Bloodstream Infections in Paediatric Cancer Patients. Prospective Comparative Study in 2 University Hospitals

Blutstrominfektionen bei Kindern mit Krebserkrankungen: Eine prospektive vergleichende Beobachtungsstudie in 2 Universitätskliniken

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Key words
- bacteraemia
- Broviac
- port
- children with cancer

Schlüsselwörter
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Abstract

Background: Preventive approaches (including those related to care of long term central venous catheters, CVADs) and the incidence of bloodstream infections (BSI) in 2 German university affiliated paediatric oncology units.

Patients and Methods: Non-interventional prospective observational study using the Oncoped surveillance module.

Results: Center A included 85 patients in 31 months and Center B 84 patients in 21 months. The populations did not differ in terms of age, gender, malignancy and disease status (first illness vs. relapse). Center A used ports (46%) and 2 different Broviac catheters (54%), in Center B nearly all patients with a CVAD had Broviacs (96%). 30 BSI (24 patients) were diagnosed in Centre A and 28 BSI (22 patients) in Center B. Patients with relapsed malignancy experienced more BSI (51.4% vs. 20.9%; p = 0.001). Incidence rates were significantly lower in Center A (3.47 vs. 7.93 BSI/1000 CVAD days; p = 0.037). Poisson regression analysis revealed a significant lower incidence density (BSI/100 inpatient days) for all BSI in Center A (RR 0.47 CI95 0.27–0.81, p = 0.006). Overall, 52% of all pathogens detected in blood cultures in Center A were Gram-positive (57% in Center B) and 48% Gram-negative (43 in Center B). One ALL patient without a CVAD died due to overwhelming sepsis caused by an ESBL-producing *E. cloacae* isolate.

Conclusion: Paediatric cancer treatment centers differ substantially in regard to management of CVADs and in other preventive strategies. The most important use of local surveillance data is longitudinal internal assessment in close cooperation with microbiology and hospital hygiene experts.

Zusammenfassung

Hintergrund: Vergleich präventiver Konzepte, einschl. des Managements von dauerhaften zentralen Venenkathetern (CVADs) und von Bakteriämien (BSI) bei pädiatrisch-onkologischen Patienten in 2 Universitätskliniken.

Patienten und Methoden: Nicht interventionelle prospektive Beobachtungsstudie mit dem Oncoped-Surveillance-Modul.

Ergebnisse: Zentrum A schloss in 31 Monaten 85 Patienten ein, Zentrum B 84 Patienten in 21 Monaten. Die Populationen unterschieden sich nicht signifikant in Bezug auf Alter, Geschlecht, Erkrankung und Status (Ersterkrankung vs. Rezidiv). Zentrum A nutzte ports (46%) und 2 verschiedene Broviac-Katheter (54%); im Zentrum B hatten nahezu alle Patienten einen Broviac (96%). In Zentrum A wurden 30 BSI bei 24 Patienten, im Zentrum B 28 BSI bei 22 Patienten diagnostiziert. Patienten mit Rezidiv hatten mehr BSI (51,4% vs. 20,9%; p = 0,001). Die Inzidenzrate für BSI war in Zentrum A niedriger (3,47 vs. 7,93 Ereignisse/1 000 CVAD Tage; p = 0,037). In der Poisson-Regression war nur der Unterschied in der Inzidenzdichte aller BSI (BSI/100 Patiententage) signifikant (RR 0,47 CI95 0,27–0,81, p = 0,006). 52% der Blutkulturisolate in Zentrum A waren Gram-positiv (57% in Zentrum B) und 48% Gram-negativ (43% in Zentrum B). Ein ALL-Patient ohne CVAD verstarb an einer Sepsis, verursacht durch ein ESBL-bildendes *E. cloacae* Isolat.

Schlussfolgerung: Zwischen pädiatrisch-onkologischen Zentren bestehen erhebliche Unterschiede in Bezug auf Strategien der Infektionsprävention. Prospektive standardisierte Surveillance-Daten dienen daher vor allem der longitudinalen Qualitätssicherung vor Ort in enger Zusammenarbeit mit Mikrobiologen und Krankenhaushygienikern.

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Introduction

In paediatric patients with cancer, alterations in host defence mechanisms against infection are related to the underlying illness (e.g. haematologic malignancy), to intensive treatment with immunosuppressive drugs (neutropenia, lymphocytopenia), radiotherapy, surgical interventions, and to additional side effects such as gastrointestinal mucositis. In this setting, fever with or without neutropenia is an important complication [17]. Fever of unknown origin accounts for up to 60% of all infections in addition to a wide spectrum of clinically or microbiologically defined infections. Bacteraemia due to *Gram*-positive and *Gram*-negative pathogens significantly affects morbidity and even mortality in this high risk population [1]. Most patients with bacteraemia have a long term central venous access device (CVAD) in use. In paediatric cancer patients, the term 'CVAD' refers to tunnelled Broviac/Hickman or subcutaneously implanted Port catheters [1,21,25]. These devices are of proven benefit for patients and caregivers but their use increases the risk of bacteraemia [11].

Paediatric cancer treatment centers still differ substantially in approaching the management and care of CVADs. Unfortunately, it remains an unresolved issue, which combination ('bundle') of preventive strategies is effective in reducing CVAD-associated infection rates [23]. The prospective surveillance of bacteraemias with adapted case definitions and standardised methods for data analysis and reporting has been established in some German treatment centers as quality assurance initiative. Surveillance efforts aim at the identification of critical control points for the reduction of health-care associated infections in paediatric cancer patients [21,25]. Prospective surveillance data from different participating units may be compared and used for benchmarking discussion ('share experiences and learn from the best') [8].

Herein, data derived from the prospective surveillance of all consecutive bacteraemias in 2 German treatment centers for paediatric patients with cancer is reported and compared. One aim of this report is to elucidate important differences in CVAD management and care in the corresponding units. This eventually leads to the discussion how local surveillance data about bacteraemias (with or without any association to the CVAD) may be used to improve patients' safety in the long term.

Methods

To both university affiliated paediatric cancer treatment centers participating in this prospective surveillance study about 50 paediatric cancer patients are admitted per year with newly diagnosed or relapsed malignancies. Center A is a 16 bed and center B a 12 bed inpatient unit. Both centers run a specialised outpatient clinic in addition to inpatient facilities. Anticancer treatment of childhood malignancies refers to the cooperative protocols of the German Society for Paediatric Oncology and Haematology (GPOH). In patients with acute leukaemia, both centers adhere to protocols derived from the international BFM group.

Fever was defined as body temperature > 38.5 °C for at least 4 h or once > 39 °C. Neutropenia was defined as a total number of granulocytes $< 0.5 \times 10^9$/L or a total number of leukocytes $< 1.0 \times 10^9$/L without differential counts available.

The comparative investigation of simultaneously sampled central and peripheral blood cultures in terms of differential time to positivity [9] adds to the early identification of the CVAD as the probable source of bacteraemia [3]. Without simultaneous peripheral venous cultures up to 14% of all positive blood cultures remain undetected [20]. In clinical practice, routine use of this technique is hampered by specific circumstances. First, patients and their parents are reluctant to tolerate additional pain and anxiety related to peripheral venous blood culture drawing in children with an easily accessible CVAD. This limits compliance with the corresponding diagnostic standard. Despite a written hospital-wide policy recommending the collection of additional peripheral blood cultures these are sampled in only 58% of all cases in clinical practice [7]. Second, the practical impact of this procedure on the choice and duration of antibiotic treatment is negligible in most cases [3]. Supportive care recommendations published on behalf of the German Society for Paediatric Oncology and Haematology (GPOH) and the German Society for Paediatric Infectious Diseases (DGPI) do not recommend the additional collection of peripheral venous blood cultures from febrile paediatric cancer patients with a long term central venous catheter (CVAD) [3,13,23]. In this study, 2 blood culture samples (aerobic and anaerobic) were collected from patients with fever under aseptic conditions and after disinfection of the CVAD hub with isopropanole from the CVAD before the first dose of intravenous antibiotics.

Blood cultures were processed using the BD BACTEC™ automatic detection system (Beckton Dickinson, Heidelberg) and species differentiation according to standard microbiological procedures.

Bacteremia (bloodstream infection; BSI) was defined as growth of a bacterial pathogen in blood culture derived from a patient with fever or other signs of infection. Patients with bacteremia and systemic inflammatory response syndrome was allocated to the clinical severity grade 'sepsis' according to paediatric consensus criteria [10]. The same criteria were used for patients with growth of *Candida spp.* in blood cultures to differentiate Candidemia and Candida sepsis.

At least 2 positive blood culture bottles 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 primary focus of infection. To allocate the BSI to the category 'CVAD-related infection' blood cultures taken from the device had to be subsequently 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 microbiologically or clinically defined primary focus of infection, the corresponding BSI was allocated as secondary bacteraemia. The prospective Oncoped tool for the surveillance of healthcare-related infections in paediatric cancer patients in Germany has been previously described in detail [21,24,25]. Incidence densities (BSI per 100 inpatient days) and incidence rates (BSI per 1000 CVAD utilization days) were calculated. Since the risk of CVAD related infection is highest during inpatient treatment (in particular in patients with ports) the Oncoped module uses inpatient CVAD utilization days as denominator [24,25]. This is an important difference to studies published by other groups [1,5].

In Center A, no selective decontamination of the gastrointestinal tract was performed because the attending paediatric oncologists were not convinced of the available evidence supporting its use [26]. In Center B, colistin was used for this purpose in high-risk patients (leukaemia, lymphoma, autologous stem cell transplantation).

The study protocol was approved by the ethics committee of the medical faculty, University of Bonn and by the German Society of Infectious Diseases in Childhood (DGPI). Informed consent to participate in the collection and anonymized analysis of surveillance data was obtained according to institutional policies from patients or their parents.

The whole study population (n = 169 patients) was used to investigate the data for any correlation between basic patient characteristics (**Table 2**) and the risk to experience at least one BSI; for this analysis, repeated BSIs in the same patient were excluded. Since continuous variables were not normally distributed, median and interquartile range (IQR; 25.–75. percentile) was 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). Center-specific incidence rates with their exact 95% confidence intervals were calculated. Rate ratios between the centers and their 95% confidence intervals were calculated using exact Poisson regression (StatXact 9.0 und LogXact 9.0, both from Cytel Software Inc., Cambridge, MA). All analyses were calculated as two-sided tests, and p-values < 0.05 were considered to be statistically significant.

Results

The periods of prospective surveillance were 31 months in Center A and 21 months in Center B. In both centers, all eligible patients participated in the study. Center A included 85 and Center B 84 patients subsequently. **Table 1** (online) refers to basic issues of CVAD care and certain practices to prevent bacteraemias implemented in the 2 participating units. The basic patients' characteristics are shown in **Table 2**. There were no significant differences between the 2 patient populations in terms of median age, gender, underlying malignancy or disease status (first illness or relapse).

Table 2 Basic patient characteristics in both participating centers.

	Center A n = 85 patients		Center B n = 84 patients	
Median Age (IQR) in years	**10.3 (3.0–15.5)**		**9.7 (5.2–15.1)**	
Male/female (%)	**55/45**		**61/39**	
	n	**%**	**n**	**%**
acute lymphoblastic leukaemia	26	31	27	32
acute myeloblastic leukaemia	12	14	5	6
brain tumor	14	16	14	17
chronic myeloid leukaemia	0	0	1	1
ewing sarcoma	5	6	7	8
germ cell tumor extracranial	2	2	2	2
hepatoblastoma	1	1	1	1
hodgkin lymphoma	3	4	3	4
nephroblastoma	3	4	5	6
neuroblastoma	4	5	4	5
non hodgkin lymphoma	5	6	8	10
osteosarcoma	5	6	3	4
retinoblastoma	0	0	1	1
rhabdomyosarcoma	3	4	2	2
others	2	2	2	2
patients with relapsed malignancy	17	20	19	23

IQR interquartile range; 25.–75. percentile

No significant difference in any item between both centers

In Center A, only 1 patient had no CVAD in use (1%). In the remaining 84 patients, 3 different CVAD types were used: Ports (46%), conventional silicon Broviacs (25%), and Broviac CVADs impregnated with silver (VYGON Lifecath™) (29%). Most CVAD changes were elective (e.g. from Port to Broviac in high risk leukaemia) or due to mechanical problems (CVAD occlusion, dislocation or fracture).

The cumulative number of in- and outpatient days with a CVAD (Broviac plus Port) in Center A was 24.651 days; the median duration from implantation to removal was 269 days (IQR; 171–496 days) for Ports; 108 days (IQR; 69–153 days) for conventional Broviacs, and 131 days (IQR; 63–240 days) for the VYGON Lifecath™.

In Center B, 9 patients (11%) had no CVAD. Nearly all patients with a CVAD in Center B (73 of 76; 96%) had a Broviac in use; only 3 (4%) of all patients had a Port implanted. The cumulative number of in- and outpatient days with a CVAD (Broviac plus Port) in Center B was 16.350 days; for Broviac CVADs, the median duration from implantation to removal was 192 days (IQR; 110–288 days).

During the prospective surveillance study, 30 BSI were diagnosed in 24 patients in Center A and 28 BSI were diagnosed in 22 patients in Center B. **Table 3** shows the resulting infection rates.

Table 3 Bloodstream infections (BSI) and corresponding infection rates.

Item	Center A 85 patients	Center B 84 patients
prospective surveillance (months)	31	21
inpatient days	10.735	6.317
inpatient CVAD utilization days	8.282	3.610
age of patients with BSI** in years (range)	10.6 (0.3–30.4)	10.1 (2.7–22.5)
proportion of all patients with at least one BSI	28% (24/85)	26% (22/84)
proportion of patients with neutropenia at the onset of BSI	67% (20/30)	57% (16/28)
no of BSI	30†	28§
– incidence density BSI*	0.28	0.44
– incidence rate BSI#	3.62	7.76
BSI, Gram-positive pathogen	N = 17	N = 15
– ID BSI Gram-positive	0.16	0.24
– IR BSI Gram-positive	2.1	4.16
BSI, *CoNS*	N = 5	N = 9
– ID BSI *CoNS*	0.05	0.14
– IR BSI *CoNS*	0.60	2.49
BSI, Gram-negative pathogen	N = 14	N = 12
– ID BSI Gram-negative	0.13	0.19
– IR BSI Gram-negative	1.69	3.32
type of BSI		
CVAD-related BSI	3 (10%)	1 (4%)
CVAD-associated BSI	3 (10%)	6 (21%)
secondary BSI	24 (80%)	21 (75%)
clinical severity		
bacteraemia	22 (73%)	17 (60%)
sepsis	7 (23%)	10 (36%)
candiaemia	–	1 (4%)
canida sepsis	1 (4%)	–

BSI = bloodstream infection

† One BSI was due to a *Gram*-positive and a *Gram*-negative pathogen (*S. aureus and P. aeruginosa*)

§ 1 BSI due to *C. parapsilosis*

*Incidence density (ID), number of BSI/100 inpatient treatment days; cumulative values

**median in years (range)

Incidence rate (IR), number of BSI/1000 inpatient CVAD utilization days; cumulative values

Results of statistical analysis, see text

Table 4a Center A: Pathogens detected in 30 BSI (24 patients).

Pathogen	n*	%#
S.aureus	2	6
Coagulase-negative staphylococci (CoNS)	5	15
Streptococcus, viridans group	9	27
Vancomycin-resistant *E. faecium*	1	3
E. coli	5	15
E. coli (ESBL positive)	1	3
E. cloacae	4	12
A. baumannii	1	3
K. oxytoca	1	3
K. pneumoniae	1	3
P. aeruginosa	2	6
Salmonella spp.	1	3
C. parapsilosis	1	

*3 polymicrobial BSI (in a single patient, see text)

Proportions refer to 33 bacterial isolates

Table 4b Center B: Pathogens detected in 28 BSI (22 patients).

Pathogen	n*	%#
S. aureus	1	3
Coagulase-negative staphylococci (CoNS)	10	33
Streptococcus, viridans group	3	10
S. pneumoniae	1	3
Enterococcus spp.	1	3
R. mucilaginosa	1	3
E. coli	6	20
E. cloacae	2	7
E. cloacae (ESBL positive)	1	3
P. aeruginosa	3	10
K. pneumoniae	1	3
C. parapsilosis	1	–

*2 polymicrobial BSI

Proportions refer to 30 bacterial isolates

In **Table 4a**, **b** the pathogens detected in blood cultures are listed in detail. Overall, 52% (17/33) of all bacterial pathogens detected in blood cultures in Center A were Gram-positive and 48% (16/33) Gram-negative. The corresponding proportions in Center B were 57% (17/30) for Gram-positive and 43% (13/30) for Gram-negative pathogens, respectively.

The difference in the proportion of CoNS bacteraemias between Center A and Center B (5/30 vs. 9/28; 17% vs. 32%) was not statistically significant (p=0.224). Polymicrobial bacteraemias accounted for 10% in Center A and 7% in Center B. In Center A, 1 BSI was caused by a Vancomycin-resistant *E. faecium*, and 1 CoNS infection was due to a Teicoplanin-resistant *S. haemolyticus*. In both Centers, one BSI was caused by ESBL-producing Gram-negative *Enterobacteriaceae* and one by *C. parapsilosis*.

In Center B, 37 of 84 consecutive patients (44%) received at least 1 course of orally administered Colistin (3 times daily 0.5–1 Mio Units). Although 9 of 12 patients who eventually experienced a BSI caused by Gram-negative bacterial pathogens would have been eligible for Colistin prophylaxis, only 1 of these patients received Colistin immediately before the event.

In Center A, the CVAD was removed during the course of the infection in 6 events (20%), 1 deep port pocket soft tissue infection with secondary bacteraemia (*S. aureus*); 3 consecutive polymicrobial sepsis events in a single patient (see text below) and 2 CVAD-associated infections (no bacteria detected on the catheter tip) with persistent fever, 1 due to CoNS and 1 due to VRE, respectively.

In Center B, 2 BSI (7%) lead to early removal of the device: 1 CVAD-related BSI (*E. cloaecae*) as well as 1 secondary BSI event in which the CVAD was suspected, but not confirmed as the primary source of *P. aeruginosa* bacteraemia. In Center B, none of the CVADs had to be removed prematurely due to a BSI caused by Gram-positive pathogens and persistent infection.

The median duration of inpatient treatment related to the infection was 13 days (IQR 10–21 days; range, 7–80 days) in Center A and 8.5 days (IQR, 4–13 days; range, 3–28 days) in Center B (p=0.03).

In Center A, 1 patient with severe haemophilia with factor VIII inhibitors experienced 3 consecutive polymicrobial BSIs, clinically presenting as septic shock events. This patient was included in the analysis, because he had previously received intensive immunosuppression with steroids, rituximab, cyclophosphamide and plasmapheresis. Host related reasons for this series of severe BSIs (severe combined acquired immunodeficiency) and the source of the bacteraemias (internal or external) could not be elucidated in detail.

Status of disease was the only significant risk factor out of the basic patients' characteristics (**Table 2**). Differences in age, gender and underlying malignancy were not correlated with BSI events. In patients with relapsed malignancy a significant higher proportion experienced at least 1 BSI (51.4% vs. 20.9%; p=.001). This difference was due to a higher proportion of patients with at least 1 Gram-positive BSI in those with relapsed malignancy (34.3% vs. 11.2%; p=0.002).

Incidence rates (described as mean cumulative IR in 4-months intervals) were significantly lower in Center A (3.47 vs. 7.93 BSI/1000 CVAD days; p=0.037). *Poisson* regression analysis revealed a significantly lower incidence density (BSI/100 inpatient days) for all BSI in Center A (0.36 vs. 0.78; RR 0.47, CI95, 0.27–0.81, p=0.006). Differences of Gram-positive and Gram-negative BSI rates did not reach statistical significance.

Mortality attributable to the BSI events was 3.4% (2/58). One 15-year old patient was admitted on day 40 of induction chemotherapy for T-ALL with fever and neutropenia. He had no Broviac or port, received first line treatment with Piperacillin-Tazobactam and Gentamicin, and died less than 48 h later from septic shock with multi-organ failure despite early intensive care and second line treatment with Meropenem. Blood cultures yielded *E. coli* and *Enterbacter cloacae*. The *E. cloacae* isolate displayed in vitro multi-drug resistance due to the expression of an extended spectrum betalactamase (ESBL) and in vitro resistance to Gentamicin and Tobramycin. In the second patient (21 years; bone marrow failure after allogeneic bone marrow transplantation for high-risk ALL, severe GVHD, mucositis) secondary *E. coli* septicaemia contributed to fatal outcome. The *E. coli* isolate showed in vitro resistance to first-line Piperacillin-Tazobactam, but was sensitive to Gentamicin and Meropenem.

Discussion

To our knowledge this is the first study from Germany comparing preventive measures and prospectively collected data on bloodstream infection rates as well as the distribution of pathogens derived from blood cultures between 2 centers for inpatient treatment for pediatric cancer patients. Both units were comparable in terms of inpatient treatment days, the distribution of age, gender, underlying malignancy and disease status

(first diagnosis or relapsed malignancy) in the corresponding patient population. The practice of long term CVAD care differed substantially between both centers (**Table 1** online).

There was no higher BSI rate in Center A compared to Center B despite important differences in catheter management. In Center A, CVADs were implanted prior to induction chemotherapy in children with acute lymphoblastic leukaemia (in contrast to the practice to postpone the CVAD implantation after day 33 in Center B) [11]. Intravenous administration sets were routinely changed after 7 days (compared to every 48 h in Center B) [27] and Broviacs were flushed only once a week (compared to twice a week in Center B).

Only in Center A, a silver impregnated Broviac catheter (VYGON Lifecath™) was used in 30 of 84 patients with at least 1 CVAD (36%). We did not find a lower proportion of patients with at least one BSI in patients with a silver impregnated Broviac (data not shown), but our study was observational and in principal not meant to confirm or exclude any significant influence of the catheter material on infection rates. This would be subject to a different study which, to our knowledge, is still awaited for paediatric cancer patients.

The lower number and incidence rate of BSIs related to CoNS in Center A (without statistical significance) may be related to the prophylactic use of a Taurolidine containing lock solution instead of heparin (100 E/ml sterile NaCl 0.9%). One single center non randomized study using historical controls investigating this intervention in paediatric cancer patients confirmed a significant benefit [22]. A prospective randomized single center study with taurolidine vs. heparin has recently been completed in Aarhus, Denmark. The publication of the results is awaited (Moller-Handrup M., Schroder H., personal communication).

In general, Port catheters have a lower risk of CVAD-related bloodstream infections than Broviac catheters [2]. This may have been 1 cause of lower BSI rates in Center A. The choice of CVAD depends on the type of malignancy, the age of the patient, and - to a significant extend - on local clinical practice [2,21].

In contrast to our results, Cesaro et al. identified the patients' age (<4.7 years) as significant predictor for premature removal of the CVAD [5]. In this Italian study, the overall rate of CVAD associated BSI was 0.44/1000 CVAD days but in- and outpatient CVAD utilisation days were used as denominator. This method of calculation leads to 'lower' incidence rates. The vast majority of non-elective removals in the Italian study were due to mechanical complications and not the consequence of CVAD-related infections. The same group compared 2 different modalities of flushing central venous catheters in paediatric patients with cancer in 1 of the very few available prospective randomised studies [6]. During a 25-month study period 203 paediatric patients who had newly placed Broviac-Hickman CVC were randomly assigned to standard flushing with heparin solution (twice a week) or to flushing with normal saline via a positive-pressure connecting device (experimental arm, once a week) [6]. A higher incidence of bacteremia was found in the experimental arm (incidence rate, 0.62 vs. 0.24/1000 CVAD days; P=0.01). Nonetheless, the only factor significantly associated with premature removal of a CVC was a diagnosis of leukaemia or lymphoma (HR, 2.3; CI95 1.1 to 4.7). Due to methodical limitations (e.g. flushing once vs. twice weekly; leaving the connecting device in place for 7 days, no details on local disinfection of the device, more patients with stem cell transplants in the experimental arm) it remains difficult to form tentative conclusions from this study.

In both centers compared in our investigation, children, whose fever disappeared and who did not have additional risk factors for a complicated clinical course (e.g. mucositis, expected long lasting neutropenia for more than 10 days), received inpatient intravenous empiric antibiotic treatment of FUO for only 48 to 72 h. This approach is held to be safe and effective [16]. In both centers, the use of the glycopeptide teicoplanin was restricted to certain indications in order to limit its use in empirical treatment and to prevent the selection of Vancomycin-resistant Enterococci [28].

Oral prophylaxis with non-absorbable antibiotics directed against aerobic *Gram*-negative *Enterobacteriaceae* (selective gut decontamination; SGD) has been proposed in early studies for patients with high risk ALL, high risk Non Hodgkin Lymphoma, AML induction treatment or after bone marrow transplantation [29]. Although used in practice in many centers, there is still no clear scientific evidence for the preventive efficacy of SGD in paediatric cancer patients [12]. One group of paediatric oncologists from Liverpool, UK, recommended the use of SGD to prevent bacteraemias caused by *P. aeruginosa*[19].

Nonetheless, in their prospective study the proportion of Gram-negative BSIs due to *P. aeruginosa* (7.8%) was in the same magnitude or even higher as in other centers which never use SGD [21]. In the study presented here, Colistin prophylaxis was not prospectively followed as a separate item in the surveillance module. Data considering Colistin prophylaxis from patients in center B had to be extracted from the patients' files retrospectively. Thus, it was not possible to reconsider the reasons in detail, why only a small proportion of eligible patients eventually received Colistin prophylaxis just before the event. We can only speculate whether this prophylaxis would have prevented Gram-negative BSIs.

A recent international survey asked for supportive care practices for paediatric patients with AML [14]. Antibacterial prophylaxis was more common among Berlin-Frankfurt-Muenster institutions compared to Children's Oncology Group institutions (15/46, 33% vs. 24/180, 13%, P<0.0001). The same authors investigated compliance issues related to anti-infective preventive measures in 216 children and adolescents [15]. Compliance rates were the highest for food restriction (89%), the use of topic antimycotics (88%) and cotrimoxazole for *Pneumocystis jirovocii* prophylaxis (87%). Lower compliance rates were found for the use of face masks (69%), antiseptic mouth rinses (67%), non-absorbable antibiotic agents (67%), and restrictions in social contacts (66%). The most frequent reasons for drug non-compliance were forgetfulness and patient refusal. Compliance issues have to be considered in any preventive strategy recommended during outpatient care and compliance is suspected to be low if bad tasting antimicrobial tablets or solutions have to be swallowed regularly by the patient.

One interesting observation is the successful in situ treatment of all Gram-positive BSIs in Center B without premature removal of the CVAD. This argues for ethanol locking of Broviacs suspected to be the source of the infection [18] since this practice was routinely followed only in Center B.

Of outstanding practical importance is the observation of Gram-negative isolates resistant to first line empirical treatment with Piperacillin-Tazobactam combined with Gentamicin or Tobramycin. Although such an ESBL-producing isolate was demonstrated only once in each center in blood culture the fatal outcome of one child with *E. cloacae* sepsis underlines the par-

ticular risk associated with bloodstream infections caused by multidrug resistant pathogens.

Paediatric cancer patients with neutropenia and severe sepsis requiring intensive care should receive second or third line antibiotics right from the beginning of empirical treatment (e.g. Meropenem plus Amikacin plus Teicoplanin) [17]. This extremely broad spectrum therapy may be deescalated and adjusted to in vitro sensitivity data as soon as the results of blood cultures and other diagnostic microbiological specimens become available [4].

Although the patient populations were comparable, our study revealed significant variations in supportive care measures aiming at preventing bloodstream infections in the participating units. The complexity of the corresponding 'bundle approach' by the attending paediatric oncology team limits tentative conclusion on the preventive efficacy of single components in particular in the long term care of CVADs. Therefore, it obviously does not make sense to use the data derived from prospective surveillance primarily for benchmarking between different units by external observers [8]. The most important use of such standardised data on local infection rates is longitudinal internal assessment in close cooperation with experts from local microbiology and hospital hygiene and infection control facilities.

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