Catheter salvage of central venous catheter-related bloodstream infections caused by *Enterobacterales* in paediatric oncology patients.

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Abstract

Purpose The aim of this study was to determine whether salvage treatment of a central venous catheter (CVC) can be safely and effectively achieved after the diagnosis of a CVC-related bloodstream infection caused by *Enterobacterales* in paediatric oncology patients.

Methods A retrospective study including all consecutive oncology and stem cell recipient patients from 0-20 years old with a CVC and a positive blood culture with *Enterobacterales* at the Princess Máxima Centre was performed. Patients were followed for 60 days. The primary outcome of this study was the event-free survival after follow-up in patients for whom salvage treatment was attempted for a central line-associated bloodstream infection (CLABSI) caused by *Enterobacterales*.

Results A total of 122 CVC-related bloodstream infection episodes were included. In seventeen episodes the CVC was immediately removed. In 105 episodes catheter salvage was attempted. Of these, 53 episodes met the CLABSI criteria. Event-free survival for catheter salvage through systemic antibiotic treatment in bloodstream infections caused by *Enterobacterales* in general and specific for CLABSI classified episodes were 41.1% and 26.7%, respectively. Of all included children, 15.6% were admitted to a paediatric intensive care unit and one patient (1.9%) died due to the *Enterobacterales* CLABSI episode. No risk factors appeared to be significantly associated with CLABSI related events.

Conclusion In conclusion, our study demonstrates low event-free survival after catheter salvage therapy in CLABSI caused by *Enterobacterales* in paediatric oncology patients, ultimately resulting in high rates of delayed CVC removal. Immediate central venous catheter removal upon *Enterobacterales* isolation should therefore be advised in the majority of children suffering from a central line-associated infection.

1. Introduction

Central venous catheters (CVCs) play a key role during the treatment of paediatric oncology patients, providing long-term venous access for chemotherapy, blood products, parenteral nutrition and blood testing (Carraro *et al.*, 2013). The most common and serious CVC-related complication that occurs is a CVC related-bloodstream infection (Cesaro *et al.*, 2004; Wolf *et al.*, 2013). CVC-related bloodstream infections not only necessitate antibiotic treatment but often lead to CVC removal, postponement of cancer treatment, prolonged hospital stays and in some cases intensive care unit admissions or even death (Bosch *et al.*, 2019; Ullman *et al.*, 2015). Paediatric oncology patients are at particular risk of CVC-related bloodstream infections due to their immunocompromised and often neutropenic state (Miliaraki *et al.,* 2017; Taveira *et al.*, 2016).

Based on the pathogen cultured, immediate removal of the CVC may be indicated following the guidelines described by the Infectious Diseases Society of America (IDSA) in 2009 (Mermel *et al.*, 2009). In case of uncomplicated CVC-related gram-negative bacilli (GNB) bloodstream infections, such as *Enterobacterales,* salvage treatment through systemic antibiotic treatment (SAT) is recommended over immediate CVC removal (Mermel *et al.*, 2009). Unsuccessful salvage treatment can eventually lead to uncontrolled infection, deterioration of the clinical status of the patient, resulting in intensive care unit admissions, and may have negative impact on the continuation of oncological treatment (Benjamin *et al.*, 2001; Tsai *et al*., 2015).

Currently, only one study has looked at catheter salvage rates for CVC-related bloodstream infection caused by *Enterobacterales* specifically (Nazemi *et al.*, 2003). This study was performed in neonates and observed successful treatment in 45% of cases. However, the outcome of salvage treatment for CVC-related bloodstream infections caused by *Enterobacterales* has, to our knowledge, never been studied directly in paediatric oncology.

The aim of this study was to determine whether salvage treatment of a CVC can be safely and effectively achieved after the diagnosis of a CVC-related bloodstream infection caused by *Enterobacterales* in paediatric oncology patients.

2. Methods

2.1 Study design and participants

A retrospective study including all consecutive oncology and stem cell recipient patients from 0-20 years old with a CVC and a positive blood culture with *Enterobacterales* in the Princess Máxima Centre for paediatric oncology in Utrecht, the Netherlands between April 2015 and July 2022 was performed. Since 2018, all paediatric oncology care in the Netherlands is concentrated in this centre. We identified patients for inclusion from the microbiological laboratory system (GLIMS CliniSys | MIPS, Gent, Belgium). For patients who had multiple positive blood cultures for *Enterobacterales* over the specified follow-up period, only the first

episode was included. Patients with multiple CVCs *in situ* at the time of bloodstream infection (BSI) onset were excluded. All patients were followed-up from date of collection of the positive blood culture until a maximum of 60 days or until CVC removal, whichever came first. A waiver for informed consent was obtained from the Medical Ethics Committee NedMec, Utrecht, the Netherlands (file number 22-036). Adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies was maintained throughout this study (von Elm *et al.*, 2007).

2.2 Outcomes and data-collection

The primary outcome of this study was the event-free survival after 60 days in patients for whom salvage treatment was attempted for a central line associated bloodstream infection (CLABSI) caused by *Enterobacterales*.

The secondary outcome was the event-free survival of all episodes of CVC-related *Enterobacterales* bloodstream infection (BSI). Additionally, time-to-event, percentages of patients with immediate CVC removal after a positive *Enterobacterales* blood culture, micro-organisms cultured, relapses, reinfections, intensive care unit admissions, and death were evaluated.

Furthermore, the patient files were retrospectively assessed for patient characteristics (age, gender and underlying diagnosis), CVC characteristics (insertion and removal date, catheter type, diameter, lumen number, access vein, side of access, reason for removal) as well as certain risk factors (stem cell transplantation (SCT) 30 days prior to BSI onset, SCT with graft versus host-disease (GvHD) more than 30 days prior to BSI onset, administration of total parenteral nutrition (TPN) during follow-up, presence of mucositis, CVC thrombosis, local irritation/infection and neutropenia at BSI onset and during follow-up). If data was not explicitly reported in the patient files, this was reported as missing data. If essential data regarding the primary outcome such as date or reason of CVC removal was missing, the patient was excluded.

2.3 Definitions

Immediate removal was defined as CVC removal within 48 hours upon notification of the treating infectious disease specialist regarding the presence of an *Enterobacterales* isolate in the blood culture. Salvage treatment was defined as empiric antibiotic treatment started upon blood culture determination in patients where immediate CVC removal was determined as avoidable at discretion of the treating physician.

BSI-related events were defined as CVC removal, intensive care unit admission or death related to the primary episode. Event-free survival was defined as a patient without any of these events during the follow-up period.

Central line-associated bloodstream infections (CLABSI) were defined following the CLABSI criteria of the Centres for Disease Control and Prevention (CDC), which are the preferred criteria for paediatric oncology patients since peripheral blood cultures, which are required for diagnosis by other commonly used criteria, are rarely obtained in this patient group (Centers for Disease Control and Prevention, 2022). CLABSI was scored if the patient met one of the following criteria: (1) the patient had a recognized pathogen cultured from ≥ 1 blood cultures, or (2) the patient had at least one of the following signs: fever (> 38°C), chills or hypotension, and the same matching potential contaminant micro-organism had to be cultured from ≥ 2 blood cultures drawn on separate occasions. A CLABSI could only be scored if the CVC was in place for >48 h on the date of the event, if no CLABSI with the same micro-organism was scored in the past two weeks (infection relapse time frame), and if the pathogen cultured was not related to an infection at another site (Centers of Disease Control and Prevention, 2022).

A relapse was defined as the isolation of the same micro-organism (i.e. the same species and a similar resistance pattern) after appropriate antibiotic treatment (antibiotics for which the micro-organism is sensitive) for the primary episode has ended without negative blood cultures for the same micro-organism found in between. A reinfection was defined as the growth of the same micro-organism after appropriate antibiotic treatment for the primary episode has ended and where a negative blood culture was found in between. A negative blood culture after antibiotic treatment of the initial episode has ended is needed in order to differentiate between a reinfection and relapse.

A paediatric intensive care unit (PICU) admission and/or death was scored as a BSI-related event if sepsis was the reason for admission or death, or if sepsis was a contributing factor in PICU admission or death determined by two infectious disease specialists based on the electronic patient files.

The presence of neutropenia was defined as a neutrophil granulocyte count of less than $1.5x10^9$/L on at least two separate days collected within a 7-day time period. Local infection and/or irritation was defined as redness, pain, purulent drainage and haematoma on the skin surrounding CVC exit site detected by visual inspection or through positive exit-site culture. Thrombosis of the CVC was diagnosed by radiological imaging.

2.4 CVC-related bloodstream infection management

In patients with a suspicion of a CVC-related infection, empirical systemic antibiotic treatment was started. Resistance patterns of the cultivated bacteria and clinical state of the patients were naturally taken into account. Directed antibiotic treatment was started after determination of the pathogen. Systemic antibiotic treatment was intended as salvage treatment in patients where immediate CVC removal was found avoidable at discretion of the treating physician. In case of severe sepsis, if blood culture results remain positive despite 72 hours of appropriate antibiotic therapy, or if *Staphylococcus aureus*, *Pseudomonas*

aeruginosa, fungi, or *mycobacteria* were cultured, the CVC was removed (Mermel *et al.*, 2009). After CVC removal, whether immediate or delayed, antibiotic treatment was switched to oral antibiotics if possible.

2.5 Statistical analysis

Categorical data were presented as contingency tables; frequencies and percentages. For continuous data summary statistics of median, minimum, maximum, first quartile and third quartile were presented. To study the survival during and following salvage treatment, event-free survival was calculated and Kaplan-Meier survival curves were created. Univariate and multivariate Cox proportional hazards regression models were used to test association between patient baseline characteristics and survival. IBM SPSS version 26.0.0.1 was used to perform the statistical analyses.

3. Results

3.1 Clinical characteristics of the patients and the central venous catheters

A total of 140 *Enterobacterales* positive blood cultures were identified through the microbiological laboratory system (Figure 1). Eighteen episodes were excluded: in 11 episodes the patient had two or more CVCs *in situ*; in 4 episodes there was no CVC *in situ* at the moment of blood culture collection; in 2 episodes it concerned a patient whose first episode was included but whose CVC was replaced and where subsequently another blood culture was positive for *Enterobacterales* within the original follow-up period; in 1 episode essential data regarding date and reason for removal was missing.

Over the 88-month study period, a total of 122 episodes of bacteremia concerning *Enterobacterales* that occurred in 106 patients were included. In 17/122 (13.9%) episodes the CVC was immediately removed within 48h upon blood culture results notification, 16 of these met the CLABSI criteria. Characteristics of the children who underwent immediate CVC removal are shown in Table 1. Immediate removal was indicated following the IDSA guidelines due to, in addition to isolation of *Enterobacterales*, the isolation of *Staphylococcus aureus* in 3 cases, *Pseudomonas aeruginosa* in one case and *Candida parapsilosis* in one case.

Line salvage was attempted in the remaining 105/122 (86.1%) episodes, that occurred in 90 patients (57.8% males, 42.2% females). The median age at blood culture collection was 4 years. Solid tumours and haematological malignancies accounted for 43.3% (39) and 40.0% (36) of the underlying diagnoses, respectively. Most episodes of bacteremia occurred in patients with tunneled cuffed external CVCs (56, 53.3%), followed by totally implantable venous access devices (TIVAD) (42, 40.0%). The CVCs were *in situ* for a median length of 95 days (range 2-1276). Out of 105 bacteremia episodes in which salvage was attempted, 53 (50.5%) met the CLABSI criteria. These CLABSI episodes occurred in 40 patients. All patient characteristics, CVC characteristics and potential risk factors are presented in Table 1.

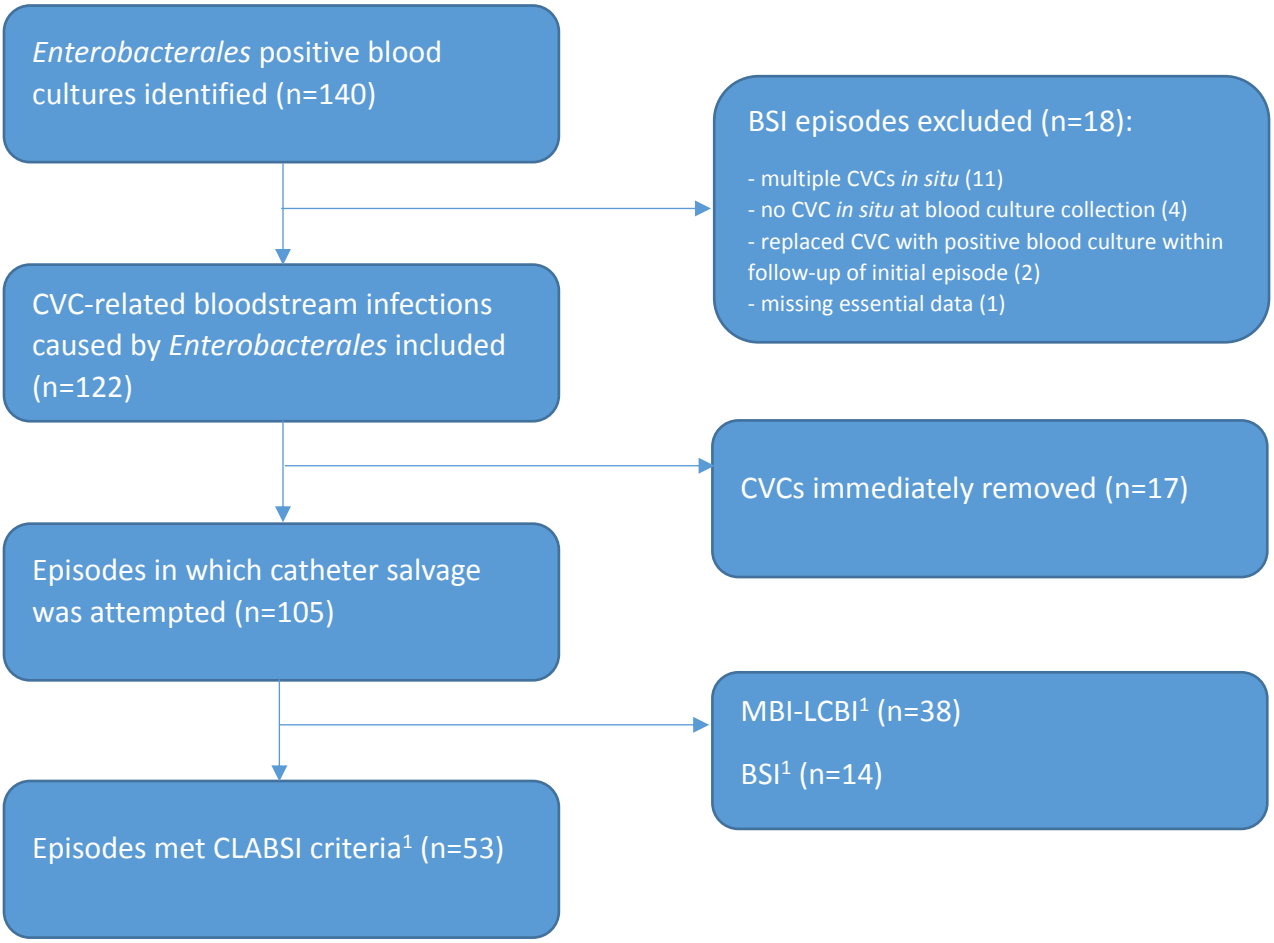

Figure 1. Flow diagram of all study participants. CVC, central venous catheter; BSI, bloodstream infection; CLABSI, central line-associated bloodstream infection; MBI-LCBI, mucosal barrier injury laboratory confirmed bloodstream infection.

[1] Centers of for Disease Control and Prevention.

Table 1. Baseline characteristics of patients, central venous catheters and clinical characteristics for the complete cohort, CLABSI specific and immediate removals

		Salvage treatment				Immediate removal	
		All patients		CLABSI			
		n = 90 (%)	Median (min-max)	n = 40 (%)	Median (min-max)	n = 17 (%)	Median (min-max)
Age			4 (0-19)		3 (0-19)		3 (0-6)
Gender	Female	38 (42.2)		14 (35.0)		4 (23.5)	
	Male	52 (57.8)		26 (65.0)		13 (76.5)	
Category of initial diagnosis	Solid tumour*	39 (43.3)		22 (55.0)		11 (64.7)	
	Neuro-oncology	3 (3.3)		1 (2.5)		2 (11.8)	
	Haematological malignancy	36 (40.0)		12 (30.0)		3 (17.6)	
	Benign stem cell transplant	2 (2.2)		1 (2.5)		1 (5.9)	
	Lymphoma	7 (7.8)		1 (2.5)		0 (0.0)	
	Other	3 (3.3)		3 (7.5)		0 (0.0)	

		Salvage treatment				Immediate removal	
		All BSI episodes		CLABSI			
		n = 105 (%)	Median (min-max)	n = 53 (%)	Median (min-max)	n = 17 (%)	Median (min-max)
Days of CVC *in situ*			95 (2-1276)		86 (2-689)		48 (4-384)
Type of CVC	Tunnelled external CVC	56 (53.3)		34 (64.2)		11 (64.7)	
	TIVAD	42 (40.0)		14 (26.4)		4 (23.5)	
	Non-tunneled CVC	2 (1.9)		2 (3.8)		2 (11.8)	
	PICC-line	5 (4.8)		3 (5.7)		0 (0.0)	
Single, double or triple lumen	Single	45 (42.9)		17 (32.1)		6 (35.3)	
	Double	51 (48.6)		34 (64.2)		9 (52.9)	
	Triple	9 (8.6)		2 (3.8)		2 (11.8)	
Type of vein	Jugular	79 (76.0)		37 (71.2)		14 (87.5)	
	Subclavian	14 (13.5)		7 (13.5)		2 (12.5)	
	Femoral	1 (1.0)		1 (1.9)		0 (0.0)	
	Brachial	4 (3.8)		2 (3.8)		0 (0.0)	
	Basilic	2 (1.9)		2 (3.8)		0 (0.0)	
	Missing	4 (3.8)		3 (5.8)		0 (0.0)	
Side of access	Left	22 (21.2)		12 (23.1)		5 (29.4)	
	Right	78 (75.0)		37 (71.2)		12 (70.6)	
	Missing	4 (3.8)		3 (5.8)		0 (0.0)	
Stem cell transplant	No	97 (92.4)		50 (94.3)		16 (94.1)	
	<30 days prior to BSI	7 (6.7)		2 (3.8)		1 (5.9)	
	Missing	1 (1.0)		1 (1.9)		0 (0.0)	
GvHD of the gut	No	98 (93.3)		49 (92.5)		100 (100.0)	
	>30 days prior to BSI with GvHD	6 (5.7)		3 (5.7)		0 (0.0)	
	Missing	1 (1.0)		1 (1.9)		0 (0.0)	
Neutropenia at BSI onset	No	55 (52.4)		41 (77.4)		12 (70.6)	
	Yes	50 (47.6)		12 (22.6)		4 (23.5)	
	Missing	0(0.0)		0(0.0)		1 (5.9)	

CLABSI; central line-associated bloodstream infection; CVC, central venous catheter; TIVAD, totally implantable venous access device; PICC, peripherally inserted central catheter; BSI, bloodstream infection; GvHD, graft versus host disease.
*The category solid tumours predominantly consisted of the underlying diagnosis neuroblastoma. This concerned 27 patients (30.0%) and 18 patients (45.0%) for the entire cohort and the CLABSI cohort, respectively.

3.2 Characteristics of the infectious episodes

Table 2 lists the prevalence of all *Enterobacterales* isolated. Most of the 105 bacteremic episodes concerned *Escherichia coli* (35.2%), followed by *Enterobacter cloacae complex* (21.0%) and *Klebsiella pneumoniae* (12.4%). Twenty-four (22.9%) *Enterobacterales* were extended spectrum beta-lactamase (ESBL) producers.

Most of the 53 CLABSI episodes concerned *Enterobacter cloacae* (22.6%), followed by *Escherichia coli* (20.8%). Six (11.3%) *Enterobacterales* causing CLABSI episodes were extended spectrum beta-lactamase (ESBL) producers.

Table 2. Bloodstream infections caused by *Enterobacterales,* distribution of bacterial species

	All BSI episodes	CLABSI
Micro-organisms	n = 105 (%)	n = 53 (%)
Citrobacter braakii	1 (1.0)	1 (1.9)
Citrobacter freundii (including 1 ESBL+)	2 (1.9)	1 (1.9)
Enterobacter cloacae complex (including 7 ESBL+)	22 (21.0)	12 (22.6)
Nissabacter archeti	1 (1.0)	0 (0.0)
Escherichia coli (including 8 ESBL+)	37 (35.2)	11 (20.8)
Hafnia alvei	1 (1.0)	0 (0.0)
Klebsiella oxytoca	4 (3.8)	2 (3.8)
Klebsiella pneumoniae (including 8 ESBL+)	13 (12.4)	5 (9.4)
Mixed	7 (6.7)	7 (13.2)
Pantoea agglomerans	4 (3.8)	3 (5.7)
Pantoea eucrina	1 (1.0)	1 (1.9)
Pantoea septica	9 (8.6)	8 (15.1)
Raoultella species	1 (1.0)	1 (1.9)
Serratia marcescens	2 (1.9)	1 (1.9)

CLABSI, central line-associated bloodstream infection; BSI, bloodstream infection; mixed, poly-microbial infection with more than one *Enterobacterales* bacteria cultured in initial blood culture at bloodstream infection diagnosis.

3.3 Event-free survival of salvage therapy in all bloodstream infections

The event-free survival of 105 episodes in which line salvage was attempted were analyzed. The event-free survival for catheter salvage treatment after 60 days of follow-up estimated with a Kaplan-Meier model for all BSIs was 41.1% (Figure 2).

After 60 days of follow-up, 58 (55.2%) of the patients had experienced a BSI related event at a median of 5 days (IQR 8). Fifty-one (48.6%) of all line salvage attempts resulted in CVC removal related to the infection at a median of 6 days (IQR 10). Infectious disease specialists scored 17 (16.2%) out of 21 paediatric intensive care unit admissions and 4 (3.8%) out of 8

deaths attributable to CVC-related bloodstream infections (Table 3). Systemic antibiotic treatment was given for a median of 10 days (IQR 4).

3.4 Event-free survival of salvage therapy in CLABSI

Of the 105 episodes in which line salvage was attempted, 53 episodes met the CLABSI criteria. The event-free survival for catheter salvage treatment after 60 days of follow-up estimated with a Kaplan-Meier model for CLABSI specifically was 26.7% (Figure 3).

In 35 (66.0%) of these 53 CLABSI episodes, patients experienced a BSI related event due to their CLABSI at a median of 5 days (IQR 18). Thirty-three (62.3%) of the line salvage attempts resulted in CVC removal at a median of 6 days (IQR 17). Eight (15.1%) patients were admitted to the paediatric intensive care unit and 1 (1.9%) patient died during the 2-month follow-up related to the CLABSI episode. Systemic antibiotic treatment was given for a median of 10 days (IQR 3.5). The *a priori* probability (i.e. inclusion of immediate removals) of CVC removal within 60 days due to CLABSI when *Enterobacterales* is isolated is 71.0%.

3.5 Relapses and re-infections

Relapse with the same *Enterobacterales* as the initial episode during follow-up occurred in 6 (5.7%) episodes, all six of them concerned CLABSIs, after a median of 20 (IQR 30) days (Table 3). Of all relapses, 3 (50%) concerned *Enterobacter cloacae complex* (including 1 ESBL+), 2 (33%) *E. coli* and one (17%) *Pantoea agglomerans*. Re-infection was seen in 6 (5.7%) and 3 (5.7%) episodes after a median of 32 (IQR 28) and 43 (IQR 31) days for the whole cohort and CLABSI episodes respectively. Two re-infections were associated with *Enterobacter cloacae complex* (including 1 ESBL+) (33%), two with *Escherichia coli* (including 1 ESBL+) (33%), one with *Pantoae agglomerans* (17%) and one with *Serratia marcescens* (17%). All relapses necessitated catheter removal as well as 5 out of the 6 re-infections. No children were admitted to the paediatric intensive care unit or died due to relapses or re-infections.

3.6 Predictors of events

To identify risk factors for BSI related events when attempting catheter salvage, underlying diagnosis, catheter type, SCT 30 days prior to BSI onset, and neutropenia at BSI onset were evaluated in a multi-variate analysis (Table 4). None of the factors that were analyzed appeared to be a significant risk factor for BSI-related events when attempting catheter salvage.

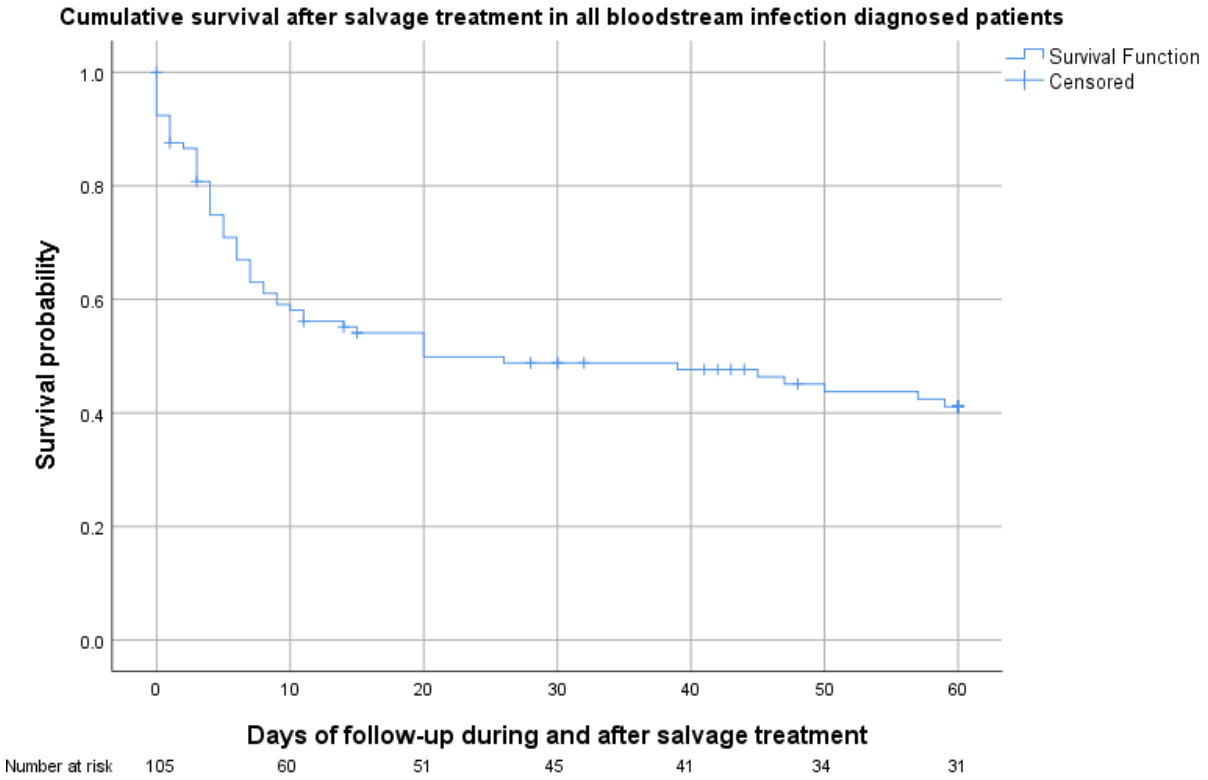

Figure 2. Kaplan Meier survival curve of event-free survival during 60 days of follow-up after salvage treatment in patients with BSI diagnosis. BSI, Bloodstream Infection; SAT, Systemic Antibiotic Treatment. Day 0 represents BSI diagnosis through positive blood culture followed by the start of salvage treatment through SAT. Event-free survival of 41.1% after 60 days of follow-up was estimated after attempted salvage in a total of 105 BSI diagnosed patients.

Table 3. Bloodstream infection related events, relapses and re-infections

		All BSI episodes		CLABSI	
		n = 105 (%)	Median (Q1-Q3)	n = 53 (%)	Median (Q1-Q3)
BSI-related events	No	47 (44.8)		18 (34.0)	
	Yes	58 (55.2)		35 (66.0)	
	Days until		5 (3-11)		5 (2-20)
CVC removal related to BSI	No	53 (50.5%)		20 (37.7)	
	Yes	52 (49.5%)		33 (62.3)	
	Days until		6 (3-13)		6 (3-20)
PICU admission related to BSI	No	88 (83.8)		45 (84.9)	
	Yes	17 (16.2)		8 (15.1)	
	Days until		1 (0-4)		1 (0-1)
Death related to BSI	No	101 (96.2)		52 (98.1)	
	Yes	4 (3.8)		1 (1.9)	
	Days until		3 (0-7)		1
Relapse	No	99 (94.3)		47 (88.7)	
	Yes	6 (5.7)		6 (11.3)	
	Days until		20 (17-47)		20 (17-47)
	CVCs removed due to relapse	6 (5.7)		6 (11.3)	
Re-infection	No	99 (94.3)		50 (94.3)	
	Yes	6 (5.7)		3 (5.7)	
	Days until		32 (16-44)		43 (16-47)
	CVCs removed due to re-infection	5 (4.8)		3 (5.7)	

CLABSI, central line-associated bloodstream infection; BSI, bloodstream infection; CVC, central venous catheter; PICU, paediatric intensive care unit; Q1, first quartile; Q3, third quartile. Bloodstream infection related events, relapses and re-infections during a 60-day follow-up period.

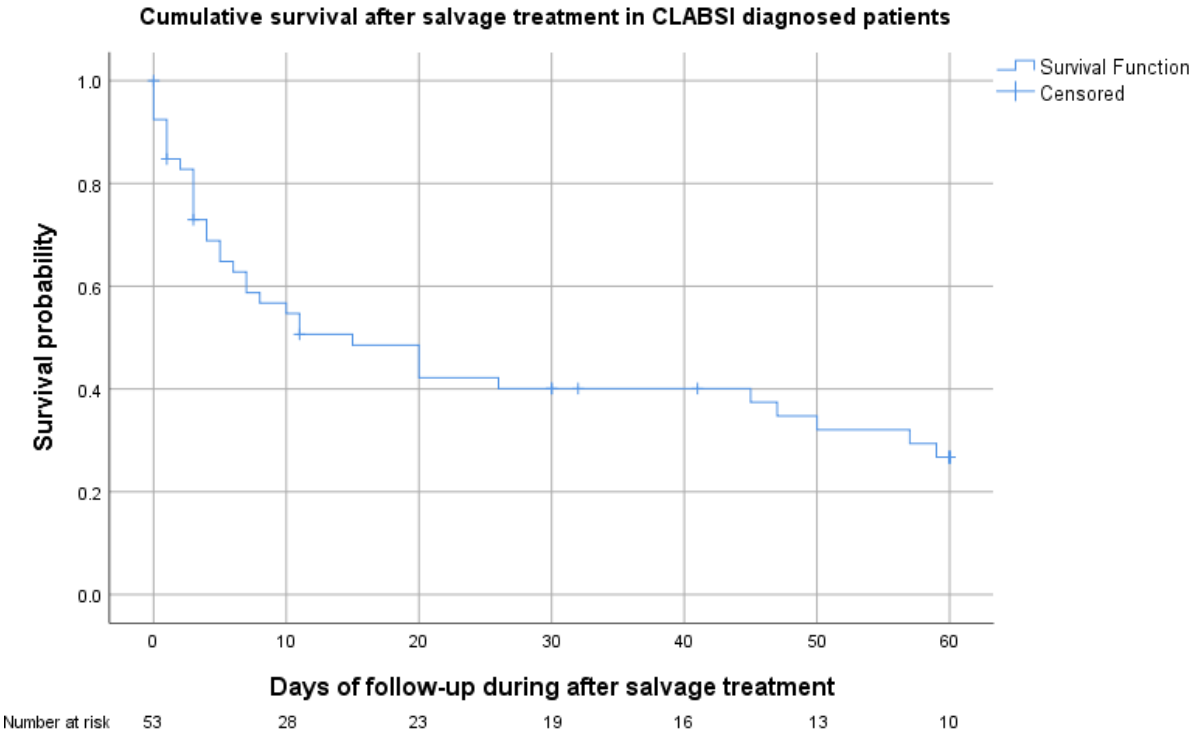

Figure 3. Kaplan Meier survival curve of event-free survival during 60 days of follow-up after salvage treatment in patients with CLABSI diagnosis. CLABSI, Central Line Associated Bloodstream Infection; SAT, Systemic Antibiotic Treatment. Day 0 represents CLABSI diagnosis through positive blood culture followed by the start of salvage treatment through SAT. Event-free survival of 26.7% after 60 days was estimated after salvage treatment in a total of 53 CLABSI diagnosed patients.

Table 4. Multivariate analysis of factors associated with BSI-related events during salvage therapy

	All BSI episodes	CLABSI
Risk factor	HR (CI)	HR (CI)
Solid tumour	1	1
Hematological malignancy	1.17 (0.62-2.18)	1.18 (0.50-2.77)
Hickman/Powerline	1	1
TIVAD	0.64 (0.34-1.20)	0.95 (0.40-2.24)
No stem cell transplantation	1	1
Stem cell transplantation	2.38 (0.82-6.96)	4.70 (0.48-45.75)
No neutropenia at BSI onset	1	1
Neutropenia at BSI onset	0.69 (0.37-1.27)	0.58 (0.21-1.61)

CLABSI; central line-associated bloodstream infection; TIVAD, totally implantable venous access device; BSI, bloodstream infection; HR, hazard ratio; CI, confidence interval.

4. Discussion

The overall result of the study demonstrates low event-free survival after catheter salvage treatment in central venous catheter related bloodstream infections caused by *Enterobacterales* in paediatric oncology patients. We report event-free survival for catheter salvage through systemic antibiotic treatment in bloodstream infections caused by *Enterobacterales* in general and specific for CLABSI classified episodes as 41.1% and 26.7%, respectively. Of all included children, 15.6% were admitted to a paediatric intensive care unit and one patient (1.9%) died due to the *Enterobacterales* CLABSI episode.

Current IDSA guidelines recommend CVC removal for CVC-related bloodstream infection caused by *Enterobacterales* in case of severe sepsis and persisting bloodstream infections. In uncomplicated infections, catheter salvage is recommended. Benefits of catheter salvage are continuity of care and avoidance of exposure to general anesthesia and most significantly, the avoidance of vascular damage by new catheterization. However, we have found that in the majority of the cases, catheter removal at a certain point during the infection appeared unavoidable. Delaying the decision to remove the CVC, can have significant consequences regarding the clinical status of the children, such as severe sepsis development, intensive care unit admission and possibly death.

Event-free survival for CLABSIs is lower compared to all CVC-related bloodstream infections. This can be explained by bloodstream infections originating from other sources such as urinary tract infections or translocation of bacteria through a weakened mucosal barrier in the gut that are included in the whole cohort, preventing these patients from experiencing any CLABSI related events.

When comparing our results to those of older studies, it must be pointed out that the primary outcome of most studies is successful salvage rate. Generally, this means salvage treatment without CVC removal or re-infection. This definition does not take into account the clinical status of the patient. In this study, admission to the paediatric intensive care unit with inotropic support due to their central line-related bloodstream infection during salvage treatment is not considered successful salvage. Therefore, the event-free survival in this study is not directly comparable to successful salvage rates in most prior studies.

Nevertheless, the event-free survival estimated in our study for all central line-related bloodstream infections in which salvage was attempted is in accordance with findings reported by Nazemi *et al.* (2003). This study described a 45% successful salvage rate for central line-related bloodstream infection caused by *Enterobacterales*. However, their study population consisted solely of neonates and included mostly peripherally inserted central catheters instead of long-term CVCs.

A meta-analysis on catheter salvage strategies in children has recently been published reporting a catheter salvage rate of 47% for CLABSI caused by gram-negative bacilli (Buonsenso *et al*., 2022). However, when looking at the studies included in the analysis individually, it is not entirely clear what definition of catheter salvage was used and which

gram-negative bacilli were included (Alby-Laurent *et al.*, 2019; Hecht *et al.*, 2019; McGrath *et al*., 2017; McGrath *et al*., 2011; Tsai *et al.*, 2015; Valentine *et al.*, 2011; Zembles *et al*., 2018). Also, the populations and types of CVCs included in the studies were highly heterogeneous.

Salvage rates for CLABSI reported by literature of 34-100% are higher than the event-free survival after catheter salvage for CLABSI observed in this study (Ashkenazi-Hoffnung *et al.*, 2020; Benjamin *et al.*, 2001; Buonsenso *et al.*, 2022; Tsai *et al.*, 2015). This might partly be explained by the additional use of antimicrobial lock therapy (ALT) as a salvage strategy in most catheter salvage studies (Ashkenazi-Hoffnung *et al*., 2020; Buonsenso *et al.*, 2022; Tsai *et al.*, 2015). ALT seems promising in improving the successfulness of salvage treatment but further research is needed to determine its safety and efficacy (Ashkenazi-Hoffnung *et al.*, 2020; Buonsenso *et al.*, 2022).

Another possible explanation of the low event-free survival estimated in this study is the relatively large number of patients with the underlying diagnosis of neuroblastoma that were included. These patients were treated with immunotherapy between 2015 and 2018 in our centre, which was associated with high infection rates, possibly affecting the course of their central venous catheter-related bloodstream infections studied here (Blom *et al.*, 2021).

No comparable information on intensive care unit admissions due to infectious causes during CVC-related bloodstream infection was found in literature. The contributory mortality for CVC-related bloodstream infection caused by *Enterobacterales* was 3.8%, which is comparable to the 5% case fatalities that was reported in a previous study (Nazemi *et al.*, 2003). For CLABSI episodes specifically, 1.9% of the deaths were contributable to the infection, compared to 7% found in literature (Tsai *et al*., 2015).

Relapse of the same *Enterobacterales* was observed in 6 CLABSI episodes (11.3%) and re-infections in 3 (5.7%) episodes within a 2 month period. So in 9 (17.0%) out of 53 episodes patients experienced either a relapse or re-infection, exceeding the 6.9% relapse rate over a period of 3 months reported by Nazemi *et al.* (2003). This combined relapse and re-infection rate of 17.0% is slightly higher than CLABSI relapse and re-infection rates in general of 11% reported in literature (Ashkenazi-Hoffnung *et al.*, 2020). In our multivariate analysis, no potential risk factor appeared to be associated with the occurrence of an event.

The strengths of this study include its large sample size and the comprehensive definition of catheter salvage treatment failure, which includes late treatment failure. Furthermore, exclusion of patients with multiple CVCs *in situ* allowed for careful evaluation of each central line, its possibly related infection and therefore the effect of CVC removal. Nevertheless, our study has two limitations. First, patients were treated at home or in a different hospital during periods of time due to the shared care structure that was used in the early stages of centralization. Major complications of the CVC-related bloodstream infection in other institutions were shared and documented in our institution. However, it is possible that minor complications in the course of the infection are missing since the medical files of other institutions were not reviewed. Secondly, the central line related bloodstream infection

(CRBSI) criteria are technically the most accurate definition of describing infections related to the CVC (O' Grady *et al.*, 2011). However, in practice, the lack of peripheral blood cultures and catheter tip cultures in paediatric patients that are required in order to meet CRBSI criteria meant only the CLABSI criteria could be met.

In conclusion, our study demonstrates low event-free survival after catheter salvage therapy in central venous catheter-associated bloodstream infection (CLABSI) caused by *Enterobacterales* in paediatric oncology patients, ultimately resulting in high rates of delayed CVC removal. Immediate central venous catheter removal upon *Enterobacterales* isolation should therefore be advised in the majority of children suffering from a central line-associated infection. Potentially, further prospective research on the safety and efficacy of antimicrobial lock therapy for CLABSI may prove its beneficial effect on salvage rates compared to systemic antibiotic therapy alone.

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