BSI in allo-HCT patients.[46]

Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) produces virulent biofilms on invasive, foreign devices like endotracheal tubes and endovascular catheters.[47,48] Biofilm facilitates MRSA survival and multiplication, prolonging the organism's exposure to antibiotics as well as promoting the transfer of antibiotic resistance genes among strains.[49] Use of antibiotics, particularly cephalosporins and fluoroquinolones, strongly correlates with MRSA colonization and infection. In 2007, Shaw *et al.* evaluated the frequency and outcome of patients who developed MRSA BSI over a 5-year period. The frequency of MRSA infections in autologous, MSD and MUD transplants was 3, 6 and 9%, respectively and in 7% of the infections MRSA was directly implicated in patient mortality.[50]

MDR gram negative bacteria

MDR bacterial strains are defined by their resistance to three or more antibiotic classes: carbapenems (imipenem, meropenem); penicillins (piperacillin, ticarcillin and piperacillin–tazobactam); cephalosporins (ceftazidime, cefepime); monobactams; aminoglycosides and fluoroquinolones. In the aforementioned 2014 European survey, median reported rates of ESBL-producing gram negative bacteria (15–24%), aminoglycoside-resistant gram negative bacteria (5–14%) and carbapenem-resistant *P. aeruginosa* (5–14%) were substantial.[38] Consistent with the European survey, a recent study reported a 17.5% ESBL gram negative colonization rate among HCT patients in Germany with only 2% of colonized patients developing bacteremia.[51] In a 2015 report from MD Anderson Cancer Center,[52] rates of stool colonization with MDR *Pseudomonas* were 1.2% (12/794); however, seven (58%, 7/12) of the colonized patients went on to develop MDR *Pseudomonas* BSI. Differences in geography, infection control and antibiotic stewardship likely contribute to the variable rates of infection by these resistant pathogens.

Carbapenem-resistant *Enterobacteriaceae* (CRE) and *Klebsiella* (CRK)

Previously, *Enterobacteriaceae* were reliably susceptible to carbapenems despite resistance to other antimicrobial classes. Unfortunately, carbapenem-resistant *Enterobacteriaceae* (CRE) are now reported globally. In the US, CRE infections are almost exclusively caused by *K. pneumoniae* carbapenemase production. Importantly, CRE infections in HCT patient are rapidly lethal and have very limited therapeutic options. Satlin *et al.* reported that CRE caused 2.2% of all BSIs and 4.7% of BSI by gram negative bacteria in neutropenic patients with hematologic malignancies in two institutions.[53] Multiple antibiotics, steroids and prior CRE colonization were determined to be risk factors for CRE BSI, and delay in receipt of CRE-active therapy was associated with worse outcomes. First described in India, New Delhi metallo-β-lactamase-1 (NDM-1)-producing CRE have since spread globally. NDM-1 confers resistance to all available β-lactams except aztreonam and is associated with mortality rates exceeding 50%. In a recent study from MD Anderson, the rate of CRE in BSI isolates was 2.5% among adult oncology patients, with 55% carrying the NDM-1 gene in a non-outbreak setting.[54] All these isolates were resistant to ceftazidime-avibactam.[54]

Carbapenem-resistant *Klebsiella pneumoniae* (CRK) has recently been described in the HCT population. Germenia *et al.* determined the epidemiology and outcomes of HCT recipeints who develop a CPK BSI.[55] CPK infections were diagnosed in 0.4% of autologous HCT recipients and 2% of allo-HCT recipients at a median of 8 (±11.6) and 15 (±83.6) days post transplant, respectively. In addition, CRK infection increased over sevenfold from 2010 to 2013 in allo-HCT patients (0.4–2.9%). CRK colonization documented before or after transplant was followed by an infection in 39% of allo-SCT patients, which was associated with a 64% infection-related mortality.[55]

MICROBIOLOGICAL DETECTION OF BLOODSTREAM INFECTIONS IN HCT PATIENTS

Bloodstream infection detection

The Infectious Disease Society of America produced guidelines for the detection of bacteremia in patients with a CVC.[16] These recommendations include the timing and volume of blood culture collection. New modalities such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and multiplex molecular blood culture diagnostics may allow for more rapid identification of certain BSI pathogens in clinical specimens, thus improving time to effective and optimal antimicrobial therapy.[56] Whether application of these diagnostic methods has a measurable impact on HCT patient outcomes remains to be elucidated.[57]

Role of surveillance blood cultures

A retrospective study of asymptomatic adult allo-HCT recipients with CVCs who had 6801 surveillance blood cultures performed showed surveillance cultures infrequently yielded significant results (0.59% of all surveillance blood cultures drawn) and were associated with unnecessary medical interventions and added cost.[58] A prospective observational study in allo-HCT recipients receiving steroids who underwent daily blood culture surveillance also did not demonstrate a clear benefit and rarely identified a CLABSI.[59] Similarly, small case series of weekly BSI surveillance in asymptomatic children undergoing HCT demonstrated very low yield and significant cost, with no clear improvement in patient outcomes and higher rates of detection of contaminants.[60,61] Taken together, the published literature do not support the utility of surveillance blood cultures in HCT.

Screening for resistant bacteria

Transformation of non-resistant to MDR organisms in HCT patients occurs through antibiotic selection, patient-to-patient transmission and *de novo* development of antibiotic resistance.[62,63] Active surveillance may reduce transmission of MDR organisms when performed in high-risk patient care units.[64] Surveillance cultures for MRSA, VRE and other MDR gram negative bacteria can be obtained from skin, nasal and rectal swabs, or stool samples.

Although research on the prevalence and prevention of MRSA exists in other vulnerable populations, data on MRSA carriage, screening and associated morbidity and mortality in the HCT population is limited. National HCT guidelines do not offer recommendations for routine screening for MRSA carriage, as no studies have demonstrated associations between pre-transplant carriage and post-transplant infections. A retrospective study conducted at a large comprehensive cancer center demonstrated that the prevalence of pre-transplant MRSA nasal carriage detected by culture was low in HCT recipients.[65] Furthermore, no patients with proven pre-transplant nasal carriage developed post-transplant MRSA complications. Interestingly, only a minority of *S. aureus* acquisitions can be explained by patient-to-patient transmission.[66]

Patients with known VRE colonization have a higher risk of developing VRE BSI than patients without VRE.[67] However, VRE surveillance has not conclusively demonstrated reduction in VRE bacteremia in HCT recipients. Surveillance for MDR organisms (including CRE and MDR *Pseudomonas spp.* and intrinsically resistant organisms like *Acinetobacter spp.*) should be considered on a case-by-case basis for patients who come from areas with high endemicity, in an outbreak setting and in patients who have had previous infections with MDR pathogens.[68]

MANAGEMENT OF BLOODSTREAM INFECTIONS

Antimicrobial therapy

Pathogen-directed antibiotic therapy should be determined by identifying the causative organism and defining its associated susceptibility patterns. Once a pathogen is isolated by blood culture, repeat cultures are recommended until clearance of BSI is achieved. Duration of antimicrobial therapy varies by site of infection, pathogen and extent of neutropenia. Uncomplicated MBI-LCBIs require 7–14 days of antibiotic therapy from the date of first sterile blood culture or resolution of neutropenia, whichever is longer. Similarly, in the absence of an endovascular or metastatic foci of infection, uncomplicated CRBSI, duration of antimicrobial therapy is generally 7–14 days (depending on pathogen) from the date of catheter removal, blood culture sterilization and resolution

of neutropenia.[16] For common skin contaminants, a shorter duration (5–7 days) may be considered for patients who are clinically stable. Patients with complicated CLABSI, including those with persistent bacteremia despite ⩾72 h of effective antibiotic therapy or after catheter removal, may require prolonged treatment of up to 4–6 weeks given concern for an endovascular source for persistent infection.

Antimicrobial therapy for resistant pathogens—VRE

Four drugs active against VRE have been licensed for use: quinupristin-dalfopristin, linezolid, tigecycline and daptomycin. Linezolid has been used as treatment for VRE in the cancer and transplant settings. Specifically, empiric use of linezolid in VRE-colonized hematology patients did not impact infection-related mortality (IRM), which appears to be associated with persistence of neutropenia vs in HCT patients, in whom IRM was associated with GvHD.[69] In the HCT population, VRE colonization prior to allo-HCT was a risk factor for increased day 100 mortality, which appeared to be related to development of subsequent VRE bacteremia, and persisted after adjusting for baseline variables.[39]

Daptomycin is also used for treatment of VRE BSI, particularly in patients where there is concern for linezolid-induced hematologic toxicity. In 2009 surveillance studies from US hospitals demonstrated that more than 99.5% of VRE isolates were susceptible to daptomycin. However, subsequent emergence of daptomycin-resistant VRE during therapy has been described, particularly in adult oncology patients. At Memorial Sloan Kettering, daptomycin-resistant VRE bacteremia increased from 3.4% in 2007 to 15.2% in 2009.[70] Furthermore, daptomycin minimal inhibitory concentrations of 3–4 μg/mL in the initial *E faecium* blood isolate predicted microbiological failure of daptomycin therapy, suggesting that the recommended daptomycin dose is suboptimal for treating VRE bacteremia and modification in the daptomycin breakpoint for *Enterococci* may need to be considered.[71,72] Despite high treatment failures of up to 60% and meta-analyses comparing linezolid to daptomycin, the optimal treatment for VRE BSI has not been established.[73] These data suggest that without susceptibility data, empiric daptomycin therapy for VRE infections should be used with caution, particularly in patients who have received prolonged therapy with vancomycin.

Antimicrobial therapy for MDR pathogens—carbapenem-resistant *Enterobacteriaceae* and *Klebsiella*

Widespread use of carbapenems has contributed to the development of carbapenem-resistant bacteria, with an increasing number of MDR gram negative isolates being reported to the NHSN.[74] Critically ill HCT patients with a prior history of infection or colonization with MDR CRE require tailored empirical antimicrobial regimen at the time of initial fever and blood culture acquisition. Despite limited effective antibiotic options, targeted antimicrobial therapy for proven MDR CRE infections should include at least two active agents. Antimicrobial therapies used for MDR CRE include polymyxin, colistin, aminoglycosides (if susceptible), tigecycline, high-dose continuous carbapenem infusions, ceftolozane/tazobactam and ceftazidime/avibactam.[75] Ceftolozane/tazobactam and ceftazidime/avibactam are novel β-lactam/β-lactamase combination antibiotics, whose antimicrobial spectrum of activity includes MDR gram negative bacteria, including *P. aeruginosa*. Ceftazidime/avibactam also has activity against *K. pneumoniae* carbapenemases. Clinical trials demonstrated efficacy of both agents when used in the treatment of complicated urinary tract infections and complicated intra-abdominal infections when used with metronidazole. However, neither agent is currently indicated for the treatment of BSI CRE; and no clinical trials have been published using these two agents for MDR CRE infections in immunocompromised patients.[76] In patients with CRK, combination therapy with colistin/polymyxin B, tigecycline and gentamicin with the addition of meropenem is recommended.[68] In summary, keys to successful management of MDR pathogens are correct identification of bacteria, early initiation of effective therapy and stringent infection control measures to prevent transmission to other patients.[68]

Antimicrobial lock therapy

Intraluminal colonization and biofilm formation allow pathogens to evade immune clearance and attenuate antimicrobial efficacy. Antibiotic locks provide a small, but high concentration of an antimicrobial agent active against the CLABSI pathogen that dwells for an extended time in the CVC lumen in an attempt to eradicate both the pathogen and its associated biofilm, thus enabling catheter salvage. The addition of an antibiotic lock to concomitant intravenous antimicrobial therapy is recommended by current IDSA guidelines for uncomplicated CLABSI when catheter salvage is indicated and attempted.[16] However, in a retrospective, case-matched cohort study of CLABSI in pediatric oncology patients, one-third of whom were HCT recipients, no evidence of additional benefit from adjunctive antibiotic lock therapy was demonstrated.[77] In addition, vancomycin locks have been found to increase risk for selecting gram positive bacteria with reduced susceptibility to vancomycin.[78]

Ethanol locks are attractive options for adjunctive therapy for CLABSI given that ethanol readily penetrates biofilm, has thrombolytic and anticoagulant properties, and has activity against both bacteria and fungi without promoting emergence of antimicrobial resistance. However, ethanol locks are generally restricted to patients with silicone-based CVCs based upon concerns for possible mechanical complications when used in polyurethane catheters. Efficacy of ethanol locks has been demonstrated mostly in other populations requiring CVCs (for example, short bowel syndrome patients), as published data on ethanol locks in the HCT population is limited. One small, randomized, prospective trial in adult hematology patients with tunneled CVCs did not show differences in CLABSI rates, comparing heparinized saline with 70% ethanol locks with 2 h dwell times.[79] Review of published data of ethanol locks for both prevention and adjunctive treatment of CLABSI in children demonstrated improvement in CLABSI rates after implementation, but also reported some adverse events in pediatric oncology patients.[80] Additional data are required to assess the efficacy of ethanol locks for standard therapy and prevention of CLABSIs in HCT patients prior to making recommendations regarding its use in these patients.

When to remove/replace a central line

Current guidelines recommend CVC removal when there is an implantable port pocket or tunnel infection and for CLABSI caused by *S. aureus*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, MDR bacteria, VRE, *Candida* spp. and atypical mycobacteria.[16,81] In addition, catheter removal is advised when there is evidence of complicated CLABSI (for example, thrombophlebitis, endocarditis, severe sepsis) and continued BSI despite ⩾72 h of effective antibiotic therapy. For uncomplicated CLABSI involving less virulent pathogens like *Bacillus*, *Micrococcus* or *Propionibacterium* spp., catheters should be removed if CLABSI is proven based on ⩾two blood cultures revealing the same organism. In the aforementioned clinical settings, catheter removal has been associated with reduced infection relapse and metastatic complications. However, in patients who require ongoing, long-term CVC access, catheter removal may not always be feasible and catheter salvage may be required. (Figure 3).

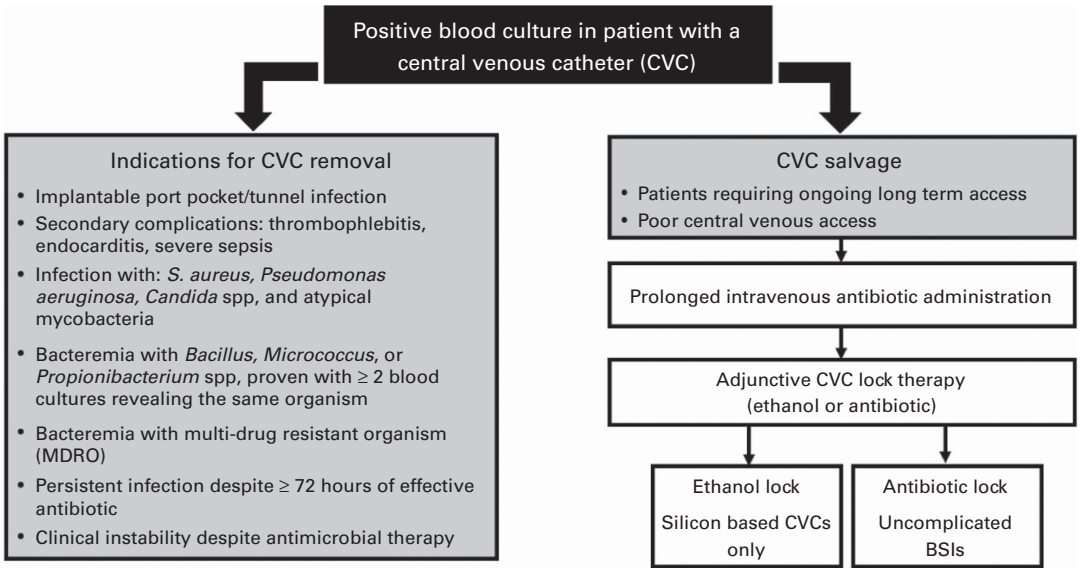

Figure 3. Disposition of the central venous catheter (CVC) following bloodstream infection. Indications for CVC removal and retention and potential use of lock therapy are listed.

Table 3. Recommendations for prevention of central venous cather (CVC)-related infection in HCT recipients

Education, Training and Staffing	● Regular education should be provided for all staff caring for and placing CVCs ● Regular assessment of provider knowledge and adherence to guidelines is advised ● Designate only trained personnel who demonstrate competence for placement and maintenance of CVCs ● Ensure appropriate nursing staff levels
Catheter type, insertion site and placement	● CVCs should be placed by well-trained personnel ● Selection of CVC should be determined by the duration of use and ability of the patient to provide care ● The minimum number of lumens required for patient management is recommended ● CVC insertion in the femoral vein should be avoided, otherwise there is insufficient evidence to recommend one insertion site over another ● Avoid the subclavian site in hemodialysis patients and patients with advanced kidney disease, to avoid subclavian vein stenosis ● Image guided insertion of CVC is recommended ● Prophylactic use of systemic antibiotics is not recommended before CVC insertion ● Promptly remove any CVC that is no longer essential
CVC care	● CVC bundled care including hand hygiene, maximal barrier precautions, chlorhexidine skin antisepsis during insertion and regular assessment of the CVC is recommended

Abbreviation: HCT = hematopoietic cell transplantation. Recommendations for prevention of CVC-related infections, adopted from evidence-based guidelines Healthcare Infection Control Practices Advisory Committee[84] and the American Society of Clinical Oncology.[93]

Empiric antibiotics in febrile patients

After fever develops in HCT recipients, rapid administration of empiric antibiotics has been shown to reduce patient mortality.[82,83] Choice of empirical antimicrobial therapy incorporates patient's clinical manifestation (severity and type of signs and symptoms associated with fever and clinical risk factors for infectious complications), disease severity, and risk factors. Specific knowledge of resistance patterns in the HCT population is crucial as HCT patients tend to harbor more resistant bacteria compared with the general hospital population.[84]

Stoma *et al.*[83] recently showed an increase in 30 day all-cause mortality in patients who received inadequate empirical antibiotics which were defined by: (a) resistance of the isolated microorganisms to the administered antibiotics; (b) empiric antibacterial therapy that was administered >24 h after collection of blood cultures; or (c) a dosing regimen that conflicted with standard dosing recommendations. This finding underscores the importance of knowledge of the local spectrum of pathogens, which is imperative for selecting the appropriate empiric antibacterial regimen.

BLOODSTREAM INFECTION PREVENTION

Catheter care bundles

Catheter care bundles consist of a standard combination of evidence-based interventions that have been shown to be effective in preventing CLABSIs and improving patient outcomes.[81,85] Germane bundle components include performance of hand hygiene, full-barrier precautions including use of sterile technique and chlorhexidine cleansing during insertion, and proper procedures for CVC access, manipulation and dressing changes.

In 2011, the Healthcare Infection Control Practices Advisory Committee composed of members from professional organizations representing various major disciplines of healthcare created the 'Guidelines for the Prevention of Intravascular Cather-Related Infections'.[81] These recommendations included focusing on education of healthcare providers who place and maintain CVCs, utilization of sterile techniques in CVC insertion and maintenance and implementation of standardized bundled strategies to prevent infections.[81] In 2013, the American Society of Clinical Oncology created evidence-based guidelines for CVC care in patients with cancer,[85] incorporating all relevant literature associated with CVC placement and care in patients with cancer. The summary of the recommendations from both initiatives are detailed in Table 3. Standardization of bundle elements coupled with systematic implementation and compliance has been shown to effectively and significantly reduce CLABSI rates across multiple studies involving pediatric oncology and HCT patients in the inpatient setting.[86–90] Best practice bundle implementation with particular focus on maintenance strategies also reduces CLABSI rates in the ambulatory setting.[86,91]

As part of a multicenter quality improvement initiative, 32 pediatric hematology/oncology and HCT centers across the United States implemented a standardized CVC care bundle. Average compliance with the CVC care bundle across the institutions was more than 80% during the study period; and the collaboration demonstrated a 29% reduction in CLABSI rates from 2.85 CLABSI to 2.04 CLABSI/1000 CVC days (RR: 0.71, 95% CI: 0.55–0.92).[92] This multi-institutional collaborative improvement effort succeeded at reducing CLABSI rates through standardized CVC bundle care in immunocompromised patients. In a recent study from MSKCC, rates of hospital-acquired CLABSI in high-risk adult patients including HCT recipients decreased by 34% to 2.3/1000 days after implementing a disinfection cap and resulted in substantial cost savings.[93]

Prophylactic antibiotics

According to recent BMT guidelines, fluoroquinolone prophylaxis should be considered for HCT patients with anticipated neutropenic periods of $\geqslant 7$ days.[94] Antibacterial prophylaxis is generally started at the time of hematopoietic cell infusion and continued until recovery from neutropenia or initiation of empirical antibacterial therapy for fever.[94]

Use of prophylactic antibiotics in neutropenic adult oncology patients has consistently shown efficacy in reducing the incidence of fever and microbiologically-documented bacterial infections, but has not improved OS.[95,96] Furthermore, some reports addressing the utility of prophylactic antibiotics in HCT patients are contradictory. Liu *et al.* showed that levofloxacin prophylaxis did not affect time to BSI development, 6-month mortality and incidence of gram positive and gram negative isolates.[97] In addition, prophylaxis may have increased MDR bacterial strains.[97] Satlin *et al.*[98] reported 27% absolute reduction in BSI and 31% absolute reduction in febrile neutropenia episodes within 30 days after HCT in patients receiving levofloxacin prophylaxis. However, they also demonstrated a non-significant increase in *Clostridium difficile* and fluoroquinolone-resistant *Enterobacteriaceae* infections.[98] Finally, levofloxacin prophylaxis was not associated with decreased BSI rates complicated by severe sepsis or ICU admission.[98]

It is important to note that any benefit for fluoroquinolone prophylaxis could potentially be offset by increased rates of emerging resistant pathogens.[99,100] The proportion of BSIs caused by fluoroquinolone-resistant bacteria has increased (Tables 1 and 2), likely secondary to the use of fluoroquinolone prophylaxis. Epidemiological data should be reviewed closely prior to implementing fluoroquinolone prophylaxis and if applied, centers should actively monitor for emergence of resistant organisms.[94]

Prophylactic antibiotics after Day 100

Antibiotic prophylaxis is recommended for preventing *S. pneumoniae* infections among allo-HCT recipients receiving immunosuppressive therapy directed against chronic GvHD. Antibiotic selection should be predicated on the local resistance patterns, but usually involves oral penicillin or first-generation cephalosporin use in penicillin-allergic patients.[94]

Ig prophylaxis

Routine prophylaxis with IV Ig is not recommended given no demonstrable benefit for reducing incidence in bacterial, fungal and viral infections.[101] However, IVIG is typically used in adult and pediatric HCT patients with hypogammaglobinemia (serum IgG < 400 mg/dL) and recurrent bacterial infections.[101]

Vaccination

Invasive *Streptococcus pneumoniae* is a significant complication following HCT and is associated with 20% mortality in transplant recipients.[102] Vaccination is an important strategy to prevent *S. pneumoniae* infection after HCT.[94] Pneumovax (PPSV23) is a polysaccharide vaccine representing 23 of the most prevalent serotypes of *Pneumococcus*. Prevnar (PCV13) is a 13-valent conjugate vaccine that is approved for all individuals over 6 weeks of age.[103] Prevnar is more immunogenic than Pneumovax secondary to inducing more durable, T-cell dependent memory responses.[104,105] Unless a patient is severely immunocompromised, Prevnar should be started at 6 months post HCT for a total of three doses, each administered two months apart.[105,106] One dose of Pneumovax should be given 6 to 12 months after the last Prevnar dose.[106,107] The recent 10-year decline in invasive pneumococcal disease among patients with hematologic malignancies in the US coincides with incorporation of Prevnar in universal childhood immunization.[108]

Interventions to prevent bacteremia from oral bacteria

Mucositis has a profound negative effect on nutritional status, oral intake of food and medications, and quality of life in HCT patients.[109] Chemotherapy and irradiation not only damage the gastrointestinal tract, allowing bacterial constituents to enter the systemic circulation (that is, bacterial transmigration and subsequent bacteremia), but also activate aGvHD, an inflammatory cytokine-associated alloreactivity that causes further insult to gastrointestinal epithelium.[110] Surprisingly, mucositis severity does not correlate with incidence of BSI. For example, prospective studies evaluating interventions that are effective in reducing mucositis like keratinocyte growth factor[111] and cryotherapy[112] have not shown a beneficial effect in reducing BSI rates.

Gingivitis is closely associated with dental plaque on the teeth and gingival tissues[113] and is an important contributor to mucosal toxicity seen after HCT.[114] One cubic millimeter (mm^3) of dental plaque contains about 100 million bacteria that serve as a persistent reservoir for potential bacteremia.[115] Dental plaque is a well-documented cause of gingivitis[116] and is significantly associated with bacteremia in healthy subjects[117] and HCT patients.[118] Interestingly, a meta-analysis confirms that plaque accumulation and gingival inflammation score significantly to increase BSI risk following tooth brushing in healthy subjects.[119] However, how dental plaque contributes to mucositis in HCT patients remains unstudied.

Oral rinses have been used to enhance oral hygiene and to decrease oral mucositis in HCT patients. Bland rinses such as 0.9% saline or sodium bicarbonate/saline as well as analgesics, mucosal coating agents and topical anesthetic solutions like

viscous lidocaine and diphenhydramine solutions have been studied.[120,121] Chlorhexidine has also been widely used as a bacteriostatic/cidal agent to reduce bacterial colony-forming units (CFUs), but has not been shown to reduce BSI from oral flora.[122,123] Furthermore, chlorhexidine has a bitter taste, and is unpalatable to patients, particularly children, reducing compliance.

A comprehensive dental evaluation and plan for oral care peri- and post-HCT are important in preventing odontogenic infection and mucositis throughout the HCT period.[124] A definitive dental treatment plan that includes oral hygiene reduces the incidence and severity of mucositis and may prevent infections and decrease infection-related mortality.[121,125–127] In a small prospective evaluation of periodontal disease in adult HCT recipients, periodontal status correlated with frequency of bacteremia, particularly due to viridans streptococci and *Staphylococcus epidermidis*.[118] Recent oral care guidelines recommend brushing with an ultra-soft toothbrush two to three times daily and using non-flavored chlorhexidine gluconate 0.12–0.2% solution as an oral antiseptic twice daily when oral hygiene is suboptimal after HCT.[128] Adjunctive therapies with some supporting evidence include the use of KGF, patient-controlled analgesia and low-level laser therapy for mucositis prevention in patients receiving high-dose chemotherapy or irradiation for HCT.[127]

Skin decontamination

Use of chlorhexidine washes in the intensive care unit setting and in patients undergoing cardiac surgery prevents CLABSI and surgical site infections, respectively.[129,130] A multicenter, cluster-randomized, non-blinded crossover trial that included patients in HCT units found that daily bathing with chlorhexidine-impregnated washcloths significantly reduced acquisition of MDR organisms and development of hospital-acquired CLABSIs, particularly those caused by gram positive bacteria and fungi.[131] Current clinical trials are evaluating whether receipt of daily chlorohexidine topical skin wipes for 90 days decreases CLABSI rates in children after allo-HCT.

Maintaining the microbiome

The human body is host to microbial communities (microbiome)[132] that influence human physiology through processes related to development, nutrition, immunity and resistance to pathogens.[133] Taxonomic profiling the GI microbiome reveals large diversity in obligate anaerobic bacteria in healthy individuals.[134] The host's immune system keeps the gut microbiota stable and prevents overgrowth of pathogenic species by producing antimicrobial peptides. The gut microbiota also influences immune responses by triggering differentiation of T_H17, regulatory and memory T cells and maturation in NKT cells.[135] Disturbances in the microbiome (dysbiosis) are linked to intestinal inflammation and increased prevalence of potentially harmful facultative anaerobic bacteria.[136]

During HCT, patients experience dramatic alterations in the intestinal microbiota with marked decreases in overall bacterial diversity, increasing risk for aGvHD and BSI.[137] In many instances, a single bacterial taxon can predominate and replace a previously rich and diverse milieu of organisms.[137] Low microbiome diversity and dysbiosis have independently been associated with BSI and transplant-related mortality.[138] That is, conditioning regimen insult to the GI tract in combination with antibiotic use prior to neutrophil engraftment decreases microbiome diversity and increases subsequent risk for bacteremia from MBI-LCBI organisms.[77,137,139] Loss of microbiome diversity leads to domination of MBI-LCBI pathogens within the GI tract and subsequent systemic infection with the corresponding blood pathogen.[137] This observation corroborates that neutropenia-associated BSIs arise largely from a gastrointestinal source via a transformation in the gut microbiome resulting in loss of colonization resistance and subsequent overgrowth by a single bacterial species that then translocates through damaged epithelium into the bloodstream.

Several lines of evidence confirm that antibiotic administration can result in gut microbiota dysbiosis or aberrant alteration in the GI commensal bacteria.[132,140] Broad-spectrum antibiotics can influence bacterial species in the gut community, causing rapid and significant reductions in taxonomic richness, diversity and evenness.[140] In addition, antibiotics alter the composition of taxa, affecting gene expression and protein activity as well as overall metabolism of the gut.[141] In a retrospective analysis of 857 allo-HCT recipients, Shono *et al.* found that empiric fever and neutropenia (F&N) therapy using imipenem-cilastatin and piperacillin–tazobactam antibiotics was associated with increased GvHD-related mortality at 5 years (21.5% for imipenem-cilastatin–treated patients vs 13.1% for untreated patients, $P = 0.025$; 19.8% for piperacillin–tazobactam–treated patients vs 11.9% for untreated patients, $P = 0.007$).[31] However, two other antibiotics also used to treat F&N, aztreonam and cefepime, were not associated with GvHD-related mortality ($P = 0.78$ and $P = 0.98$, respectively). Analysis of stool specimens from allo-HCT recipients showed that piperacillin–tazobactam administration was associated with perturbations in gut microbial composition.[31] In addition, when compared to a contemporaneous hospital cohort, HCT recipients developed more resistance against commonly isolated bacterial organisms. These findings have important clinical implications regarding use and selection of both prophylactic and empiric antibiotic regimens.

Emerging data parsing MBI-LCBI from CLABSI highlight that almost half of BSI in pediatric HCT are indeed MBI-LCBIs and are associated with a significant increased risk of non-relapse mortality.[5] This distinction may contribute to further reduction in true CLABSI rates in this population[15,142–144] and may provide an opportunity for identification of risk factors specific to MBI-LCBI in HCT patients, enabling more targeted prevention strategies, distinct from current CLABSI prevention strategies.

Table 4. Outcomes in pediatric HCT patients developing BSI

	MBI-LCBI (N = *80*)	*CLABSI* (n = *68*)	*Secondary BSI* (n = *22*)
Septic shock within 24 h of BSI	37 (46%)	34 (50%)	10 (45%)
Central line removed Within 7 days	31 (39%)	30 (44%)	10 (45%)
Death within 10 days	7 (9%)	7 (10%)	3 (14%)
Transfer to ICU within 48 h of BSI	17 of 73 (23%)	14 of 59 (24%)	2 of 13 (15%)
Patients in ICU at time of infection	7	9	9
Median ICU days in patients transferred from floor (IQR)	6 (3–10)	5 (3–15)	32 (18–46)

Abbreviations: BSI = bloodstream infection; CLABSI = central line-associated bloodstream infection; ICU = intensive care unit; IQR = interquartile range; MBI-LCBI = mucosal barrier injury laboratory-confirmed bloodstream infection. Adapted from Dandoy *et al.*[6] Retrospective review of 374 consecutive pediatric hematopoietic cell transplants, in which 100 patients developed at least one infection (170 infections analyzed).

OUTCOMES IN TRANSPLANT PATIENTS WHO DEVELOP BLOODSTREAM INFECTIONS

BSI alone is a significant independent predictor of TRM. Poutsiaka *et al.* described increased TRM (HR 1.79, 95% CI 1.18–2.73, $P = 0.007$) after adjusting aGvHD and allo-HCT with both predicting death three months after HCT. In addition, they found that bacteremia with GN rods and VRE were also significantly associated with increased morality.[4] Liu *et al.*[97] confirmed the negative impact of BSI on 6-month survival post HCT and demonstrated that patients who developed BSI had increased length of hospital stay. In a retrospective analysis, Dandoy *et al.*[5] studied outcomes from 170 BSIs diagnosed in 100 (27%) of 374 pediatric patients undergoing HCT. They showed that BSIs were associated with increased morbidity and mortality, leading to significant resource utilization as detailed in Table 4. Specifically, 1-year non-relapse mortality was significantly increased in patients with one (20/58, 34%) and more than one (17/30, 56%) BSI in the first year post-HCT compared with those who did not develop BSI (27/194, 14%; $P = < 0.0001$). In addition, increased risk of one-year non-relapse mortality was noted in patients with at least one MBI-LCBI (OR 1.94, $P = 0.018$) and at least one secondary BSI (OR 2.87, $P = 0.0023$), but not in patients with CLABSI (OR 1.17, $P = 0.68$).[5] Levinson *et al.*[29] showed that in addition to increased non-relapse mortality, patients who developed early BSI during the conditioning regimen and within 10 days after HCT (and prior to engraftment) had a twofold increase risk in developing aGvHD. Taken together, these results demonstrate that BSI, in general, and MBI-LCBI, in particular, not only cause significant harm to HCT patients, increasing their risk for adverse outcomes as well as aGvHD, but also prolong hospitalization and potentially increase significant hospital resource utilization.

HEALTHCARE COSTS ASSOCIATED WITH BLOODSTREAM INFECTIONS

A published meta-analysis of healthcare associated infections (HAIs) revealed that CLABSIs are associated with the highest cost of any HAI, averaging $45 814 per event.[145] A recent evaluation in pediatric HCT and oncology patients with ambulatory BSIs demonstrated a $40 852 median hospital charge with room, pharmacy and procedure charges accounting for more than 70% of total charges.[146] Finally, Wilson *et al.*[6] utilized propensity scoring with matched cases while controlling for other covariates and defined the attributable cost of CLABSI to approximate $70 000 per BSI event in pediatric hematology oncology patients. In addition, patients with CLABSI had length of stay that were 21.2 days longer than those without CLABSI ($P < 0.0001$).[6]

SUMMARY

BSIs are a leading cause of transplant-related morbidity and mortality in allo-HCT recipients. In particular, emergence of antimicrobial-resistant bacterial pathogens is daunting, as antimicrobial agents with efficacy to eradicate such infections are limited. Therefore, judicious use of antimicrobial agents and optimal prevention strategies are needed to reduce CLABSI-related infection burden in allo-HCT patients. Additional research efforts should focus on defining the etiology and resistance patterns of bacterial pathogens responsible for BSI given their rising incidence and detrimental impact on the allo-HCT patient outcomes.

CONFLICT OF INTEREST

JJA: Advisory Board, Shire Pharmaceuticals (2016). The remaining authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

CED: Primary manuscript writing and review; MIA and GAP: Manuscript writing and review; JJA: Manuscript writing, review and overall concept design.

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