Central venous line bloodstream infections during hematopoietic stem cell transplantation for primary immunodeficiency disorders

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ABSTRACT

Background: A central venous line (CVL) is a large-pore intravascular catheter placed into a large vein and dedicated for infusion, withdrawal of blood, and administration of chemotherapy, as in hematopoietic stem cell transplantation (HSCT) patients. One of the serious complications of CVL is central-line–associated bloodstream infection (CLABSI). We described CLABSI incidence in primary immunodeficiency disorder (PID) patients who underwent HSCT at Queen Rania Children's Hospital in a retrospective analysis.

Methods: A retrospective analysis of 58 PID patients who were admitted for HSCT from 2014 through 2019 at the Bone Marrow Transplant Unit (BMT); positive CLABSI isolates were analysed.

Results: Out of 58 total patients who underwent HSCT for PID over the study period, 28 (48.3%) were positive for CLABSI. Among those CLABSI-positive patients, 52 CLABSI episodes were isolated over the study period, which were categorized into gram-positive bacteria in 28 episodes (58%), gram-negative bacteria in 19 (36.5%) episodes, and fungi in five (9.5%) episodes. The most frequently isolated pathogens were *Staphylococcus epidermises*, *Klebsiella* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), and *Enterococci* spp., in 17%, 11.5%, 7.7, and 7.7%, respectively.

Conclusions: Primary immunodeficiency disorder (PID) patients who underwent HSCT had a different order of CLABSI causative pathogens from what had been reported in paediatric oncological disease and HSCT patients.

Keywords: Bloodstream infections, hematopoietic stem cell transplantation, central venous line

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Introduction

A central venous line (CVL) is a large-pore intravascular catheter placed into a large vein like the internal jugular or subclavian vein that terminates close to the heart. A CVL is dedicated for infusion, withdrawal of blood, and administration of chemotherapy, as in hematopoietic stem cell transplantation (HSCT) patients, who require a permanent tunnelled CVL for long-term use (1).

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One of the serious complications of CVL is central-line–associated bloodstream infection (CLABSI), which carries a significant financial burden and increases mortality in HSCT patients [2]. The National Healthcare Surveillance Network (NHSN), in partnership with the Centers for Disease Control (CDC), has established a definition for CLABSI: a laboratory-confirmed bloodstream infection where an eligible bloodstream infection (BSI) organism is identified and an eligible central line is present on the date of event of the laboratory-confirmed bloodstream infection (LCBI) or the day before [1,2].
CLABSI's reported incidence in children varies between 0.46 and 26.5 infections/1,000 catheter-days. The source of infection is either extraluminal contamination (microorganisms migrating from the insertion site along the outside of the catheter) or intraluminal contamination (pathogens migrating from the catheter hub through the lumen of the catheter) with subsequent colonization and biofilm formation [3].
Primary immunodeficiency disorders (PID) are a heterogeneous group of disorders resulting from mutations in genes involved in immune host defence and immunoregulation. The latest report of the International Union of Immunological Societies (IUIS) coined the term "inborn errors of immunity", which encompasses various PID clinical phenotypes other than infection susceptibility, such as autoimmunity, lymphoproliferation, inflammatory manifestations, atopy, immune dysregulation, and malignancy. HSCT represents a rational therapeutic approach for many inborn errors of immunity disorders [4].
Although there are many studies that have reported CLABSI in children who underwent HSCT, the reporting on PID is still scant, and to the best of our knowledge, no single paper has been published describing CLABSI in PID patients who have undergone HSCT. However, this is a retrospective analysis of CLABSI in paediatric patients who underwent HSCT for a PID at a single centre.

PATIENTS AND METHODS

This was a retrospective cohort study of children who underwent allogeneic HSCT for a PID diagnosis at the Queen Rania Children's Hospital (QRCH) Immunology Unit from January 2014 to September 2019. All patients had a double lumen HICKMAN® CVL inserted before admission to the Bone Marrow Transplant (BMT) Unit. All catheters were inserted at the Interventional Radiology Unit at King Hussein Medical Centre under sedation. Infection control measures in CVL-related infections at the BMT Unit were applied per the QRCH infection control policy and surveillance. Data were gathered and tabulated in a Microsoft Excel spreadsheet, including patients' age, gender, HSCT indication, conditioning regimen, neutropenia duration, total BMT stay in days, CLABSI episodes, and isolated pathogens. The study was approved by the Royal Medical Services Ethical Committee, no (10/2019).
We had applied NHSN definitions for CLABSI (LCBI) but not Mucosal Barrier Injury LCBI (MB-LCBI) because it was a retrospective analysis, not all data of MBL-LCBI were retrieved.

RESULTS

Out of 58 total patients who underwent HSCT for PID over the study period, 28 (48.3%) were positive for CLABSI. Of those, 11 (39.3%) were males, while 17 (60.7%) were females. The age ranged from 1 to 60 months, with a mean of 26.4 months. All patients underwent allogeneic HSCT

for a PID diagnosis (Table I); 16 (57.1%) had a matched related donor, either a sibling or a parent, while 12 (42.9%) had a haploidentical transplant from a parent. Two-thirds of the patients (67.9%) got a myeloablative conditioning regimen using fludarabine, busulfan, and anti-thymocytes globulin (ATG) as serotherapy; the rest (32.1%) had HSCT without conditioning. The most common diagnosis was severe combined immunodeficiency (SCID). The mean neutropenic phase was 25.5 days; all non-conditioned patients did not have neutropenia during transplant, and the BMT stay ranged from 17 to 96 days. The overall survival rate was 67.9%; all mortalities were transplant-related.

Table I: Patients' characteristics

HSCT for PIDs N=28	No	Percent
Male	11	39.3
Female	17	60.7
Age in months: range, mean	1–60	26.4
Allogeneic HSCTs:		
Matched related donor	16	57.1
Mismatched related donor	12	42.9
Non-conditioned	9	32.1
Fludarabine/Busulfan/ATG conditioning	19	67.9
Neutropenia duration in days: range, mean	0–60	25.5
BMT stay in days: range, mean	17–96	51.5
Diagnosis:		
SCID	9	32.1
FHLH	4	14.3
CD-40 L deficiency	3	10.7
MHC-II deficiency	3	10.7
Griscelli Syndrome-II	2	7.1
LAD-1	2	7.1
CGD	1	3.6
IPEX	1	3.6
WAS	1	3.6
Osteopetrosis	1	3.6
SCN	1	3.6
TOTAL	28	100.0
Alive	19	67.9
Dead	9	32.1

Abbreviations
SCID: Severe combined immunodeficiency, FHLH: Familial hemophagocytic lymphohistiocytosis, CD-40 L: CD 40 ligand deficiency, MHC-II**:** Class II major histocompatibility complex molecules deficiency, LAD-1: Leukocyte adhesion defect type 1
CGD: Chronic granulomatous disease, IPEX: Immunodysregulation, Polyendocrinopathy, Enteropathy X-linked Syndrome, WAS: Wiskott Aldrich syndrome, SCN: Severe congenital neutropenia.

Fifty-two CLABSI episodes were isolated in 28 patients over the study period (Table II).
We categorized isolated pathogens into three categories: (1) gram-positive bacteria in 28 episodes (58%), of which the most common microorganism was *Staphylococcus epidermidis* in 17 episodes;

(2) gram-negative bacteria in 19 episodes (36.5%), of which the most common microorganism was *Klebsiella* spp. in 5 episodes; and (3) fungi in 5 episodes (9.5%), all of which were *Candida*, but with different species.

We reviewed the number of episodes in each patient (Table III) and found that 14 patients (50%) showed a single episode of CLABSI (monomicrobial), while the other half had more than one CLABSI episode (polymicrobial); eight patients had two episodes, and six patients had three or more episodes. The duration of neutropenia and BMT unit stay were proportionally correlated to the number of episodes; the patients who had the longest neutropenic phase and BMT stay had more frequent CLABSI episodes, as shown in Table III.

Table II

Pathogen group (N) (%)	Microorganism	N	%
Gram-positive (28) (54%)	*Staphylococcus epidermidis*	17	32.7
	MRSA	4	7.7
	Streptococcus alpha hemolyticus	3	5.8
	Streptococcus viridans	1	1.9
	Streptococcus faecium	1	1.9
	Enterococci spp.	2	3.8
Gram-negative (19) (36.5%)	*Klebsiella* spp.	5	9.6
	Escherichia coli	4	7.7
	Pseudomonas aeruginosa	3	5.8
	Stenotrophomonas maltophilia	2	3.8
	Maroxella catarrhalis	1	1.9
	Acinetobacter baumanni	1	1.9
	Acinetobacter calcoaceticus	1	1.9
	Acinetobacter hemolyticus	1	1.9
	Klebsiella pneumoniae	1	1.9
Fungi (5) (9.5%)	*Candida albicans*	3	5.8
	Candida parapsolosis	1	1.9
	Candida guilliermondii	1	1.9
Total		52	100.0

Table III

CLABSI Episodes	No. of Patients	Mean Neutropenia	Mean BMT stay
1	14	16.2	39.4
2	8	32.8	59.9
≥3	6	35.2	70.5

DISCUSSION

Children undergoing HSCT are at high risk for bloodstream infections (BSI) due to several risk factors: the preparative conditioning regimens, underlying disease, graft-versus-host disease (GVHD), and the requirement of total parenteral nutrition in conjunction with having a central venous line (CVL) in place [5]. Many reports have been published studying CLABSI in paediatric HSCT, but to the best of our knowledge, there was no single report that described CLABSI in PID paediatric patients who underwent HSCT.

The BMT Unit at Queen Rania Children's Hospital is shared between haemato-oncology and immunology services. We did a retrospective analysis of CLABSI in PID patients over 4 years, and we found that out of 58 patients who underwent HSCT for PID, 28 (48.3%) had CLABSI; this incidence is comparable to that from the Center for International Blood and Marrow Transplant Research (CIBMTR) 2015 report, which showed that BSIs occurred in approximately 50% of children in the first 100 days of HSCT for cancer patients [5]. However, our cohort showed CLABSI during the BMT unit stay, so we expected the incidence of CLABSI in our cohort would be higher. Poutsiaka *et al.* reviewed BSI in HSCT and its mortality in paediatrics and adults; BSI incidence was observed to occur in 13–60% of HSCT recipients. The differences in these studies' findings are likely due to factors such as different study designs, study populations, conditioning regimens, and prophylactic antibiotic protocols [6].

A total of 52 CLABSI episodes were isolated from 28 patients over the study period, which were categorized into gram-positive bacteria in 28 episodes (58%), gram-negative bacteria in 19 episodes (36.5%), and fungi in five episodes (9.5%). The most frequently isolated pathogens were *Staphylococcus epidermidis, Klebsiella* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), and *Enterococci* spp., in 17%, 11.5%, 7.7, and 7.7% of cases, respectively. The National Healthcare Safety Network (NHSN) currently receives reports of CLABSI from more than 4,000 acute care hospitals across the United States; the standardized infection ratios (SIRs) 2015 report showed the top five ranked CLABSI pathogens for adult and paediatric patients in acute care and critical access hospitals were coagulase-negative *Staphylococci* (12.9%), *Staphylococcus aureus* (12.4%), *Klebsiella pneumoniae/oxytoca* (8.7%), *Enterococcus faecalis* (7.5%), and *Escherichia coli* (7.5%) [7]. Our cohort showed higher incidence of coagulase-negative staphylococcus (*Staphylococcus epidermidis),* and all isolated *Staphylococcus aureus* was methicillin-resistant.

Dandoy CE *et al.* conducted a multicentre retrospective analysis for patients who developed a BSI in centres involved in the Childhood Cancer and Blood Disorder Network within the Children's Hospital Association; in their study, 1,075 BSIs were isolated, of which 67% were CLABSI; the most frequent pathogens were *Streptococcus viridans* (16%), coagulase-negative *Staphylococcus* spp. (14%), *Escherichia coli* (8%), *Klebsiella pneumonia* (7%), and vancomycin-susceptible *Enterococcus faecalis* (5%), whereas MRSA was isolated only in 2% of cases [8]. One explanation for the higher presence of MRSA in our cohort could be pretransplant long-term use of antibiotics for PID patients, either as a prophylaxis or as an empirical treatment for frequent infections, however other causes need to be addressed like interventional radiology unit contamination rate and pretransplantation colonization of the patients. A report from the Paediatric Stem Cell Transplantation Unit at the Children's Cancer Hospital in Cairo, Egypt, compared BSIs pre- and post-engraftment in paediatric allogeneic and autologous hematopoietic stem cell transplantations for haemato-oncological disorders; the most frequent microorganisms in a total of 141 isolates were coagulase-negative

Staphylococcus (36.87%, which is comparable to our cohort), *Escherichia coli* (17.73%, which is much higher than we reported), *Enterococcus* spp. (9.92%, slightly higher than our cohort), and *Klebsiella pneumoniae* (6.38%; we reported *Klebsiella pneumoniae* only in 1.9% of case, and *Klebsiella* spp. in 11.5%) (9). One of the important factors that could explain the variable epidemiological data of CLABSI at different institutions is the NHSN subclassification of CLABSI adopted in 2015, which defined a new category of infection, termed "mucosal barrier injury laboratory-confirmed bloodstream infection" (MBI-LCBI) (8). See *et al*. conducted a multicentre field test study to assess challenges in the implementation of the new NHSN surveillance definition of MBI-LCBI; 38 acute care hospitals field-tested MBI-LCBI at 193 oncology and bone marrow transplant inpatient locations; out of 228 CLABSI cases, 103 met the MBI-LCBI definition, where the top ranked microorganisms were *Enterococcus faecium* (16.0%), *Escherichia coli* (14.9%), coagulase-negative *Staphylococci* (12.6%), *Klebsiella* spp. (7.4%), and *Streptococci viridans* (7.4%) (10). The authors concluded that the implementation of the new CLABSI classification would be an important step toward ensuring the reliability and clinical relevance of CLABSI surveillance data and prevention strategies. One of our cohort limitations was inability to implement the MBI-LCBI definition as a CLABSI reclassification because it was a retrospective data in which not all MBI-LCBI had been documented.

All fungal infections in our cohort were *Candida spp.* (9.5%), this percent is comparable to many reports (6,12), other reports showed changes in the epidemiology of candidiasis in HSCT patients in terms of reduced *Candida* albicans infection and higher *Aspergillus species* incidence, as a result of using prophylactic antifungal agents during HSCT (13).

One-half of the patients had more than one CLABSI episode (polymicrobial), and the duration of neutropenia and BMT unit stay were proportionally correlated to the number of episodes; the patients who had the longest neutropenic phase and BMT unit stay had more frequent CLABSI episodes. Grossmann *et al.* retrospectively reviewed the records of 463 consecutive cases of patients who underwent HSCT at Cincinnati Children's Hospital Medical Center, finding 108 BSIs diagnosed in the 23 patients who showed three or more BSI episodes; the authors found that graft versus host disease and transplant-associated thrombotic microangiopathy had been implicated as predisposing factors to the development of polymicrobial BSI (11). However, we did not study the association of polymicrobial CLABSI and transplant-related mortality, and this is another study limitation.

CONCLUSION

Primary immunodeficiency disorder (PID) patients who underwent HSCT had a different order of CLABSI-causative pathogens from what was previously reported in paediatric oncological patients who underwent HSCT. This category of patients' needs further research, as PID patients have different pretransplant risk factors for CLABSI than other paediatric patients. Our study was limited by its nature as a retrospective analysis and its small sample size; in addition, the MBI-LCBI definition was not implemented.

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