Central venous catheter-related bloodstream infections caused by Enterobacterales in pediatric oncology patients: catheter salvage or removal

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Central Venous Catheter-related Bloodstream Infections Caused by *Enterobacterales* in Pediatric Oncology Patients

Catheter Salvage or Removal

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Background: The aim was to determine whether salvage treatment with systemic antibiotics is a safe and effective strategy for *Enterobacterales* bloodstream infections (BSI) in pediatric oncology patients with a central venous catheter (CVC).

Methods: A retrospective study was performed on oncology and stem cell recipient patients with a CVC and blood culture with *Enterobacterales*, at the Princess Máxima Centre for Pediatric Oncology, Utrecht, the Netherlands. Analyses were performed for all BSI and for episodes meeting central line-associated bloodstream infection (CLABSI) criteria. The cumulative incidence of an event (ie, removal, intensive care admission or death) was estimated after blood culture collection for episodes primarily treated with antibiotics. The effect of prognostic factors on the hazard of the event of interest was assessed by estimating a Cox proportional hazard regression model.

Results: In total, 95 CVC-related *Enterobacterales* BSIs in 82 patients were included; 12 (13%) BSIs required immediate CVC removal and for 83 (87%) BSIs CVC salvage was attempted. The cumulative incidence of events at 60 days was 53.0% [95% confidence interval (CI): 41.7–63.1] for BSIs (n = 83), and 64.4% (95% CI: 48.3–76.7) for CLABSIs (n = 45). The events occurred after a median of 6 (Q1–Q3: 2–15) and 6 (Q1–Q3: 2–20) days for BSIs and CLABSIs, respectively. Intensive care admission after salvage treatment was required in 16% of the BSIs and CLABSIs, resulting in death in 5% and 2% of cases, respectively. No significant association between risk factors and events was found.

Conclusions: The cumulative incidence of an event at 60 days after salvage treatment for *Enterobacterales* CLABSIs and BSIs in pediatric oncology patients is high. Immediate CVC removal appears recommendable for this patient group.

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Central venous catheters (CVCs) play a key role during the treatment of pediatric oncology patients.[1] One of the most common and severe CVC-related complications observed are bloodstream infections (BSI); 30% of pediatric oncology patient that receive a CVC develop 1 or multiple central line-associated bloodstream infections (CLABSI), incidence rate of 1.51 per 1000 CVC-days.[2–4] CLABSIs 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 (ICU) admissions or even death.[4,5] Pediatric oncology patients are at particular risk of CLABSIs due to their immunocompromised and often neutropenic state.[6,7]

In our hospital, *Enterobacterales* spp. were cultured during 12% of the reported CLABSIs[4] The Infectious Diseases Society of America (IDSA) guidelines from 2009 recommend to remove a long-term CVC in patients with a Gram-negative CLABSI (excl. *Pseudomonas aeruginosa* where immediate removal is indicated), such as *Enterobacterales,* in case of persistent bacteremia or severe sepsis despite antibiotic (systemic and lock) therapy. They classify the strength of their recommendation as "poor." They additionally state that for pediatric patients, the benefits of removal should carefully be weighed against the difficulty of inserting a new CVC.[8] Evidence for the use of antibiotic lock therapy (ALT) for salvage in pediatric oncology patients is still scarce.[9,10] Salvage treatment with systemic antibiotic treatment (SAT) over the CVC is therefore, in the majority of cases, the first treatment method of choice for *Enterobacterales* CLABSIs. Unsuccessful salvage treatment, however, can potentially lead to uncontrolled infection, discontinuation of the oncologic treatment, deterioration of the clinical status of the patient, ICU admissions and sometimes even death due to sepsis.[11]

Successful salvage rates for multiple micro-organisms have previously been investigated in a variety of patient populations.[12–21] However, no studies were identified investigating the outcome of salvage treatment with SAT only for CLABSIs caused by *Enterobacterales* in pediatric oncology patients. The aim of this study was therefore to determine whether salvage treatment with SAT can be safely and effectively achieved after the diagnosis of a CLABSI caused by *Enterobacterales* in pediatric oncology patients.

MATERIALS AND METHODS

Study Design and Participants

This retrospective study included all consecutive oncology and stem cell recipient patients with an *Enterobacterales* positive blood culture, cultured in the Princess Máxima Centre for Pediatric Oncology, Utrecht, the Netherlands, between April 2015 and July

2022. Since 2018, all pediatric oncology care in the Netherlands has been centralized at this hospital.

Eligible patients were identified from *Enterobacterales* positive blood culture lists of the microbiologic laboratory system (CliniSys GLIMS, Gent, Belgium) of our hospital. Patients were screened for eligibility if they and/or their parents/legal guardians gave their written informed consent for the use of their data for research purposes. Inclusion criteria were: oncologic diagnosis or stem cell recipient treated in our hospital, and a CVC in situ during the *Enterobacterales* positive blood culture collection. Exclusion criteria were: multiple CVCs in situ at the onset of the positive blood culture episode, an *Enterobacterales* positive blood culture episode already included in the study in the last 60 days, and essential data (ie, date or reason for CVC removal) missing for analysis. All patients were followed up from the date of blood culture collection 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 guidelines for cohort studies was maintained throughout this study.[22]

Outcomes and Data Collection

The primary outcome of this study was the cumulative incidence of an event at 60 days after *Enterobacterales* blood culture collection for patients where salvage treatment was attempted for an *Enterobacterales* CLABSI (definition described below). Events were defined as CVC removal, ICU admission or death related to the primary episode.

Secondary outcomes were the incidence of immediate CVC removal, relapse, reinfection, ICU admission and death related to the primary CLABSI episode in the 60 days after *Enterobacterales* blood culture collection. Furthermore, the time to events since blood culture collection were recorded.

All outcomes were also described for all *Enterobacterales* BSI episodes (ie, positive blood culture with an *Enterobacterales*; CLABSI and non-CLABSI episodes).

Furthermore, the patient files were retrospectively assessed for patient characteristics (age, gender and underlying diagnosis), CVC characteristics (insertion and removal date, catheter type, lumen size/number, access vein, reason for removal) as well as risk factors for the occurrence of events (stem cell transplantation 30 days prior to BSI onset, stem cell transplantation >30 days prior to BSI onset and gastro-intestinal graft vs. host disease during episode, neutropenia at BSI onset and adequate empirical antibiotic treatment). If data was not explicitly reported in the patient files, this was reported as missing data.

Definitions

Salvage treatment was defined as antibiotic treatment started upon *Enterobacterales* blood culture determination in patients where immediate CVC removal was determined as avoidable at the discretion of the treating physician. Immediate removal was defined as CVC removal within 48 hours after *Enterobacterales* blood culture determination where salvage treatment was not attempted at the discretion of the treating physician.

CLABSI was defined following the CLABSI criteria of the Centers for Disease Control and Prevention, which are the preferred criteria for pediatric oncology patients since peripheral blood cultures, which are required for diagnosis by other known criteria, are rarely obtained in this patient group.[23] A CLABSI was scored if the patient met 1 of the following criteria: (1) the patient had a recognized pathogen cultured from ≥1 blood cultures or (2) the patient had at least 1 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 hours on the date of the event, if no CLABSI with the same micro-organism was scored in the past 2 weeks (infection relapse time frame), if the presence of a mucosal barrier injury-laboratory confirmed bloodstream infection (MBI-LCBI) was excluded, and if the pathogen cultured was not related to an infection at another site. An MBI-LCBI was scored if only intestinal organisms from the MBI organism list were cultured and the patient met 1 of the following criteria: (1) allogeneic stem cell transplant recipient within the past year with documented grade III/IV gastro-intestinal graft versus host disease or diarrhea of ≥1 L or more in 24 hours during the same hospitalization period as the positive blood culture or (2) neutropenic on 2 separate days with an absolute neutrophil count of <500 cells/mm^3 within 3 days before and after the positive blood culture.[4,23]

CVC removal, pediatric intensive care unit (PICU) admission and/or death were scored as related to the primary episode if the *Enterobacterales* BSI was noted as the reason for the event, or was a contributing factor as determined by an infectious disease specialist (T.W.) based on the electronic patient files.

A relapse was defined as the isolation of the same micro-organism (ie, the same species and resistance pattern) after finishing appropriate antibiotic treatment (ie, antibiotics for which the micro-organism is sensitive) for the primary episode without a negative blood culture control being obtained in between. A reinfection was defined as the isolation of the same micro-organism after finishing appropriate antibiotic treatment for the primary episode and where a negative blood culture control was obtained in between.

The presence of neutropenia was defined as a neutrophil granulocyte count of less than 0.5×10^9/L on at least 2 separate days, collected within a 7-day time period. Local infection and/or irritation was defined as redness, pain, purulent drainage and hematoma on the skin surrounding CVC exit-site detected by visual inspection or through positive exit-site culture. Thrombosis of the CVC was diagnosed by radiologic imaging.

Infection Guidelines of the Princess Máxima Centre for Pediatric Oncology

In patients with fever in neutropenia, empirical SAT over the CVC lumen was started; that is, ceftazidime (with vancomycin in case of severe mucositis, high-dose cytarabine treatment, hemodynamic instability, exit-site redness or fever after flushing the CVC), or another antibiotic such as meropenem in case of colonization with ceftazidime-resistant Gram-negative bacteria. In patients with fever without neutropenia, the treating physicians carefully consider if SAT is necessary. If SAT is deemed necessary and no clear focus is present, a combination of amoxicillin/clavulanic acid and gentamicin, or ceftriaxone is given. When indicated, antibiotic treatment was tailored after identification and susceptibility testing results of the pathogen were obtained. The choice between immediate CVC removal or salvage treatment was made based on the discretion of the infectiologist, oncologist and surgeon, taking into account the IDSA guidelines.[8] Immediate removal (ie, within 48 hours after blood culture determination after which salvage with SAT was not attempted) was deemed necessary if a *Staphylococcus aureus*, *P. aeruginosa*, fungi, mycobacteria, *Acinetobacter baumannii* or *Stenotrophomonas maltophilia* next to the *Enterobacterales* was cultured, or in case of severe sepsis. After salvage treatment was started, removal was deemed necessary in case of severe sepsis, when blood cultures remained positive, or when the symptoms persisted after 72 hours of appropriate antibiotic therapy.[8] Antibiotic treatment was switched to oral antibiotics whenever deemed possible and safe. ALT is not used in our hospital due to the scarcity of evidence and recommendations for pediatric oncology patients.[9,10]

Statistical Analysis

Categorical data were presented as contingency tables; that is, frequencies and percentages. For continuous data summary statistics of the median, mean, minimum–maximum, first quartile-third quartile, standard deviation, were presented. Different episodes within 1 patient were seen as independent. The cumulative incidence of an event (ie, removal, ICU admission or death) from *Enterobacterales* blood culture collection was estimated by using a competing risk model, with CVC removal or death due to non-(CLA) BSI-related reasons as competing events.[24,25] To study the association between risk factors and the hazard of an event, a cause-specific Cox proportional hazard regression model was estimated. Prognostic factors incorporated in the model were based on known risk factors[4–6,26–29]: diagnosis (hematologic malignancies/lymphomas vs. solid tumors and benign stem cell recipients), CVC type (tunneled external CVC vs. Totally Implantable Venous Access Port and nontunneled CVC), neutropenia at BSI onset (no vs. yes) and adequate empirical antibiotics (yes vs. no). Data was analyzed using IBM SPSS statistics (version 26.0.0.1) and R software environment (version 1.3.1093) by using the cmprisk library.[30,31]

RESULTS

In total 110 *Enterobacterales* positive blood culture episodes were identified of which 15 (14%) were excluded based on the in- and exclusion criteria, see inclusion flow diagram in Figure 1. This resulted in the inclusion of 95 (86%) episodes which were observed in 82 patients. Immediate removal was deemed necessary in 12 (13%) of these episodes and salvage treatment was attempted in 83 (87%). Of these 83 episodes where salvage was attempted with systemic antibiotics, 45 (54%) episodes met the CLABSI criteria, 30 (36%) met the MBI-LCBI criteria and 8 (10%) were classified as a BSI due to other reasons.

The baseline characteristics of the patients and CVCs included in this study are described in Table 1. Many patients receiving salvage treatment were diagnosed with a solid tumor (42%), received a tunneled external CVC (51%) or a totally implantable venous access device (42%), and their CVCs were in situ for a median length of 113 days. During the 83 salvage treatment episodes, systemic antibiotic salvage treatment was given for a median of 10 (IQR: 4) days for the primary episode.

Escherichia coli (37%), *Enterobacter cloacae* complex (17%) and *Klebsiella pneumoniae* (12%) were the most cultured isolates (see Table, Supplementary Digital Content 1, http://links.lww.com/INF/F255).

The cumulative incidence of the primary endpoint/events at 60 days was 64.4% [95% confidence interval (CI): 48.3–76.7] for CLABSIs (Fig. 2A) and 53.0% (95% CI: 41.7–63.1) for BSIs (Fig. 2B).

ICU admission or death related to the primary BSI was not observed after the episodes where the CVC was immediately removed. After CLABSI *Enterobacterales* episodes where salvage treatment (N = 45) was attempted, the following events related to the primary episode were observed: 27 (60%) CVC removals, 7 (16%) PICU admissions and 1 (2%) death. Furthermore, 6 (13%) relapses and 2 (4%) reinfections were observed, which in all cases required CVC removal. No children were admitted to the PICU or died due to relapses or reinfections. Of all CLABSI *Enterobacterales* events (N = 29), 11 (35%) events occurred more than 10 days after the start of the primary episode. Of these 11 events, 9 (82%) occurred after adequate antibiotic treatment for the primary episode was stopped, 1 (9%) occurred during adequate antibiotic treatment for the primary episode and 1 (9%) occurred after a primary episode that was never adequately treated. Symptoms of these events were observed after a median of 8 (Q1–Q3: 1–32) days after adequate treatment for the primary episode was stopped. These results are described for all and CLABSI *Enterobacterales* episodes where salvage treatment was given in Table 2. Including also the 12 immediate removal patients (N CLABSI = 56 and N BSI = 95) and counting these removals as an event, 40 (71.4%) and 56 (58.9%) events occurred during the follow-up in the *Enterobacterales* CLABSI and BSI group, respectively.

No notable difference in the presence of a thrombosis or local infection during episodes with and without a BSI-related event were observed (see Table, Supplementary Digital Content 2, http://links.lww.com/INF/F256).

No risk factors were significantly associated with the hazard for both CLABSIs and BSIs (see Table 3 and Table, Supplementary Digital Content 3, http://links.lww.com/INF/F257, respectively).

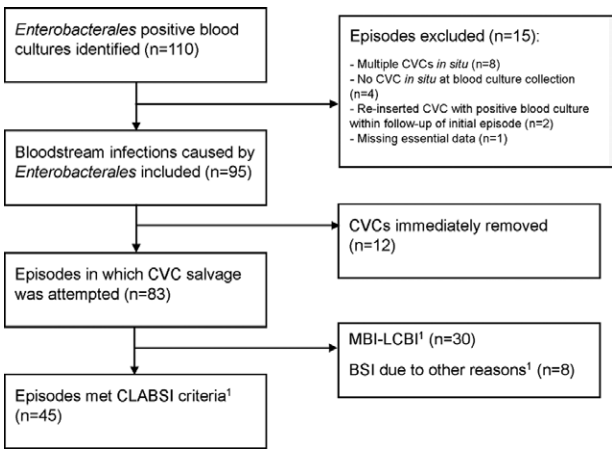

FIGURE 1. Flow diagram of all study participants. [1]Centers for Disease Control and Prevention. BSI indicates bloodstream infection; CLABSI, central line-associated bloodstream infection; CVC, central venous catheter; MBI-LCBI, mucosal barrier injury-laboratory confirmed bloodstream infection.

DISCUSSION

In this study, the cumulative incidence of an event at 60 days after salvage with antibiotics for the treatment of *Enterobacterales* CLABSIs and BSIs in pediatric oncology patients is high. Furthermore, severe sepsis requiring PICU admission appeared to be a common complication of *Enterobacterales* CLABSIs.

The IDSA guidelines only recommend CVC removal for CLABSIs caused by *Enterobacterales* in case of severe sepsis or persisting infections.[8] Benefits of CVC salvage are continuity of care and avoidance of general anesthesia and vascular damage. However, the results of this study suggest that, in most cases, CVC removal at a certain point was unavoidable. Delaying the decision to remove the CVC, can have significant consequences regarding the clinical status of the children; that is, severe sepsis requiring PICU admission and possibly even resulting in death. PICU admission and death were in this study not observed in the patients where the CVC was immediately removed, which further suggests that this might be avoidable by immediately removing the CVC upon *Enterobacterales* CLABSI diagnosis.

When only *Enterobacterales* CLABSIs were included in the analyses, the cumulative incidence at 60 days increased from 53.0% (95% CI: 41.7–63.1) to 64.4% (95% CI: 48.3–76.7). This difference can be explained by the inclusion of BSIs originating

TABLE 1. Baseline Characteristics

		Salvage Treatment (n = 83)				Immediate Removal (n = 12)	
		Total (n = 83)		CLABSI (n = 45)			
Age at blood culture collection*, median (min-max)		4 (0–19)		3 (0–19)		4 (0–6)	
Gender*, n (%)	Female	35	42.2%	17	37.8%	4	33.3%
	Male	48	57.8%	28	62.2%	8	66.7%
Diagnosis*, n (%)	Solid tumor	38	45.8%	26	57.8%	9	75.0%
	Hemato-oncology and lymphomas	40	48.2%	15	33.3%	2	16.7%
	Benign stem cell recipient	5	6.0%	4	8.9%	1	8.3%
CVC-days, median (min-max)		113 (2–1.276)		100 (2–647)		95 (4–384)	
CVC type, n (%)	Tunneled external CVC	42	50.6%	28	62.2%	8	66.7%
	TIVAD	35	42.2%	12	26.7%	2	16.7%
	Nontunneled CVC	2	2.4%	2	4.4%	2	16.7%
	PICC-line	4	4.8%	3	6.7%	0	0.0%
Lumen number, n (%)	Single	38	45.8%	15	33.3%	4	33.3%
	Double	39	47.0%	29	64.4%	6	50.0%
	Triple	6	7.2%	1	2.2%	2	16.7%
Vein, n (%)	Jugular	62	74.7%	30	66.7%	9	81.8%
	Subclavian	11	13.3%	6	13.3%	2	18.2%
	Femoral	1	1.2%	1	2.2%	0	0.0%
	Brachial	3	3.6%	2	4.4%	0	0.0%
	Basilic	2	2.4%	2	4.4%	0	0.0%
	Missing	4	4.8%	4	8.9%	0	0.0%
Side, n (%)	Left	17	20.5%	9	20.0%	5	41.7%
	Right	62	74.7%	32	71.1%	7	58.3%
	Missing	4	4.8%	4	8.9%	0	0.0%
Stem cell recipient, n (%)	<30 days before BSI	6	7.2%	2	4.4%	0	0.0%
	>30 days before BSI and gastro-intestinal GvHD during episode	5	6.0%	3	6.7%	0	0.0%
	None of the above	71	85.5%	39	86.7%	12	100.0%
	Missing	1	1.2%	1	2.2%	0	0.0%
Neutropenia $<0.5 \times 10^9$/L at BSI onset, n (%)	No	47	56.6%	38	84.4%	10	83.3%
	Yes	36	43.4%	7	15.6%	1	8.3%
	Missing	0	0.0%	0	0.0%	1	8.3%
Signs of local infection, n (%)	No	62	74.7%	32	71.1%	7	58.3%
	Yes	20†	24.1%	13	28.9%	5	41.7%
	Missing	1	1.2%	0	0.0%	0	0.0%
Signs of thrombosis, n (%)	No	10	12.0%	5	11.1%	1	8.3%
	Yes	4	4.8%	3	6.7%	0	0.0%
	No radiologic imaging	69	83.1%	37	82.2%	11	91.7%
Empirical antibiotics adequate‡, n (%)	Yes	72	86.7%	38	84.4%	NA	NA
	No, adjustment required after antibiogram was available	11	13.3%	7	15.6%	NA	NA
Days of salvage antibiotic treatment, median (IQR)		10 (4)		10 (2)		NA	

*Data described per episode, in total 95 episodes in 82 patients were included.

†During 7 episodes, signs of local infection were observed, but following the CLABSI criteria a mucosal-barrier injury laboratory confirmed bloodstream infection was scored.

‡Adequate empirical antibiotic treatment was defined as patients who received antibiotics directly after the start of the episode for which the *Enterobacterales* that was eventually identified was susceptible.

BSI indicates bloodstream infection; CLABSI, central line-associated bloodstream infection; CVC, central venous catheter; GvHD, graft versus host disease; NA, not applicable; PICC, peripherally inserted central catheter; TIVAD, totally implantable venous access device.

from other sources than the CVC (eg, *E. coli* from the urinary tract or translocation due to a weakened mucosal barrier in the gut), in which the CVC may not have become colonized or infected.

Previously performed comparable studies investigating the safety and efficacy of salvage treatment in pediatric oncology patients for *Enterobacterales* BSI were not identified. Nazemi et al.[12] reported an unsuccessful salvage rate of 55% for *Enterobacterales* BSIs in neonates with mostly peripherally inserted central catheters. Furthermore, a meta-analysis from 2022 including 7 studies, reported a pooled unsuccessful salvage rate of 53% for Gram-negative CLABSIs.[20] However, the results were highly heterogeneous (I^2 95%), a variety of patient groups and CVC types were included, some studies used ALT as treatment, and the definition of catheter salvage and which Gram-negative bacteria were included was unclear.[13–20] Finally, Ashkenzani-Hoffnung et al. (2020)[32] reported an unsuccessful salvage rate of 0% (N = 16) for *Enterobacterales* CLABSIs in pediatric oncology patients with the additional use of ALT.[21] Comparable relapse and/or reinfection rates of 7%–14% have been reported previously for Gram-negative CLABSIs.[12,20] No studies investigating the incidence rate of ICU admission after salvage treatment due to *Enterobacterales* CVC-related BSI were identified. Comparable mortality rates of 4%–7% after salvage treatment (with/without ALT) for *Enterobacterales* CVC-related BSI were reported in previous studies.[12,17]

The cumulative incidence estimated in this study is higher than the 1 expected by clinicians based on the scarce previously published literature.[12–20] Differences with previous literature can be explained by multiple reasons. First, successful salvage was defined taking into account the clinical status of the patient and not solely CVC removal or reinfections as done by previous studies.[12–20] Second, this study used the CLABSI criteria, whereas other studies included all positive blood culture episodes.[12] Third, this study

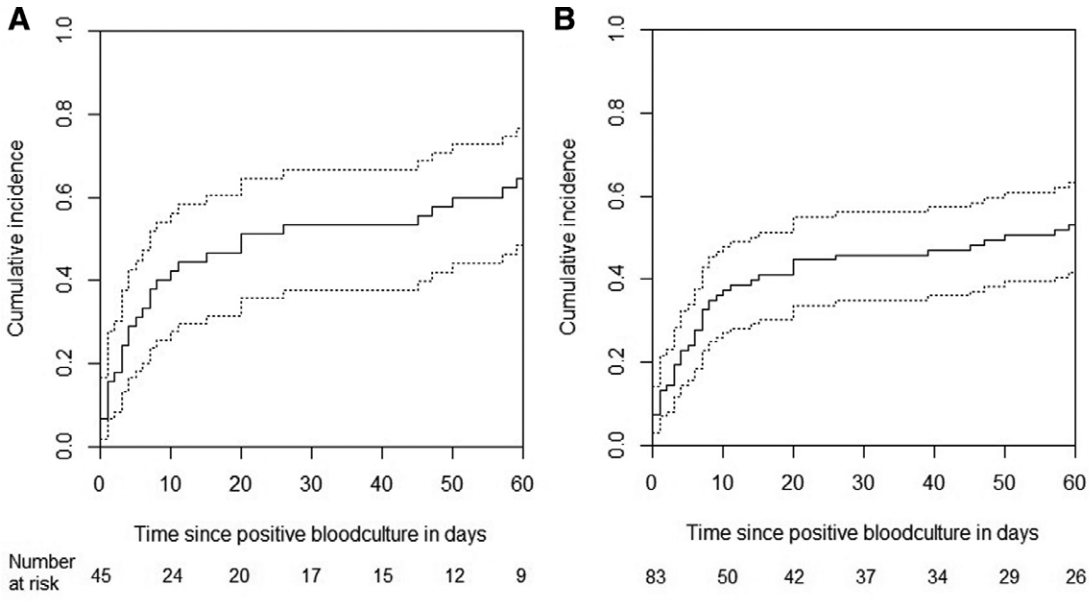

FIGURE 2. Cumulative incidence of an event from Enterobacterales blood culture collection for patients receiving salvage treatment for (A) an Enterobacterales CLABSI and (B) an Enterobacterales BSI. Day 0 represents positive blood culture collection followed by the start of salvage treatment. Event = removal, intensive care unit admission, or death related to the primary CLABSI/BSI. Three events occurred directly after blood culture collection for CLABSIs, these episodes all concerned direct intensive care unit admissions. Six events occurred directly after blood culture collection for BSIs, these episodes all concerned direct intensive care unit admissions. BSI indicates bloodstream infection; CLABSI, central line-associated bloodstream infection.

TABLE 2. Events, Relapses and Reinfections

		Salvage Treatment (n = 83)	
		Total BSI (n = 83)	CLABSI (n = 45)
		N (%) or Median (Q1–Q3)	N (%) or Median (Q1–Q3)
CLABSI/BSI-related events	No	39 (47.0%)	16 (35.6%)
	Yes	44 (53.0%)	29 (64.4%)
	Days until	6 (2–15)	6 (2–20)
CVC removal related to BSI	Yes	39 (47.0%)	27 (60.0%)
	Days until	7 (3–20)	7 (3–20)
PICU admission related to BSI	Yes	13 (15.7%)	7 (15.6%)
	Days until	1 (0–1)	1 (0–1)
Death related to BSI	Yes	4 (4.8%)	1 (2.2%)
	Days until	3 (1–6)	1 (1–1)
CLABSI/BSI-related events 10 days after start primary episode	Yes	14a (16.8%)	11a (24.4%)
	Days from stop primary antibiotics until first symptoms of event	8 (1–32)	8 (1–32)
Relapse of primary infection	Yes	6 (7.2%)	6 (13.3%)
	Days until	20 (18–44)	20 (18–44)
	Requiring CVC removal	6 (7.2%)	6 (13.3%)
Reinfection after primary infection	Yes	5 (6.0%)	2 (4.4%)
	Days until	32 (32–43)	45 (43–47)
	Requiring CVC removal	4 (4.8%)	2 (4.4%)

aDuring 1 episode no adequate antibiotics were given for the primary episode, and during another episode antibiotics for the primary episode were still continuously given during the start of the symptoms of the event after 10 days.

BSI indicates bloodstream infection; CLABSI, central line-associated bloodstream infection; CVC, central venous catheter; PICU, pediatric intensive care unit; Q1, first quartile; Q3, third quartile. Bloodstream infection-related events, relapses and reinfections.

focused on *Enterobacterales* only; including other Gram-negative micro-organisms might have resulted in higher success rates, due to a lower pathogenicity of the micro-organisms.[13–20] Fourth, some of the previously performed studies used ALT in addition to CVC salvage treatment. ALT seems promising in improving the successfulness of CVC salvage treatment in pediatric oncology patients but further research is needed to determine its safety and efficacy.[9,10,17,20,21]

TABLE 3. Estimated Cause-Specific Hazard Ratio Along With the 95% Confidence Interval From a Cox Model for all CLABSIs

	Salvage Treatment Episodes That Met CLABSI Criteria (n = 45)
	Risk of event
Risk factors	HR (95% CI)
Diagnosis	
Hematologic malignancy/lymphoma	1
Solid tumor	0.60 (0.12–3.12)
Benign stem cell recipient	1.16 (0.24–5.72)
CVC type	
Tunneled external CVCs	1
TIVAP	1.12 (0.23–5.50)
Nontunneled CVCs	1.42 (0.26–7.69)
Neutropenia at BSI onset	
No	1
Yes	1.09 (0.28–4.29)
Empirical antibiotics adequate	
Yes	1
No	1.86 (0.41–8.35)

Event = removal, intensive care unit admission or death related to the primary CLABSI. Nontunneled CVCs = PICC and nontunneled CVCs.

BSI indicates bloodstream infection; CI, confidence interval; CLABSI, central line-associated bloodstream infection; HR, hazard ratio; PICC, peripherally inserted central catheter; TIVAD, totally implantable venous access device; TIVAP, totally implantable venous access port.

Strengths of this study are the relatively large sample size for a study in pediatric oncology, the use of a comprehensive definition of treatment failure (ie, taking into account the clinical status of patients and including also late treatment failure) and the strict inclusion and excluding criteria used. Limitations of this study are the retrospective study design, and the small sample size due to which comparisons between groups based on risk factors was difficult. Furthermore, CVC removal might have been avoidable in some cases where the CVC was extracted immediately, since the decision to remove the CVC was made based on the discretion of the infectiologist, oncologist and/or surgeon. Finally, the CLABSI criteria might result in an under- or overestimation of the actual BSI caused by the CVC. For pediatric oncology patients, however, the CLABSI criteria are currently the most suitable criteria since it does not require the results of peripheral blood cultures (which are rarely obtained in children).[33] In conclusion, salvage treatment with systemic antibiotics alone for *Enterobacterales* CLABSIs in pediatric oncology patients results in a high event rate. Immediate CVC removal appears recommendable for this patient group.

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