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Original Article

Central-line–associated bloodstream infections in a pediatric oncology and hematology hospital at home program

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Abstract

Objective: Central-line–associated bloodstream infections (CLABSIs) are associated with significant morbidity among pediatric oncology-hematology patients, and risk factors remain largely unknown in the setting of hospital at home (HAH). Children in HAH receive intensive treatment (eg, chemotherapy and parenteral nutrition), with frequent central-line handling; thus, they may be at higher risk for CLABSI.

Methods: We conducted a monocentric retrospective study of patients with a central line included in our HAH program from January 1 to December 31, 2016. HAH patient characteristics for children developing CLABSIs were compared to those who did not, based on blood cultures positive for infection and clinical data of all patients included.

Results: Overall, 492 HAH stays were analyzed, with 144 patients. The overall CLABSI rate in these patients was 2.6 per 1,000 central-line days. Children who developed CLABSIs were younger (median age, 2.5 vs 8.8 years; $P < .001$), suffered more from hematological pathologies (malignant or nonmalignant, 75% vs 52%; $P = .02$), and had more frequently undergone hematopoietic stem-cell transplantation (30.8% vs 6.5%; $P = .01$). In addition, these patients often had a tunneled externalized catheter as the central line and were more frequently given parenteral nutrition at home (46% vs 8%; $P < .001$).

Conclusions: CLABSI rates for children in HAH were more similar to those of inpatients than to rates previously reported for ambulatory patients. The factors associated with infection identified herein should be further validated in multicentric studies and considered to improve HAH practices, parallel to prevention measures used in the inpatient setting.

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Central-line–associated bloodstream infections (CLABSIs) are a major health burden within the pediatric oncology and hematology population, with CLABSI rates of 0.65 and 2.2 per 1,000 central-line days for ambulatory patients and inpatients, respectively.[1,2] Prevention bundles, as a systematic prevention policy or as a response to an infection outbreak, have led to significant improvements in patient management, reducing CLABSI rate within the inpatient pediatric oncology and hematology population.[3]

In our institution, inpatients are cared for in either conventional units or protected units if they undergo hematopoietic stem cell transplant (HSCT, allogenic and autologous), intensive chemotherapy for acute myeloid leukemia or for refractory or relapsing acute lymphoblastic leukemia. In 2006, we launched a dedicated hospital-at-home (HAH) program covering the entire Auvergne-Rhone-Alpes region (recognized as an independent hospitalization department in 2009), which allowed the administration of chemotherapy at home.[4] The development of individual HAH programs follows families' wishes for fewer hospital visits,[5] and HAH has been shown to improve both physical and mental health for patients and their caregivers.[6]

Our HAH patients receive substantial care from a team of home healthcare nurses, the number and training of whom vary widely from those of inpatients. The regional general nurses, who do not have specialized experience in pediatric oncology and hematology, are registered by our institution. They are given specific training by our coordinating team of pediatricians to deal with more complex situations, including chemotherapy, palliative care, or specific care, working in close collaboration with home healthcare services.[7] In our HAH program, central lines are managed only by healthcare professionals; parents do not access their child's line.

Given the level of care of patients in our HAH programs, with intensive chemotherapy courses causing a greater immunosuppression and frequent central line handling, we sought to determine whether they were at a greater risk of developing CLABSI compared to inpatients in our institution. We conducted a monocentric retrospective study based on medical files describing CLABSIs occurring during HAH in terms of infection rates,

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microbiology, and clinical consequences (eg, treatment modifications) to obtain precise knowledge of CLABSI rates and feedback on the efficacy of our HAH practice.

Methods

Design

We conducted a retrospective monocentric study based on samples and data collected by our pediatric, oncology-hematology, French referral center between January 1 and December the 31, 2016. Yearly, our institution cares for 250 new pediatric patients and performs, on average, 50 HSCTs. Patients displaying fever are systematically admitted and hospitalized within 24 hours, providing us with large archives of blood samples and blood cultures. In accordance with current legislations, and given the retrospective nature of our study, no approval from an institutional review board for ethics was required. Nevertheless, data collection was conducted according to the MR004 reference methodology of the French data protection agency ("Commission Nationale de l'Informatique et des Libertés"). This study was registered with the National Commission for Information and Civil Liberties (CNIL). The data were anonymized, and publication of the results should not result in the patients being identifiable.

Data collection and definitions

Over the 12-month study period, our bacteriology laboratory provided us with every positive blood culture recorded. For each positive bacteremia case, we verified the situation of patients at the onset of infection: inpatient (hospitalized within the institution), HAH, or outpatient (ambulatory care not requiring hospitalization). We then extracted similar data from our files for each HAH stay as a continuous period with daily care, regardless of duration: age, sex, oncologic diagnosis, catheter type, number of days of the stay, treatment given through the central line, use of parenteral nutrition, absolute neutrophil count, treatment, catheter salvage or removal, clinical outcome. A central-line day was defined as 1 day spent in hospitalization (HAH or conventional) for 1 patient. Following the CDC guidelines,[8] we defined an HAH-related CLABSI as a febrile episode with a positive blood culture for a pathogenic organism without evidence of another infectious source for patients with central-line manipulation in HAH following 48 hours. If the patient had been admitted at the hospital (conventional hospitalization or daycare) within 48 hours of central-line manipulation, the bacteremia was not considered an HAH-related CLABSI. Infections with common skin contaminant, such as coagulase-negative staphylococci (CONS), were considered only when 2 or more blood cultures drawn on separate occasions were positive. Aplasia was defined as an absolute count of granulocytes <500 cells per mm^3. From these data, we were able to calculate the rates of CLABSI per 1,000 central-line days in HAH patients and inpatients.

Statistical analyses

Data analysis was performed using R software for Windows, version 3.1.0. i386 (R Foundation for Statistical Computing, Vienna, Austria). Patients were separated according to their status as CLABSI or non-CLABSI. Qualitative data were presented in terms of associated frequencies and percentages, and quantitative data were described by median and interquartile range (IQR). We used the Pearson χ^2 test (or Fisher exact test when needed) for qualitative data comparison. For quantitative data, we used the Mann-Whitney test for 2-group comparisons or the Kruskal-Wallis test for multiple-group comparisons. To investigate the interaction between factors associated with CLASBI, we performed a multivariate analysis using a regression model. We included in the model every parameter significantly associated with CLABSI in the univariate analysis. Statistical significance was defined as $P < .05$.

Results

In 2016, 144 patients were included in our HAH program, with 4,988 cumulative central-line days (Table 1). In total, 492 HAH stays were recorded, with a mean duration of 5 days. In comparison, conventional and protected units accounted for >11,000 days of hospitalization and 3,300 day visits in 2016.

General characteristics of HAH patients

HAH stays ranged from 1 day (repeated, mostly weekly administration of chemotherapy) to 156 days, with 194 (39%) stays lasting >1 week. The median age was 7.1 years and the male-to-female sex ratio was 0.58. Most patients were treated for leukemia (n = 64, 44%), followed by sarcoma (n = 31, 22%), and brain tumor (n = 18, 13%). Also, 4 patients (3%) suffered from nonmalignant hemopathies (primary immune deficiency). Among the 492 HAH stays, 35 (7.1%) were patients with an HSCT; 29 were patients with malignant hemopathies and 6 were patients with nonmalignant hemopathies. Each patient had a central-venous access, primarily tunnelled external catheter (TEC; n = 69, 48%) and totally internalized catheters (ie, ports; n = 59, 41%). Also, 40% of HAH stays included intravenous (IV) chemotherapy, half of which was myelosuppressive (20% of stays). During a total of 1,340 (27%) central-line days, children were aplastic. Parenteral nutrition was part of the treatment in 46 (10%) stays, either as continuous infusion over 24 hours or overnight for 12 hours. Moreover, 26% of central-line days spent in HAH were for patients in palliative care, which corresponded to 22 patients (15%). Palliative-care patients had longer stays: median duration of 12 days (IQR, 5–28) versus 5 (IQR, 2–10) for nonpalliative patients ($P < .001$) (Table 1).

Characteristics of HAH patient malignancies

Significant differences were observed between patients with different types of malignancies. Age distribution was significantly different between groups: patients with nonmalignant hemopathies were younger than those with malignant hemopathies or solid cancers ($P = .026$), and those with malignant hemopathies tended to be younger than children with solid cancers ($P = .059$). The latter 2 groups had comparable rates of parenteral nutrition days ($P = .65$), in contrast to children with nonmalignant hemopathies who received parenteral nutrition more frequently: 248 days per 1,000 patient days, compared to 104 and 99 for solid cancers and malignant hemopathies, respectively ($P < .001$) (Table 2). Compared to children who did not receive parenteral nutrition, there was no significant difference in the age of patients with parenteral nutrition (median, 4.1 vs 8.8; $P = 0.226$); however, their distribution across age groups differed significantly ($P < .001$) (Supplementary Table SI-1 online). Indeed, parenteral nutrition was more frequent for patients aged <5 years or >18 years, with 163.7 and 204.8 parenteral nutrition days per 1,000 central-line days, respectively, whereas parenteral nutrition was limited for children aged 6–18 years. Following our local protocols, patients with solid tumors mostly had ports (n = 56, 83.6%), in contrast

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Table 1. Comparison Between HAH Patients With or Without Positive Blood Cultures

Variable	Total (N = 144)	Patients With Positive Blood Cultures (n = 12)	Patients Without Positive Blood Culture (n = 132)	*P* Value
No. and duration of stays				
No. of HAH stays	492	13	479	
No. of HAH stays per patient, median (IQR)	2 (1–2)	1 (1–1)	2 (1–4)	
No. of HAH days	4,988	197	4,791	
No. of HAH days per patient, median (IQR)	23 (9–39)	11.5 (5–29)	24 (10–40)	
Age and sex				
Age, median y (IQR)	7.1 (3.8–14.7)	2.5 (1.2–4.3)	8.8 (4.1–14.8)	<.001 (MA, .015)
<6 y, no. (%)	63 (44)	11 (92)	52 (39)	.009
6–10 y, no. (%)	19 (13)	0	19 (14)	
10–18 y, no. (%)	45 (31)	1 (8)	44 (33)	
>18 y, no. (%)	17 (12)	0	17 (13)	
Sex (M/F)	0.58	0.27	0.61	.053
Underlying condition category, no.				
Overall malignant hemopathy	73 (51)	7 (58)	66 (50)	.023 (MA, .493)
Non malignant hemopathy	4 (3)	2 (17)	2 (1.5)	
Overall solid tumor	67 (47)	3 (25)	64 (48.5)	
Underlying condition, no.				
Leukemia	64 (44)	6 (50)	58 (43.9)	.003
Lymphoma	10 (7)	1 (8.3)	9 (6.8)	
Nephroblastoma	3 (2)	0	3 (2.3)	
Neuroblastoma	8 (6)	1 (8.3)	7 (5.3)	
Brain tumor	18 (13)	0	18 (13.6)	
Sarcoma	31 (22)	0	31 (23.5)	
Other solid tumor	6 (4)	2 (16.7)	4 (3.0)	
Primary immune deficiency	4 (3)	2 (16.7)	2 (1.5)	
HSCT stays				
Total	35 (7.1)	4 (30.8)	31 (6.5)	.010 (MA, .354)
Among stays of malignant hemopathy patient	29 (16.9)	2 (25)	27 (16.5)	0.128
Among stays of nonmalignant hemopathy patient	6 (85.7)	2 (100)	4 (80)	
Type of central line				
Ports	59 (41)	0	59 (45)	.003 (MA, .191)
TEC	69 (48)	10 (83)	59 (45)	
PICC	16 (11)	2 (17)	14 (11)	
Characteristics of the home care stay, no.				
Aplasia, line days	1,340 (27)	44 (22)	1,296 (27)	.143
Palliative care, line days	1,277 (26)	49 (25)	1,228 (26)	.811
Chemotherapy at home, stays	197 (40)	4 (31)	193 (40)	.489
Myelosuppressive chemotherapy, stays	101 (20)	3 (23)	98 (20)	.735
Parenteral nutrition, stays	46 (10)	6 (46)	40 (8)	<.001 (MA, <.001)

Note. HAH, hospital at home; M/F, male-to-female ratio; TEC, totally externalized catheter; PICC, peripheral-inserted central catheter; MA, multivariate analysis; HSCT, hematopoietic stem cell transplant. The multivariate regression model included factors with a significant association in univariate analysis.

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Table 2. Age, Parenteral Nutrition, and Catheter Type According to the Type of Malignancy HAD Population

Type of Malignancy	Solid Cancer (67 patients, 2,729 days)			Malignant Hemopathy (73 patients, 2,086 days)			Nonmalignant Hemopathy (4 patients, 173 days)			*P* Value
Age, median (IQR)	10 (4.2–14.9)			6 (3.7–11.8)			0.6 (0.5–4.5)			.026
Cumulative days of parenteral nutrition per 1,000 line days	104			99			248			<.001
Central venous line catheter type, no. (%)	Port	TEC	PICC	Port	TEC	PICC	Port	TEC	PICC	.001
	56 (83.6)	5 (7.5)	6 (9.0)	3 (4.1)	61 (83.6)	9 (12.3)	0	3 (75)	1 (25)	

Note. PICC, peripheral-inserted central catheter; TEC, tunnelled external catheter.

Table 3. Comparison Between HAH Patients and Inpatients

Variable	Hospital At Home	Conventional Department	Protected Department	*P* Value
No. of patients	144			
No. of stays	493	1,817	200	
No. of days	4,988	6,652	4,825	
No. of positive blood cultures per 1,000 central-line days	13 (2.6)	11 (1.65)	16 (3.3)	.194
Bacterium type	Hospital At Home, No. (%)	Hospitalization, No. (%)		
Gram-negative bacilli	6 (46)	10 (37)		.593
Enteric gram-negative bacilli	3 (23)	8 (30)		
Nonenteric gram-negative bacilli	3 (23)	2 (7)		
Gram-positive bacilli	7 (59)	16 (54)		
CONS	4 (31)	12 (44)		
S. aureus	1 (8)	2 (7)		
Streptococci	1 (8)	0		
Enterococci	0	1 (4)		
Other gram-positive	1 (8)	1 (4)		
Yeast	0	1 (4)		

Note. CONS, coagulase-negative staphylococci.

to patients with malignant hemopathies who mainly had TECs (n = 61, 83.6%). A PICC was placed in 9 patients (12.3%) with malignant hemopathies and 6 patients (9 %) with solid tumors (Table 2). The use of parenteral nutrition also differed according to the type of central line: parenteral nutrition use was more frequent with PICCs and TECs than with ports: 175.4, 133.1, and 58.5 parenteral nutrition days per 1,000 central-line days, respectively ($P < .001$) (Supplementary Table SI-2 online).

Characteristics of patients with CLABSI

In total, 13 episodes of bacteremia occurred in 2016, to 12 patients during the 4,988 central-line days of HAH. During 2016, 27 episodes of bacteremia occurred among inpatients: 11 in the conventional unit (for 6,652 hospital days) and 16 in the protected unit (for 4,825 hospital days) (Table 3). The overall rates of CLABSI were 2.6, 1.65, and 3.3 per 1,000 central-line days for HAH, conventional units, and protected units, respectively ($P = .194$).

Our patients with HAH-related CLABSIs were significantly younger than the total HAH population, with a median age of 2.5 years versus 8.8 years ($P < .001$). We detected a significant difference in the underlying conditions for HAH-related CLABSI, with more frequent malignant or nonmalignant hemopathy and fewer solid tumors ($P = .023$). HSCT recipients suffered more CLABSI than non-HSCT patients, with 4 HSCT patients (30.8%) in the CLABSI group versus 31 (6.5%) in the non-CLABSI group ($P = .01$). Infected patients were more likely to have a TEC than uninfected patients (83% compared to 45%; $P = .006$) and none had a port. The 2 groups had similar rates of aplasia (22% vs 27% in the infected group; $P = .143$), and the proportion of patients in palliative care did not differ (25% vs 26% in the infected group; $P = .811$). Likewise, there was no difference in the proportion of stays that included chemotherapy between the groups (23% vs 20%; $P = .735$). More patients in the infected group had parenteral nutrition (46%), compared to 8% in the noninfected group ($P < .001$). Importantly, with 6 HAH-related bacteremia cases occurring during the cumulated 533 days of patients with parenteral nutrition, their specific rate of CLABSI was 11.3 per 1,000 line days. Conversely, the CLABSI rate of HAH patients without parenteral nutrition was 1.6 per 1,000 line days ($P = .001$). Multivariate analysis of factors associated with HAH-related bacteremia showed a significant correlation between infection and age

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($P = .015$) and the use of parenteral nutrition ($P < .001$), but it was not significantly correlated with central-line type, with the underlying condition, or HSCT receipt (respectively, $P = .191$, $P = .493$ and $P = .354$) (Table 1).

Characteristics of CLABSI infections between HAH patients and inpatients

The type of bacterial infection did not differ between inpatients and HAH patients; most had gram-positive bacteria (n = 7, 59% for HAH patients; n = 16, 54% for inpatients), mainly CONS (4 and 12 episodes, respectively, representing 31% and 44% of all CLABSI). *Staphylococcus aureus* represented 13% of gram-positive infections, in similar proportions between the 2 groups. Gram-negative bacilli were documented in 46% and 37% CLABSI episodes for HAH patients and inpatients, respectively. We detected a trend toward more frequent nonenteric gram-negative bacilli among gram-negative bacteria, although the difference was not significant (50% for HAH patients vs 20% for inpatients; $P = .30$). Among inpatients, 1 fungal infection with *Candida albicans* occurred, and none occurred in HAH patients (Table 3). No polymicrobial infection was documented. The median duration between the start of HAH stay and the day of infection was 11 days (IQR, 5–29). HAH-related bacteremia occurred within a median time of 192 days following central-line insertion (IQR, 70–228). The only patient who suffered from 2 infections during the study period was a 2-year-old child in palliative care for refractory acute myeloid leukemia who had *S. aureus* bacteremia and the central line was removed. He presented with *Enterobacter cloacae* bacteremia 1 month later and was successfully treated with antibiotics.

CLABSI treatment

For 12 cases, the patients were hospitalized for IV antibiotherapy and closer monitoring, 4 of whom were discharged to HAH 3–6 days later. One patient remained in HAH. The empiric antibiotic therapy was appropriate in all cases of HAH-related bacteremia, except 1 patient with a resistant Enterobacteriaceae for whom treatment had to be escalated. The central line was removed in 3 of these cases because of CLABSI. For the other 10 cases, the antibiotic therapy was sufficient to cure the infection. No fatality or case of septic shock was reported following the infections. Among enteric gram-negative bacteria, 1 isolate (33%) had a multidrug-resistant profile, with extended-spectrum β-lactamase (ESBL) production, resistance to fluoroquinolones and ertapenem but conserved sensitivity to other carbapenems. *Pseudomonas* strains (n = 3) were all sensitive to piperacillin, ciprofloxacin, and carbapenems. The 1 *S. aureus* strain was methicillin sensitive, and all of the *Staphylococcus* spp were glycopeptide sensitive.

Discussion

Our study highlighted some characteristics that are overrepresented in the HAH-related bacteremia group; we identified increased risk among children with malignant hemopathies, HSCT recipients, and patients with TECs. Data vary between similar studies regarding the association of CLABSI with age: age did not differ between children with and without CLABSIs for some,[1,9–11] but a difference was seen in others, with younger children being at higher risk,[12,13] as in our cohort. This finding may be due to more difficult compliance with dressing protocols in younger children and an increased risk of accidental dressing removal by the child. Similarly, whereas previous similar research has highlighted the greater risk of TEC,[2,9,10,12,14] data concerning other pediatric populations concerned with the risk of CLABSI, such as children with long-term parenteral nutrition for intestinal failure, do not yield similar results. They show either comparable risk between TECs versus ports or fewer infections with TECs.[15,16] The greater risk for CLABSI in patients with parenteral nutrition has been documented in previous studies[13,17]; however, disease severity and/or chronic malnutrition may be confounding factors.[18] Whether parenteral nutrition constitutes a risk factor for inpatients as well needs to be explored in a prospective study.

The increased incidence of CLABSI among children with malignant or nonmalignant hemopathies is consistent with previous studies,[9,17] but others have found a lower rate of CLABSI in children with a diagnosis of primary immune deficiency.[16] In the latter study, which included 251,244 catheter days in 499 children with various conditions (ie, including hemato-oncological, gastrointestinal or renal diseases), the only risk factor for CLABSI was prior bloodstream infection. However, age, underlying pathology, catheter type, number of lumens, and insertion site did not differ between children with or without prior bloodstream infection.

Notably, the various risk factors outlined in the present study tend to overlap. Patients with hemopathies tend to be younger than those with solid cancer and to have a TEC more frequently than a port. However, the frequency of parenteral nutrition was similar in both groups and therefore seems to be independent from the other factors identified here.

In terms of CLABSI rate, our cohort was closer to hospitalized than ambulatory patients: rates for inpatients varied between 1.79 per 1, 000 central-line days[3] after implementation of central-line maintenance care bundles and 7.4 per 1,000 central-line days.[19] Rates for ambulatory patients as low as 0.32 per 1,000 central-line days[20] have been reported. Indeed, our HAH patients do not represent children treated for cancer with a central line at home, but patients with daily active care and treatment. In most cases, patients do not have their central-lines connected at all times because treatments are being given once or twice a day (eg, parenteral nutrition administered in the evening and removed in the morning), resulting in a higher risk for CLABSI. Although treatments were delivered by nurses and not dedicated pediatric hematology-oncology nurses, CLABSI rates in the HAH population were not significantly different than those of inpatients.

We did not detect a significant difference in causal bacterial strains between HAH and hospitalized patients. This finding contrasts with another study that reported an increased proportion of nonenteric gram-negative infections among outpatients.[14] However, our data agree with previous studies showing that most infections are caused by gram-positive bacteria.[12,21] This predominance of gram-positive strains, especially CONS, has also been documented in children with long-term parenteral nutrition for gastrointestinal conditions.[15] The prevalence of infections with multidrug-resistant bacteria was low in HAH-related CLABSIs, with only 1 ESBL-producing Enterobacteriaceae and no glycopeptide-resistant gram-positive strain, despite the wide use of vancomycin for all suspected CLABSIs. The predominance of *Staphylococcus* spp points out possible flaws in hygiene and central-line management at home.

Although home care is rapidly developing, few studies have analyzed the impact of central-line management outside the hospital setting. Our research provides a detailed and unique description of both CLABSI episodes and their consequences as well as the variety of care provided to our patients. However, this study had some limitations. The retrospective nature of the study may have

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led to some bias of misclassification. For instance, patients were considered in aplasia during the days between 2 low granulocyte counts (<500 cells per mm^3). Also, patients did not have daily blood samples; thus, the aplasia period could have been underestimated. However, using a pre-established definition for CLABSI enabled a standardized diagnosis. Misclassification may have influenced the various factors presented here because we relied on clinical data. Finally, the relatively small size of the cohort may have prevented the detection of significant associations and did not allow subgroup analyses to better elucidate critical mechanisms associated with CLABSI among HAH children.

Our study focused on CLABSIs in a population that has been poorly investigated previously: children with oncology and hematology diseases with active care at home. We hope to show with our data that IV chemotherapy, parenteral nutrition, and twice-daily IV treatments can be administered at home, including in children with aplasia. However, special care should be given to those at higher risk: younger children aged <6 years, bone-marrow graft recipients, children with parenteral nutrition, and those with an external central line. To provide specific training on central-line maintenance and dressing change, we are launching an e-learning program to teach and train nurses involved in pediatric hematology-oncology patient care to improve their knowledge and skills regarding central-line maintenance. Indeed, this will allow efforts that have been successfully used to reduce CLABSIs in inpatient units to be implemented in HAH programs providing similar levels of care.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2022.184

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