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Bloodstream infections in a German paediatric oncology unit: Prolongation of inpatient treatment and additional costs

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Abstract

In this matched cohort study, clinical data from 43 paediatric cancer patients with bloodstream infection (BSI) were compared with 43 thoroughly matched control patients without BSI. BSI led to a median additional length of inpatient treatment of 12 days (IQR 8.5–16 days; $P<0.001$), accounting for median additional expenses of €4400 (IQR, €3145–5920) per case [6.970 US Dollar (IQR 4.938–9.294)]. Thus, BSI substantially increased financial resources required for inpatient treatment. These data compiled from a paediatric cancer unit may be utilized to estimate the cost–benefit ratio of targeted preventive measures.

Keywords: Bloodstream infection; Nosocomial infection; Cost analysis; Length of hospitalization; Paediatric cancer patients; Central venous catheter

Introduction

In the last decades, an increased probability of long-term event-free survival has been achieved in paediatric cancer patients, due to intensive chemotherapy, surgery, radiotherapy and modern concepts of supportive care. The underlying malignant disease, the intensity of treatment and the use of long-term central venous access devices (CVAD) predispose the patients to infectious complications, in particular to bloodstream infections (BSI) (Gaur et al., 2004; Simon et al., 2006a, 2008b; Viscoli et al., 1999; Castagnola et al., 2007; Rackoff et al., 1999). Crude mortality related to BSI was 1–3% in recent studies (Paulus et al., 2005). Bloodstream infections drain restricted resources for nursing care, antimicrobials and for surgical removal of the CVAD in those cases, which do not show a clinical or microbiological response to antimicrobial treatment. Recently, a large retrospective cohort study confirmed an increased probability of prolonged inpatient treatment in paediatric cancer patients with BSI (odds ratio,

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OR, 3.14; CI95 2.79–3.53) (Basu et al., 2005). To our knowledge, no detailed analysis has been published yet, comparing the length of stay in hospital and the related costs in paediatric cancer patients with bloodstream infection treated in a German paediatric cancer unit. The matched cohort study presented here investigated the impact of BSI on length of hospital stay and on treatment costs in a paediatric oncology unit at the Children's Hospital Medical Center, University of Bonn, Germany.

Materials and methods

Setting

The paediatric oncology unit of the University Children's Hospital in Bonn, Germany, is a 17-bed tertiary care facility providing inpatient care for 900 admissions during about 5000 inpatient days (~50 newly diagnosed paediatric cancer patients) per year. More than 90% of all patients treated in this unit are children and adolescents; at about 10% are adults with relapsed malignancy, who have received initial treatment in our unit during adolescence, or who are suffering from 'childhood brain tumors', such as medulloblastoma.

The CVAD clinical-practice recommendations of the German Society of Paediatric Oncology and Haematology (GPOH) (Simon et al., 2008a), are strictly followed during in- and outpatient care, and match the CDC-Recommendations (O'Grady et al., 2002) with the following exceptions: octendine 0.1%/phenoxyethanol 2% (Octenisept®, Schuelke & Mayr, Norderstedt) is used for local antisepsis (Tietz et al., 2005; Dettenkofer et al., 2002). In addition, intravenous administration sets are changed routinely only once a week (Simon et al., 2006b) unless they have been used for lipid infusion (once a day) or for blood product administration (6 h after the transfusion) (Bundesärztekammer, 2005).

In our paediatric oncology unit, totally implanted port catheters are preferably used in patients with conventional chemotherapeutic regimens (median duration of neutropenia <7 days). Double-lumen Broviac/Hickman catheters are used in patients for whom an intensive and complicated treatment course or a stem cell transplantation is anticipated. As a result of this policy, patients have ports in place in 60–70% and Broviacs in 30–40% of all inpatient treatment days.

Patients, matching procedure, definitions

To assess the prolongation of inpatient stay and costs attributable to bloodstream infections a case–control (matched pairs) study was designed. Inpatients with blood stream infections (2001–2005) were identified from our prospective surveillance study for nosocomial infections in paediatric oncology (Simon et al., 2000). These patients with BSI were matched retrospectively with control patients without BSI.

All control patients have been treated at the same paediatric oncology unit. In most patients, treatment intensity and therefore the expected duration of neutropenia could be matched easily. In Germany paediatric oncology patients with the same diagnosis are treated in cooperative standard protocols of the German Society of Paediatric Oncology and Haematology. Matching was based on the following criteria: age, gender, underlying malignancy, chemotherapy and the exact date of the event within GPOH-protocol.

The day at which the observation period started in case patients was the first day of fever when the initially drawn blood cultures yielded a pathogen. Control patients where observed from the same day on within the standard protocol of treatment. Our matching procedure intentionally included control patients, who were not inpatients at the corresponding day of their treatment protocol.

In those control patients without a standard treatment (mostly those with relapsed malignancies), treatment cycles with identical dose intensity and expected duration of neutropenia were compared using the same latency from day 1 of the last treatment cycle to the date of the bloodstream infection in case patients. To address the financial burden related to the infection, we calculated the costs of one inpatient day in our unit. The details of this cost calculation are shown in Table 1. Our calculation focused very conservatively on treatment related expenditures (e.g., building and renovation costs were not included).

The extra costs due to intensive care treatment in the paediatric intensive care unit (ICU) were not included in the analysis, neither in case nor in control patients. We compared the duration of inpatient treatment between the two groups and defined the cost of additional

Table 1. Calculation of daily financial expenses related to inpatient treatment.[a]

Item	Cost per day (€)
Tangible means, medical personnel	130
Pharmacy	69
Laboratory investigations (including microbiology)	65
Blood products	15
Nutrition fee	14
Radiology	10
Transports	5
Administration	62
Sum (€ per day of inpatient treatment)	370

[a]In total 4.472 inpatient treatment days; 963 admissions.

inpatient treatment as a surrogate parameter for additional expenses in patients with BSI (Chrischilles and Scholz, 1999). In patients with BSI, only those inpatient days with antimicrobial treatment related to the infection were counted.

Neutropenia was defined as an absolute neutrophil count $<0.5\times10^9$/l or a leukocyte count $<1\times10^9$/l in absence of a differential WBC. The exact period of neutropenia was not determined in all patients, since daily blood cell counts are not routinely performed during in- and outpatient treatment.

The diagnosis BSI was allocated to any patient who had clinical signs of infection plus a positive blood culture result (at least two positive blood culture bottles in case of Coagulase-negative staphylococci, CoNS). To describe illness severity in patients with BSI, we used the consensus criteria published by Goldstein et al. in 2005.

Microbiological methods and empirical treatment regimen

Two blood cultures were collected consecutively from the same lumen of the CVAD in case of Port-type catheters and from both lumina in case of double-lumen Broviac catheters in all patients with fever (temperature $>38.5\,^{\circ}C$ for at least 4 h or once $>39\,^{\circ}C$) before the first dose of antibiotics was given and were routinely tested according to standard procedures (Isenberg, 2004). Blood samples were always drawn from the CVAD under aseptic conditions after disinfection of the catheter hub. According to the recommendations of the German Society of Paediatric Hematology and Oncology (Beutel and Simon, 2005; Simon et al., 2005), no peripheral blood cultures were investigated except in those patients in whom the central venous catheter did not allowed blood sampling. Patients with fever received intravenous antibiotics as empiric inpatient treatment (Simon et al., 2006c). Antifungal drugs were used in patients with prolonged neutropenia, who did not respond to broad-spectrum antibiotics after 96 h or immediately in any patients with possible, probable or proven invasive fungal infection (Ascioglu et al., 2002). The severity of BSI has been documented referring to international consensus criteria (Goldstein et al., 2005).

Statistical analysis and ethical considerations

Since continuously measured data were non-normally distributed, medians and interquartile ranges (IQR) were calculated, and nonparametric analytical methods (McNemar Test, Wilcoxon Test) were applied. All analyses were calculated as two-sided tests, and P-values <0.05 were considered to be statistically significant. In addition, a Kaplan–Meier plot was built out of the inpatient treatment days (length of stay) in both groups; the resulting curves were compared using the Log Rank (Mantel Cox) Test. The study protocol of our prospective surveillance study (Simon et al., 2000) 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 surveillance study was given by all patients or their legal guardians.

Results

In total, 51 patients with BSI were identified from the database of which 43 could be thoroughly matched with a group of 43 patients without BSI. In the remaining 12 patients, we could not identify a comparable patient with complete data required for the defined matching procedure. The two groups did not show significant differences in any of the items defined by the matching procedure, with the exception of a higher proportion of patients with relapsed malignancies in control patients without BSI (Table 2). The clinical diagnosis in those patients with BSI was bacteraemia in 30 patients (70%), sepsis in 9 patients (21%), septic shock in 3 patients (7%), and septic shock with multiple organ failure in 1 patient (2%). In 35 out of 43 BSI events (81%), the patients had severe neutropenia ($<0.5\times10^9$ granulocytes/L). No patient died secondary to the infection. Table 3 lists the causative pathogens in patients with BSI. There was no clear dominance of *Gram*-positive isolates. Coagulase-negative staphylococci and viridans streptococci accounted for 40% of all pathogens; 44% of the most prevalent isolates were *Gram*-negative with *Escherichia coli* and *Klebsiella* spp. accounting for 35%. The cost of one inpatient treatment day was calculated to €370 (times 1.57: 581 US Dollar) (Table 1). Cumulatively, patients with BSI were treated as inpatients for 702 days (vs. 152 days in patients without BSI) and showed significant differences

- Patients with BSI had an increased duration of inpatient treatment (median, 12 days; IQR 8.5–16 days; $P<0.001$).
- Patients with BSI needed an increased number of intensive care treatment days ($P=0.017$).
- In patients with BSI an increased number of surgical interventions were performed. In 10 patients from the BSI-group, the central venous catheter had to be removed; in one patient, an abscess was drained by surgical intervention. None of the patients in the control group required surgery ($P=0$; 0.004).

In the BSI Group, 9 patients (21%) required intensive care treatment for 1–25 days (mean 7 days; median 4 days); in 4 of these patients catecholamines were

Table 2. Comparison of the two patient cohorts (matched pairs), Case patients with and control patients without bloodstream infection (BSI).

Item	Case patients with BSI[a]	Control patients without BSI[a]	*P*-value
Patients	43	43	–
Male (%)	18 (42)	15 (35)	0.549
Age (years)			
Median	6.7	6.7	0.966
Range	1–28[b]	1–21[c]	0.832
IQR[d]	3.1–13.6	2.6–13.1	
Malignancy (%)			1.000
ALL/AML	24 (56)	24 (56)	
NHL	5 (12)	5 (12)	0.016
Solid tumor (except CNS)	10 (23)	10 (23)	
CNS tumor	4 (9)	4 (9)	
Relapse	11 (26)	18 (42)	
CVAD[e] (%)			
None	0 (0)	3 (7)	0.211
Broviac-type	27 (63)	25 (58)	
Port-type	16 (37)	15 (35)	

ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; NHL, high-malignant Non-Hodgkin lymphoma; CNS, central nervous system.
[a]BSI, bloodstream infection (bacteraemia, candidaemia, sepsis).
[b]Including 1 patient >18 years.
[c]Including 1 patient >18 years.
[d]IQR, interquartile range (25–75 percentile).
[e]Long-term central venous access device.

Table 3. Distribution of the isolates in 43 bloodstream infections (number of isolates: $n = 46$).

Species	Number	Proportion (%)
Coagulase-negative staphylococci[a] (CoNS)	13	29
E. coli	9	20
Klebsiella spp.	7	15
Viridans streptococci	5	11
P. aeruginosa	4	9
Miscellaneous[b] ($n = 8$), each	1	2

[a]Of these methicillin-resistant $n = 9$ (MRSE; 69% of all CoNS).
[b]*Enterococcus faecium* (*Vancomycin-sensitive*), *S. aureus*, *Streptococcus pneumoniae*, *Acinetobacter lwoffii*, *Pantoea agglomerans*, *Enterbacter* spp., *Neisseria meningitidis*, *Candida albicans*.

Table 4. Results of the comparison between the matched patient groups[a].

	Case patients with BSI[a]	Control patients without BSI[a]	*P*-value
Inpatient treatment (days)			
Median	12	0	<0.001
Range	7–59	0–34	
IQR[b]	11–18	0–7	
Surgical intervention	9	0	0.004
Neutropenia after date of the event (days)[c]			
Median	6	0	0.329
Range	0–41	0–53	
IQR[b]	3–10	0–10	

For details see result section in the text.
[a]BSI, bloodstream infection (bacteraemia, candidaemia, sepsis).
[b]IQR, interquartile range (25–75 percentile).
[c]The duration refers to days after the onset of fever in BSI patients and to the days of neutropenia during the corresponding observation period in control patients.

administered intravenously and 2 patients were mechanically ventilated due to respiratory failure.

In the control group, only 1 patient required intensive care treatment for 21 days with 3 days on catecholamines, 21 days of mechanical ventilation due to an acute respiratory distress syndrome after IDA-FLAG treatment (Fleischhack et al., 1998) for relapsed AML without isolation of a causative pathogen.

There were no significant differences in days with neutropenia after the day of the event between the two groups (Table 4).

The difference in inpatient treatment days in patients with BSI led to the calculation of additional median expenses of €4400 (IQR, €3145–5920) per case [6.970 US Dollar (IQR 4.938–9.294)]. Considering the costs, no significant differences were found in a subgroup analysis which compared BSI with *Gram*-positive and BSI with *Gram*-negative pathogens (data not shown).

Discussion

In our paediatric oncology unit, patients with BSI had a significantly prolonged hospital stay in comparison to a thoroughly matched control group of patients without BSI. This resulted in additional median expenses of €4400 (IQR, €3145–5920) per case [6.970 US Dollar (IQR 4.938–9.294)]. These data enable us to calculate the cost effectiveness of certain preventive interventions aiming at a reduction of BSI in our patients (Perenchevic et al., 2007).

Cost containment policies in healthcare institutions often only take short-term financial benefits into account. Most targeted interventions to reduce the burden of nosocomial infections are related to a short-term financial effort which has to be outweighed against the long-term financial benefit of a lower incidence of BSI (O'Grady et al., 2002). In a recently published prospective cohort study, we were able to confirm a significant decrease in the incidence density of BSI due to coagulase-negative staphylococci (including methicillin-resistant isolates) secondary to the routine use of taurolidine lock solution in paediatric cancer patients with CVAD (Simon et al., 2008c). As a result of this intervention, 6 *Gram*-positive CVAD-associated BSI were prevented per year. According to the data presented here, these events accounted for mean savings of € 26,640 (IQR, €18,870–35,520) per year.

For some reasons, the cost calculations in this study describe only the lowest margin of additional expenses and are therefore not comparable to other studies, investigating the additional costs of nosocomial bloodstream infections in paediatric inpatients (Stone et al., 2003; Slonim et al., 2001). Our calculation relied on the lowest necessary budget for radiological investigations. We only included the regular working times of physicians and nurses without considering, that many of us work overtime. In addition, we did not calculate additional expenses related to intensive care treatment. Most likely, the inclusion of these costs would have resulted in a higher overall expenditure in case patients. Further more we did not include a social cost calculation, e.g. for absenteeism from labour in parents, who stayed in hospital during inpatient BSI treatment of their child. Thus, the median costs of a BSI may in fact be underestimated in this analysis.

We did not investigate the effect of BSI on the individual schedule of chemotherapy. In patients with leukaemia and malignant lymphoma as well as in some solid tumors, the response to induction chemotherapy relies on dose-intensity. Thus, any postponement of the regular chemotherapy schedule due to treatment related complications (e.g. BSI) may have a detrimental prognostic effect on the patient's long-term outcome. No significant difference was observed in days of neutropenia between the two matched patient groups. Although an independent risk factor, neutropenia is not an obligate prerequisite for BSI in paediatric cancer patients. Severe BSI may occur in non-neutropenic patients in particular in those with long-term central venous access devices (Rackoff et al., 1999; Aledo et al., 1998).

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