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ORIGINAL ARTICLE

Bloodstream infection in paediatric cancer centres—leukaemia and relapsed malignancies are independent risk factors

R. A. Ammann[1] · H. J. Laws[2] · D. Schrey[3] · K. Ehlert[3] · O. Moser[4] · D. Dilloo[4] · U. Bode[4] · A. Wawer[5] · A. Schrauder[6] · G. Cario[6] · A. Laengler[7] · N. Graf[8] · R. Furtwängler[8] · A. Simon[8]

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Abstract In a prospective multicentre study of bloodstream infection (BSI) from November 01, 2007 to July 31, 2010, seven paediatric cancer centres (PCC) from Germany and one from Switzerland included 770 paediatric cancer patients (58 % males; median age 8.3 years, interquartile range (IQR) 3.8–14.8 years) comprising 153,193 individual days of surveillance (in- and outpatient days during intensive treatment). Broviac catheters were used in 63 % of all patients and Ports in 20 %. One hundred forty-two patients (18 %; 95 % CI 16 to 21 %) experienced at least one BSI (179 BSIs in total;

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R. A. Ammann and H. J. Laws contributed equally to this work.

✉ A. Simon
Arne.Simon@uks.eu

R. A. Ammann
Roland.Ammann@insel.ch

H. J. Laws
Laws@med.uni-duesseldorf.de

D. Schrey
Dominik.Schrey@rmh.nhs.uk

K. Ehlert
ehlertk@mednet.uni-muenster.de

O. Moser
olga.moser@ukb.uni-bonn.de

D. Dilloo
dagmar.dilloo@ukb.uni-bonn.de

U. Bode
udo.bode@ukb.uni-bonn.de

A. Wawer
angela.wawer@lrz.tu-muenchen.de

A. Schrauder
m.schrappe@pediatrics.uni-kiel.de

G. Cario
g.cario@pediatrics.uni-kiel.de

A. Laengler
a.laengler@gemeinschaftskrankenhaus.de

N. Graf
norbert.graf@uniklinikum-saarland.de

R. Furtwängler
rhoikos.furtwaengler@uniklinikum-saarland.de

[1] Department of Paediatrics, University of Bern, Bern, Switzerland

[2] Department of Paediatric Oncology, Haematology and Clinical Immunology, Medical Faculty, Center of Child and Adolescent Health, Heinrich-Heine-University, 40225 Düsseldorf, Germany

[3] Infectious Disease Research Program Centre for Bone Marrow Transplantation and Department of Paediatric Haematology/ Oncology University Children's Hospital, Muenster, Germany

[4] Paediatric Haematology and Oncology, Children's Hospital Medical Centre, University of Bonn, Bonn, Germany

[5] Department of Paediatrics, Technische Universität München and Paediatric Oncology Center, Munich, Germany

[6] Department of Paediatrics at the Christian-Albrechts-University of Kiel, University Medical Center Schleswig-Holstein, Kiel, Germany

[7] Department of Paediatric and Adolescent Medicine, Gemeinschaftskrankenhaus Herdecke, Herdecke, Germany

[8] Paediatric Oncology and Haematology, University Children's Hospital, Homburg, Saar, Germany

bacteraemia 70 %, bacterial sepsis 27 %, candidaemia 2 %). In 57 %, the BSI occurred in inpatients, in 79 % after conventional chemotherapy. Only 56 % of the patients showed neutropenia at BSI onset. Eventually, patients with acute lymphoblastic leukaemia (ALL) or acute myeloblastic leukaemia (AML), relapsed malignancy and patients with a Broviac faced an increased risk of BSI in the multivariate analysis. Relapsed malignancy (16 %) was an independent risk factor for all BSI and for Gram-positive BSI.

Conclusion: This study confirms relapsed malignancy as an independent risk factor for BSIs in paediatric cancer patients. On a unit level, data on BSIs in this high-risk population derived from prospective surveillance are not only mandatory to decide on empiric antimicrobial treatment but also beneficial in planning and evaluating preventive bundles.

What is Known:
- *Paediatric cancer patients face an increased risk of nosocomial bloodstream infections (BSIs).*
- *In most cases, these BSIs are associated with the use of a long-term central venous catheter (Broviac, Port), severe and prolonged immunosuppression (e.g. neutropenia) and other chemotherapy-induced alterations of host defence mechanisms (e.g. mucositis).*

What is New:
- *This study is the first multicentre study confirming relapsed malignancy as an independent risk factor for BSIs in paediatric cancer patients.*
- *It describes the epidemiology of nosocomial BSI in paediatric cancer patients mainly outside the stem cell transplantation setting during conventional intensive therapy and argues for prospective surveillance programmes to target and evaluate preventive bundle interventions.*

Keywords Paediatric cancer patients · Bloodstream infection · Nosocomial infection · Prospective surveillance · Oncoped study

Abbreviation

ALL	Acute lymphoblastic leukaemia
AML	Acute myeloblastic leukaemia
BSI	Bloodstream infection
CNS	Central nervous system
CoNS	Coagulase-negative staphylococci
CVAD	Long-term central venous catheter (Broviac or Port type)
ESBL	Extended spectrum beta-lactamase
HAI	Healthcare-associated infection
ICU	Intensive care unit
MRSA	Methicillin-resistant *Staphylococcus aureus*
NI	Nosocomial infection
PCC	Paediatric cancer centre
STRV	Viridans streptococci
VRE	Vancomycin-resistant *Enterococcus*

Introduction

During intensive treatment, paediatric patients with cancer face an increased risk of healthcare-associated infection (HAI) [5, 47, 51]. The most important HAI in paediatric oncology centres is bloodstream infection (BSI) [2–4, 33]. More than 80 % of all paediatric patients have a long-term central venous catheter (CVAD; Broviac or Port type) in use to alleviate anticancer as well as supportive treatment and blood sampling [15]. A significant proportion of all BSIs in paediatric cancer patients is associated with the use of CVADs. Prospective surveillance of BSI represents an important component of the comprehensive *care bundle* implemented for the prevention of HAI in paediatric cancer patients [31].

Herein, we report the results of a prospective multicentre surveillance study on BSI incidence and risk factors in paediatric cancer patients. The study was performed in eight centres in Germany and Switzerland. The Oncoped module has been developed more than 10 years ago [51] by paediatric oncologists, infectious disease consultants and hospital epidemiologists to support paediatric oncology centres (PCCs) in performing prospective surveillance of nosocomial infections.

Materials and methods

Oncoped module, inclusion criteria

The methods of the Oncoped module have been described in previous publications [34, 47, 48, 51, 52, 54]. Data entry into the intranet-based documentation tool[1] was activated on November 01, 2007 and closed on July 31, 2010. The period of participation was left at the discretion of the local investigator (paediatric oncologist) with the condition to participate for at least 6 consecutive months. At the end of the study, all bloodstream infections reported by the participating paediatric oncology units were compared with the microbiology results derived from the corresponding local microbiology laboratories in seven of eight centres. A single BSI was identified, which had been missed in one centre and added to the final database. Without age restriction, all patients treated in the participating paediatric oncology unit with newly diagnosed or relapsed cancer were eligible for inclusion into the surveillance project irrespective of their peripheral leukocyte count [18, 19]. The period of surveillance (days of surveillance) in an individual patient was terminated after the completion of conventional intensive treatment (chemotherapy, radiation or both), e.g. at the beginning of maintenance outpatient treatment in patients with acute lymphoblastic leukaemia. The Oncoped module allows for the inclusion of patients during

[1] Internet realisation: MedSurv GmbH, M. Hamann, Nidderau, http://www.hamann-software.de.

and after autologous or allogeneic stem cell transplantation, although this is not the core population of the study [47].

Objectives and outcome criteria

The main objective of this surveillance study was to describe the epidemiology of bloodstream infections (BSI) in paediatric cancer patients. The main outcome criteria were the proportion of patients with at least one BSI, the distribution of pathogens detected in blood cultures; onset during in- or outpatient treatment; last treatment before the onset of BSI; clinical severity of the BSI according to Goldstein et al. [27]; allocation of the BSI as catheter-related, catheter-associated or secondary to another focus; removal of the CVAD; and attributable mortality. Incidence rates were calculated (BSI per 1000 inpatient treatment days and per 1000 days at risk). We defined *days at risk* as the cumulative number of days of prospective surveillance in an individual patient. Thus, all BSIs were included, independent from the patient's location at the onset of symptoms (in- or outpatient). Primary data were used to identify factors associated with an increased risk of BSI in uni- and multivariate analysis.

Definitions

Fever was defined as body temperature >38.5 °C for at least 4 h or once >39 °C. Neutropenia referred to an absolute number of granulocytes $\leq 0.5 \times 10^9$/L or of leukocytes $\leq 1.0 \times 10^9$/L without differential counts available. Bloodstream infections were included irrespective of the actual neutrophil count of the patient.

We defined bacteraemia as growth of a bacterial pathogen in blood culture derived from a patient with fever or other signs of infection. Patients with bacteraemia and systemic inflammatory response syndrome were allocated to the clinical severity grade *sepsis* according to paediatric consensus criteria [27].

At least two positive blood culture bottles and a positive clinical judgement by the attending paediatric oncologist [41] were stipulated to accept coagulase-negative staphylococci (CoNS) as pathogens in this clinical context.

CVAD-associated BSI referred to a patient with BSI, a CVAD in use and no evidence of an alternative focus of infection. To allocate the BSI to the category, *CVAD-related infection* blood cultures taken from the device had to be subsequently or repeatedly positive for longer than 72 h or the bacteria were detected on the catheter tip after removal of the device. In case of patients with a different microbiologically or clinically defined primary focus of infection, the corresponding BSI was allocated as *secondary bacteraemia* (including bacterial translocation from the gut in case of a severe chemotherapy-induced mucositis).

Blood culture policies and processing

In this study, two blood culture samples (aerobic and anaerobic) were collected from patients with fever under aseptic conditions and after disinfection of the CVAD hub(s) from all lumina of the CVAD before administering a first dose of intravenous antibiotics. Peripheral venous blood cultures were collected after skin disinfection in patients without a CVAD. In most centres, the diagnostic workup of patients presenting with fever and neutropenia did not include the comparative investigation of simultaneously sampled central and peripheral blood cultures in terms of differential time to positivity [25]. According to the guidelines of the German Society of Paediatric Oncology and Haematology [8, 35], taking simultaneous central and peripheral cultures is not mandatory in febrile neutropenic patients. Collecting blood cultures through peripheral venous puncture is rare with paediatric oncology patients [24]. Blood cultures were processed using the BD BACTEC™ automatic detection system (Beckton Dickinson, Heidelberg) or BacT/ALERT™ (bioMerieux, Geneva), and species differentiation according to standard microbiological procedures.

Statistic analysis

Since continuous variables were not normally distributed, median and IQR (25–75. percentile) were calculated; differences in proportions were compared with chi-square test or Fisher's exact test when appropriate. The Mann-Whitney *U* test was performed to test the equality of continuous variables (SPSS, Version 16, Chicago, IL). Incidence rates with their exact 95 % confidence intervals were calculated. Six predefined characteristics were tested for associations with BSI: paediatric oncology centre, gender and age of the patient, underlying diagnosis, first illness versus relapsed malignancy and type of CVAD (Port vs. Broviac vs. no CVAD). For these tests, rate ratios and their 95 % confidence intervals (CI) were calculated using univariate and multivariate exact Poisson regression, stratified by centre, and with days at risk (days of surveillance) as rate multiplier (StatXact 9.0 und LogXact 9.0, both from Cytel Software Inc., Cambridge, MA). For multivariate analysis, the stepwise forward variable selection procedure was used. All analyses were calculated as two-sided tests, and *p*-values <0.05 were considered to be statistically significant.

Ethical approval and registration

The study protocol was approved by the ethics committee of the Medical Faculty, University of Bonn. Informed consent to participate in the collection and anonymised analysis of surveillance data was obtained from patients or their parents according to local institutional policies. In some centres, healthcare legislation stipulates prospective surveillance of

healthcare-associated infections as mandatory for internal quality assurance [38, 55].

The Oncoped 2006 protocol was registered at www.clinicaltrials.gov (NCT00843804) before starting patient inclusion.

Results

Centres and patients

Eight paediatric cancer centres (PCCs) participated in the study, seven from Germany and one from Switzerland. The cumulative periods of participation comprise 55,523 inpatient treatment days and 153,193 individual days (419 years) of surveillance (in- and outpatient days during intensive treatment). The centres participated for a cumulative time of 179 months (median 25 months; min. 6 months, max. 32 months). In total, 770 paediatric cancer patients were included into the study population. Of these, 327 (42 %) were females and 443 (58 %) were males.

The median age at inclusion was 8.3 years (interquartile range (IQR); 3.8–14.8 years). In 123 patients (16 %), a relapse of the underlying malignancy was diagnosed. Table 1 shows the distribution of the primary diagnoses of the patients.

At least one Broviac CVAD was implanted in 482 patients (63 %) and at least one Port CVAD in 155 patients (20 %); 133 patients (17 %) did not have a CVAD in use. Figure 1 shows the proportions of the use of the different CVAD types in the participating PCCs.

Bloodstream infections and pathogens

During the surveillance period 142 patients (18.4 %; 95 %CI 16 to 21 %) experienced at least one BSI. In total, 179 BSIs were documented; 23 individual patients experienced two to four BSIs.

The total number of pathogens detected by blood cultures in patients with BSI was 193. Table 2 shows the distribution of the bacterial isolates, excluding non-tuberculous mycobacteria (NTM). None of the *Staphylococcus aureus* isolates showed in vitro methicillin-resistance (MRSA), one *Enterococcus faecium* isolate was in vitro resistant to vancomycin (VRE) and only two Gram-negative isolates displayed an extended spectrum beta-lactamase expression in vitro (ESBL; one *Escherichia coli*, one *Enterobacter cloacae*). Of all 179 BSI, 14 (7.8 %) were polymicrobial in origin.

Candida spp. were detected on five occasions (3 *C. parapsilosis*, 1 *C. albicans* and 1 *C. tropicalis*), NTM on two occasions and *Aspergillus fumigatus* (together with *S. aureus*) in 1 BSI. In 4 of 5 BSI caused by *Candida spp*., the fungal species was the only pathogen detected in blood culture; in the fifth event, *C. parapsilosis* was detected together with *Acinetobacter baumannii*. Thus, 4 of 179 BSI (2 %) were caused by *Candida spp*. as a single pathogen.

BSIs: epidemiologic characteristics

Fifty-seven percent of the patients were inpatients immediately before diagnosis of the BSI, and 43 % were outpatients since at least 72 h. In the majority of all patients (79 %), the BSI event was observed after conventional chemotherapy.

High-dose chemotherapy with autologous stem cell transplantation and allogeneic stem cell or bone marrow transplantation had been performed as anticancer treatment before the BSI event in 13 % of the patients and in 5 % of all cases, respectively. The remaining patients had received radiation or immunosuppressive/immunomodulating therapy.

In 56 % of all BSI, the patients showed severe neutropenia at the onset of symptoms. The clinical severity of 179 BSI was allocated by the attending paediatric oncologists as follows: bacteraemia 70.4 % (n=126), bacterial sepsis 27.4 % (n=49), candidaemia 1.1 % (n=2) and *Candida* sepsis 1.1 % (n=2). The item *neutropenia at the onset of the infection* correlated

Table 1 Number and proportion of primary diagnoses (n=770 patients)

Malignancy/disease	Number	Proportion (%)
Acute lymphoblastic leukaemia (ALL)	220	29
Acute myeloid leukaemia (AML)	40	5
Non-Hodgkin lymphoma	38	5
Hodgkin lymphoma	40	5
Solid tumour outside the central nervous system (CNS)	196	25
CNS tumour	98	13
Neuroblastoma	43	6
Immune deficiency syndrome	9	1
Myelodysplastic syndrome/severe aplastic anaemia	19	2
Others[a]	67	9

[a] For example, Langerhans cell histiocytosis, haemophagocytic lymphohistiocytosis, metabolic disease as indication for bone marrow transplantation

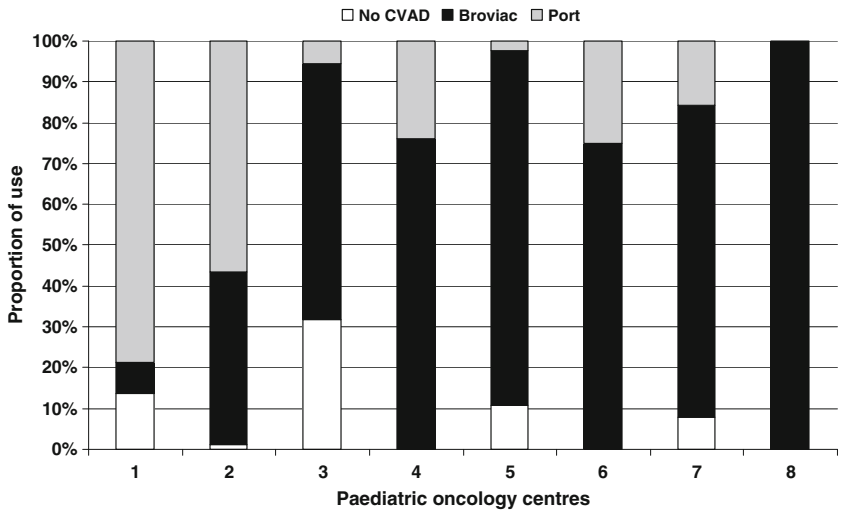

Fig. 1 Proportions of use for two different CVAD types (and no CVAD) in eight participating paediatric oncology centres

significantly with a higher propensity of sepsis in bacterial BSIs (n=175; p=0.045).

Tables 3 and 4 show the incidence and incidence rates (IR) of BSIs in the participating PCCs. The results for the eight PCCs showed significant differences in terms of all investigated parameters (Table 4). Eventually, the attending paediatric oncologists were asked to allocate the 179 BSI to three different categories. In n=27 (15.1 %), the BSI was *CVAD-related*, in n=74 (41.3 %), the BSI was *CVAD-associated*, and in n=78 (43.6 %), the BSI was classified as *secondary BSI*. Only one centre routinely used a taurolidine-containing antimicrobial CVAD lock solution to prevent CVAD-related BSIs. The role of taurolidine was not a primary issue of our investigation. In contrast to other studies [20, 29, 48], the comparison of the results from this single centre with the seven other centres in our study did not demonstrate a significant advantage in terms of a lower incidence rate of BSI/1000 days at risk.

Outcome of BSIs

Comparing BSIs caused by Gram-positive or Gram-negative bacterial pathogens, the median length of stay in the hospital and the median duration of antibiotic treatment did not show significant differences (15 vs. 14 days and 14 vs. 13 days, respectively). In contrast, clinical severity displayed a significant impact on both outcome parameters.

Patients with bacteraemia were treated as inpatients for a median of 13.5 days (with antibiotics for 12.3 days), while patients with sepsis were treated as inpatients for a median of 21.2 days (p=0.03) and with antibiotics for a median of 16.8 days (p=0.07).

Table 2 Cumulative number and proportion of 185 bacterial pathogens (100 %) detected in blood cultures of patients with bloodstream infection

Species Gram-positive	Number	Proportion (%)	Species Gram-negative	Number	Proportion (%)
CoNS	49	26	*Escherichia coli*	29	16
Streptococcus viridans	28	15	*Pseudomonas aeruginosa*	12	6
Staphylococcus aureus	16	9	*Enterobacter cloacae*	10	5
Enterococcus spp.	11	6	*Klebsiella pneumoniae*	4	2
Micrococcus luteus	6	3	*Klebsiella oxytoca*	2	1
Streptococcus pneumoniae	3	2	*Acinetobacter baumannii*	1	1
Corynebacterium spp.	3	2	*Chryseobacterium indologenes*	1	1
Bacillus cereus	2	1	*Citrobacter* spp.	1	1
Lactobacillus spp.	2	1	*Pseudomonas stutzeri*	1	1
Streptococcus pyogenes	1	1	*Pasteurella* spp.	1	1
Rothia mucilaginosa	1	1	*Salmonella* spp.	1	1
All Gram-positive	122	66	All Gram-negative	63	34.0

CoNS coagulase-negative *Staphylococci*

Table 3 Basic data from eight participating paediatric cancer centres (PCCss)

PCC	Months of prospective surveillance	Inpatient treatment (days)	In- and outpatient surveillance (days)	No. of patients	No. of patients with at least one BSI	No. of BSI
1	24	2721	9770	66	16	20
2	32	11,021	21,977	85	24	30
3	21	17,195	59,232	325	43	58
4	30	1129	4657	21	4	5
5	28	8358	17,664	84	22	28
6	6	1392	6007	32	6	6
7	26	12,673	32,736	139	22	26
8	12	1034	1150	18	5	6
Sum.	179	55,523	153,193	770	142	179

BSI bloodstream infection

In 14 BSI events (7.8 %), the CVAD was removed non-electively, causally related to the BSI. This was the case in 7 of 27 CVAD-related BSIs (26 %), in 4 of 74 CVAD-associated BSIs (5 %) and in 3 of 78 secondary BSIs (4 %).

BSI-related mortality of all 179 BSIs was 1.8 %; in three events, the BSI was causally related to a fatal outcome. One of the two BSIs caused by ESBL-producing Gram-negative pathogens took a fatal clinical course despite timely admission of the patient to the paediatric intensive care unit. The *E. cloacae* isolate derived from initial blood cultures showed in vitro resistance to the first-line treatment with piperacillin-tazobactam and gentamicin. The attending physicians received the results of in vitro testing 2 days after the patient had died on the ICU.

Further analysis of risk factors

Table 5 allocates the absolute number of BSIs to the different underlying diseases (Table 1). According to these results, the proportion of patients with at least one BSI was highest in patients with acute lymphoblastic leukaemia (ALL; 27 %) and acute myeloblastic leukaemia (AML; 48 %). The proportion of patients with at least one BSI in the paediatric transplant unit (no. 8 in Tables 3 and 4) was 28 %. Of all 142 patients with at least one BSI, patients with ALL accounted for 42 %, patients with AML for 13 % and patients with a solid tumour outside the CNS for 16 %.

Although patients with relapsed malignancy represented only 16 % of the total study population, 29 % (n=51) of all BSIs were observed in this subgroup. Accordingly, the proportion of patients with at least one BSI was significantly

Table 4 BSI incidence and incidence rates in eight participating PCCs[a]

PCC	Incidence[b]	95 % CI	No. of BSI/No. of patients	95 % CI	IR/1000 inpatient days	95 % CI	IR/1000 surveillance days	95 % CI
1	0.24	0.15 to 0.36	0.30	0.19 to 0.47	7.4	4.5 to 11.4	2.05	1.25 to 3.16
2	0.28	0.19 to 0.38	0.35	0.24 to 0.50	2.7	1.8 to 3.9	1.37	0.92 to 1.95
3	0.13	0.10 to 0.17	0.18	0.14 to 0.23	3.4	2.6 to 4.4	0.98	0.74 to 1.27
4	0.19	0.07 to 0.40	0.24	0.08 to 0.56	4.4	1.4 to 10.3	1.07	0.35 to 2.51
5	0.26	0.17 to 0.37	0.33	0.22 to 0.48	3.4	2.2 to 4.8	1.59	1.05 to 2.29
6	0.19	0.08 to 0.35	0.19	0.07 to 0.41	4.3	1.6 to 9.4	1.00	0.37 to 2.17
7	0.16	0.10 to 0.23	0.19	0.12 to 0.27	2.1	1.3 to 3.0	0.79	0.52 to 1.16
8	0.28	0.12 to 0.53	0. 33	0.12 to 0.73	5.8	2.1 to 12.6	5.22	1.92 to 11.36
Mean	0.22	0.16 to 0.21	0.23	0.20 to 0.27	3.2	2.8 to 3.7	1.17	1.00 to 1.35

BSI bloodstream infection, *PCCs* paediatric cancer centres, *IR* incidence rate

[a] Statistical analysis revealed significant differences between centres: incidence (Fisher-Freeman Halton test; p=0.01); no. of BSI/no. of patients (homogeneity of Poisson rates; p=0.021); IR/1000 inpatient days (homogeneity of Poisson rates; p=0.02)

[b] Proportion of patients with at least one BSI

Table 5 Number and proportion of bloodstream infections related to specific underlying diseases

Disease	Absolute number of BSI	Number of patients with at least one BSI	Proportion (%) of patients with at least one BSI
ALL	220	60	42
AML	40	19	13
Non-Hodgkin lymphoma	38	4	3
Hodgkin lymphoma	40	4	3
Solid tumour outside the central nervous system (CNS)	196	23	16
CNS tumour	98	14	10
Neuroblastoma	43	7	5
Immune deficiency syndrome	9	2	1
Myelodysplastic syndrome/severe aplastic anaemia	19	3	2
Others[a]	67	6	4
Sum	770	142	100

[a] For example, Langerhans cell histiocytosis, haemophagocytic lymphohistiocytosis, metabolic disease as indication for bone marrow transplantation

higher in patients with relapsed malignancy [102 of 647 patients with first diagnosis (16 %) vs. 39 of 123 (32 %) patients with relapse ($p<0.001$)]. These results prompted us to investigate a number of items, completely documented in all patients, in univariate and multivariate risk factor models (Tables 6 and 7). Interestingly, age at diagnosis and gender did not increase the risk of BSI. Eventually, patients with ALL or AML, relapsed malignancy and patients with a Broviac CVAD in use faced an increased risk of BSI in the multivariate analysis. In contrast to the two other items, relapsed malignancy was an independent risk factor for all BSIs and for Gram-positive BSIs, but not for Gram-negative BSIs.

Discussion

The study presented here is one of the most representative multicentre studies in this field in terms of the number of

Table 6 Excerpt of the univariate data analysis of the Oncoped 2006 results

Characteristic	Time (years)	BSI	Poisson rate of BSI (per year)		Test for homogeneity of Poisson rates[a]		
			Rate	95 % CI	Rate ratio	95 % CI	*p*
Gender							
Male	248	99	0.40	0.32 to 0.49	0.83	0.61 to 1.13	0.26
Female	171	81	0.47	0.38 to 0.59	Reference	–	–
Diagnosis							
ALL or AML	142	97	0.68	0.55 to 0.83	2.20	1.62 to 2.99	<0.001
Other diagnoses	278	83	0.30	0.24 to 0.37	Reference	–	–
Relapse status							
Nonrelapsed malignancy	337	125	0.37	0.31 to 0.44	Reference	–	–
Relapsed malignancy	82	55	0.68	0.50 to 0.87	1.80	1.28 to 2.51	<0.001
Age (per 10 years)	–	–	–	–	1.01	0.82 to 1.25	0.92
CVAD							
No CVAD	43	4	0.09	0.02 to 0.23	0.47	0.12 to 1.39	0.23
Port type	104	34	0.33	0.23 to 0.46	Reference	–	–
Broviac type	272	142	0.52	0.44 to 0.62	3.26	1.93 to 5.64	<0.001
CVAD lock solution							
No CVAD	43	4	0.09	0.02 to 0.23	0.20	0.07 to 0.56	0.002
Heparin	317	148	0.47	0.40 to 0.55	0.99	0.66 to 1.54	1.00
TauroLock™	59	28	0.47	0.31 to 0.68	Reference	–	–

[a] Test stratified per centre

Table 7 Characteristics with increased risk of BSI in multivariate analysis, referring to surveillance days in all patients (n=770)

BSI	Item	Odds ratio	95 % CI	p value
All BSI	ALL or AML	1.79	1.31 to 2.46	<0.001
	Relapsed malignancy	1.77	1.25 to 2.47	0.001
	Broviac CVAD[a]	3.27	1.87 to 5.83	<0.001
BSI Gram-positive	ALL or AML	1.69	1.15 to 2.49	0.007
	Relapsed malignancy	2.16	1.43 to 3.23	<0.001
	Broviac CVAD[a]	2.60	1.34 to 5.24	0.003
BSI Gram-negative	ALL or AML	2.27	1.31 to 4.00	0.003
	Broviac CVAD[a]	4.65	1.69 to 14.25	0.002

BSI bloodstream infection

[a] Port CVAD used as reference

participating centres (n=8), the number of patients included (n=770) and the total period of prospective surveillance (179 months; 55,523 inpatient treatment days and 153,193 individual days of surveillance). In contrast to our previous studies [47, 51], the main focus of the Oncoped 2006 module was bloodstream infection (BSI), as the most important healthcare-associated infection (HAI) in paediatric cancer patients [17, 43]. It seems reasonable to target surveillance efforts to those HAIs suspected to be at least in part preventable [7, 15, 17, 43]. Our prospective analysis revealed that the BSI-related mortality in this population is low (1.8 %) [36, 47]. To our interpretation, this is a consequence of early aggressive treatment in case of fever or other clinical signs of infection [6, 39]. An even lower BSI-related mortality of 0.5 % has recently been published by Miedema et al. [41]. Fifteen percent of all patients in this study from Groningen, Amsterdam and Bern were admitted to intensive care. Furthermore, the proportion of multidrug-resistant (MDR) bacterial pathogens was very low in our study and in the study of Miedema et al. [41], although broad spectrum antibiotics are often and repeatedly used in paediatric oncology patients [49, 54].

In a recent study from the National Cancer Institute in Cairo [21], the detection of a MDR pathogen in blood culture (38 %) was associated with prolonged duration of fever (>7 days) and an increased risk of an unfavourable outcome; 18 of the 25 children who died (overall BSI-related mortality 10.5 %) had a BSI due to a MDR pathogen. Continuous surveillance of BSI-related pathogens is needed to guide empirical first-line treatment.

In our study, 13 to 28 % of all patients experienced at least one BSI. This represents a significant clinical burden of disease taking into account that inpatient antibiotic treatment is still the principle therapeutic approach in the majority of patients with fever and neutropenia [6, 39].

In a very conservative calculation, the treatment for one BSI in paediatric cancer patients in Germany has been previously estimated to account for median additional expenses of € 4400 (IQR € 3145 to 5920) per case [USD 6970 (IQR 4938 to 9294)]. Referring to the 2010 German DRG system, bacteraemia in a paediatric oncology patient with neutropenia led to a reimbursement of € 3.921 and any form of sepsis to € 6.600 (pers. Com. HJ Laws, May 2014). Thus, BSI management substantially impacts on personnel and financial resources required for inpatient treatment.

Most patients in our study developed a BSI after conventional chemotherapy; only 57 % had been inpatients in the last 72 h before the infection became clinically apparent. Previous studies have shown that the incidence rates of BSIs (BSI per 1000 CVAD utilisation days) are lower in outpatients, but the absolute number of those events in outpatients may exceed the number of events in inpatients [4, 51]. Irrespective of whether the patient is actually an in- or an outpatient, the underlying disease, its chemotherapy, the adverse effects of treatment (e.g. neutropenia, mucositis) and the presence and maintenance care of the CVAD put the patient at an increased risk of BSI. In some recent studies from the USA [24, 26, 33], efforts have been made to differentiate in- and outpatient BSIs in paediatric oncology. Only those BSIs detected *after 48 h in the hospital or within 48 h after discharge* are allocated to the *preventable hospital-acquired conditions* for which the Centers for Medicare and Medicaid Services discontinued additional payments [37].

On the other hand, if the CVAD is the source of the bacteraemia or sepsis, it is impossible to ascertain when the primary bacterial contamination/colonisation of the CVAD with the causative pathogen has happened exactly. Thus, our protocol recommends the documentation and analysis of all BSIs in the attending paediatric cancer unit. The question of the local origin of CVAD-related BSIs may be of increased interest in case of an outbreak [57]. Only 56 % of the patients with BSI displayed neutropenia in peripheral white blood cell counts at the first day of symptoms, but—as in our previous study [47]—neutropenia significantly influenced clinical severity. Patients with neutropenia and positive blood cultures had an increased risk of sepsis.

The length of stay in hospital and the duration of antibiotic treatment did not depend on the *Gram*-staining results of the species detected in blood cultures. Both outcome parameters were in good accordance with our previous data, which have been used to calculate the additional cost of BSI treatment [10]. The median duration of treatment is in line with the results from Miedema et al. [41]. How long BSI due to different bacterial species have to be treated in paediatric cancer patients still remains controversial [42].

The distribution of bacterial pathogens derived from blood cultures is in accordance with most other studies on BSIs in paediatric cancer patients [1–3, 11–14, 22, 24, 26, 36, 47, 51, 56]. In a recent article from the Children's Hospital in Boston [33] on nosocomial BSIs in paediatric cancer patients, the authors strictly followed the definitions of the Centers for Disease Control and Prevention [30] without adjustment to clinical practice in paediatric oncology. This resulted in the exclusion of all BSIs in which a common skin contaminant, such as CoNS, was found in less than *2 or more blood cultures drawn on separate occasions. Due to this definition*, CoNs were detected (included) in only 4 of 59 BSIs (6.8 %). Paediatric oncologists typically start broad-spectrum antibiotics after one initial set of blood cultures has been obtained [33]. In another recent study, the revision of the CDC/NHSN surveillance definition in 2008 [30] led to the exclusion of 15 % of all bacteraemias, yielding an 18.6 % rate reduction of the catheter-linked BSI rate attributable to the definition change alone [17]. Surveillance definitions have to be adjusted to the investigated clinical population, and it should not be accepted without debate that a significant proportion of all BSIs in paediatric cancer patients is excluded from the analysis just because of a mismatch of diagnostic practice and case definitions [24, 26]. This may lead to false exclusion of real infections, for example, due to viridans streptococci in patients with severe chemotherapy-induced mucositis [17, 39]. In the Oncoped 2006 module, a consensus between the infection preventionist and the attending paediatric oncology consultant is required on the question of whether a single positive blood culture represents a contamination or an infection and to which category (CVAD-associated or CVAD-related) the infection should be assigned [45]. Some experts have recently suggested to invent a new category for those BSIs in which pathogens (as *E. coli* or viridians streptococci) translocate from the inflamed mucous membranes of the oral cavity or the lower gastrointestinal tract in patients with severe mucositis [24, 26, 44]. Those BSIs have been allocated to the category *secondary BSIs* in the Oncoped module. An international consensus on this issue is necessary to reach better comparability between studies.

The necessity to remove the CVAD non-electively in patients with CVAD-associated BSI (5 %) was in the same order of magnitude as in secondary BSIs (4 %). In contrast, the CVAD had to be removed in 26 % of all CVAD-related cases despite in situ treatment [40, 50].

Benchmarking of BSI rates between paediatric oncology centres (PCCs) is not the primary means of the Oncoped surveillance module. Even if identical methods of surveillance are used, it is important to consider the population of paediatric cancer patients treated in a specific unit [36, 47]. As expected, higher incidence densities and incidence rates were observed in centre 8 (Table 4), which is a PCC specialised on stem cell transplantation [17, 33]. The practice of CVAD care and other strategies to prevent HAIs in paediatric cancer patients differ markedly between the PCCs participating in this study [34]. A survey performed in 2012 including 29 PCCs from Germany, Austria and Switzerland [53] has confirmed this finding. According to single-centre studies, the routine use of a taurolidine-containing antimicrobial lock solution prevents BSIs in paediatric cancer patients [20, 28, 48]. The results of our study did not reveal such a benefit, but this was not a primary objective of our study, and only one centre used taurolidine routinely in nearly all patients. As well, it has to be considered that taurolidine-containing antimicrobial CVAD locks are only applied when the CVAD is not in use. A randomised multicentre study, investigating the effect of taurolidine or other innovative antimicrobial lock solutions [16, 46] is warranted. The preventive potential of routine taurolidine locks may be of particular interest in paediatric cancer patients receiving home parenteral nutrition [9].

To our knowledge, this is the first study demonstrating in multivariate analysis that patients with relapsed malignancy face an increased risk of BSI. The analysis of Kelly et al. [33] did not reveal a significant impact of *uncontrolled oncologic disease* on the risk of BSI in paediatric cancer patients, but the authors did not differentiate between first disease and relapsed disease. In addition, our data confirm an increased risk of BSI in patients with leukaemia (ALL, AML) and in patients with a Broviac CVAD compared to Ports or *no CVAD*.

A higher incidence of BSIs in patients with tunnelled external catheters (compared to Ports) has been described by others [2–4, 32, 43]. More intensive treatment regimens and younger ages were associated with higher rates of infection [1]. Frequent access to Ports and Broviacs is associated with higher infection rates [23]; this may explain the higher relative risk of BSI in inpatients [4, 51]. The recent transfusion of platelets was not a requested item in our case report form. Kelly et al. have shown that platelet infusion is an independent risk factor for subsequent BSIs in paediatric cancer patients [33]. Recently, three prospective interventional studies have consistently demonstrated that day-to-day adherence to evidence-based guidelines for maintenance care practices (preventive bundles) and their continued re-evaluation leads to a clinically relevant reduction of BSIs in paediatric cancer patients [7, 17, 43].

Conclusion

Bloodstream infection (BSI) is the most important healthcare-associated infection in patients treated in paediatric cancer centres (PCC) with intensive anticancer or immunosuppressive therapies. Prospective surveillance of BSIs generates important data on unit epidemiology in terms of incidence, leading pathogens and resistance profiles. Although the related mortality is low, BSIs represent a significant burden of morbidity with a median additional length of hospital stay of 13 days in patients with bacteraemia and 21 days in patients with sepsis. The proportion of MDR pathogens was low, but the fact that one patient died during the course of a Gram-negative infection with an ESBL-producing *E. cloacae* should be interpreted as admonition. Leukaemia (ALL, AML), the presence of a Broviac catheter and relapsed malignancy were identified as independent risk factors.

Authors Contributions RAA, HJL and AS designed the study protocol (AS is the chairman/study leader of the Oncoped study); RAA performed the data analysis; and all of them drafted and finalised the subsequent versions of the manuscript. All other authors coordinated the sampling of the clinical data and its transfer to the study office, read, commentated and approved the different versions of the manuscript.

Conflict of interest None of the authors declared a conflict of interest related to this study.

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