Surveillance with successful reduction of central line-associated bloodstream infections among neutropenic patients with hematologic or oncologic malignancies

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ORIGINAL ARTICLE

Surveillance with successful reduction of central line-associated bloodstream infections among neutropenic patients with hematologic or oncologic malignancies

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Abstract To determine nosocomial catheter-associated bloodstream infections (CA-BSIs) and to improve the prevention measures, we performed a prospective surveillance in our hematopoietic stem cell transplantation unit at our university hospital. During the 36-month study period all patients with at least two consecutive neutropenic days (NDs) were included. After the first 18 months the recorded data were analyzed and compared with reference data and were then presented to the clinical staff. An intensive training to improve the handling of central venous lines was performed afterwards. At the end of the last 18-month study period the data were evaluated and a multivariate analysis was conducted. Altogether 268 patients were treated for a period of 10,013 patient days including 4,286 NDs. A total of 202/268 (75.4%) patients underwent transplantation (157/76.6% allogeneic, 48/23.4% autologous). Eighty-seven CA-BSIs were identified. The incidence density was 24.3 CA-BSI episodes per 1,000 NDs in the first period and 16.2 in the second. A significant reduction in the CA-BSI rate of adults was achieved (OR 0.58; 95% CI 0.339–0.987; $p<0.05$). Significant risk factors for nosocomial CA-BSIs during the neutropenic phase were AML as underlying disease as well as transplantations.

Keywords Surveillance · Neutropenia · Nosocomial · Bloodstream infection

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Introduction

Central line-associated bloodstream infections (CA-BSIs) are associated with significant morbidity, mortality, and costs [1–3]. A special high risk patient group for CA-BSIs are the hematological oncology patients, because nearly 100% of these patients require indwelling central venous catheters for therapy and keep them during neutropenic episodes. Eighty-two percent of all infectious complications in patients undergoing hematopoietic stem cell transplantation appear during the neutropenic phase [4]. In addition, 65% of catheter-associated infectious episodes occur during neutropenia in recipients of bone marrow transplants [5]. Hence, the neutropenic phase represents a significantly high risk factor for cancer patients to acquire nosocomial infections. This was already described by Carlisle and other authors [6–8].

Therefore, a prospective surveillance for nosocomial infections during the neutropenic phase is an essential quality requirement for the treatment of patients with hematological malignancies to improve infection prevention measures.

The aim of this study was to introduce a prospective surveillance system for nosocomial CA-BSI, in order to improve prevention measures and to reduce this type of nosocomial infections in patients with hematological

oncological malignancies during neutropenia in a hematopoietic stem cell transplantation (HSCT) unit.

Materials and methods

Setting and study population

Hannover Medical School is a 1,400-bed university hospital in Germany. During the study period the HSCT unit was an interdisciplinary 20-bed ward (17 beds were occupied by adult patients and three beds by pediatric patients). This unit was built and opened at the beginning of 2001. Current recommendations have been taken into account for the construction of this new ward with HEPA air filtration and positive air pressure reverse isolation [9].

The study was conducted from May 2001 until April 2004 and included all adult inpatients who became neutropenic for at least two consecutive days due to their treatment in this unit.

Surveillance method

We decided to survey nosocomial bloodstream infections in adults (>18 years) in accordance with the ONKO-KISS protocol during neutropenia at our hospital [10]. This protocol was applied as part of the surveillance program of the German Hospital Infection Surveillance System (KISS). This module was introduced in the year 2000. Meanwhile, about 24 participating national and international centers for bone marrow transplantation from German speaking countries (Germany, Suisse, and Austria) have sent their data each year. Nosocomial CA-BSIs were diagnosed according to Centers for Disease Control and Prevention definitions that include clinical and laboratory criteria [11]. The CA-BSIs were recorded by the infection control team of the Hannover Medical School regardless of whether the patients had undergone HSCT or not.

Neutropenia was defined as the absolute white blood cell count being less than 1×10^9 cells/L for at least 2 days, since at this time the absolute neutrophil count definitely was <1,000/μL even in the absence of a differential count. The neutropenic phase was declared to have ended once the patient had a neutrophil count $>1\times10^9$ cells/L for at least 2 days. Nosocomial bloodstream infections that occurred during the neutropenic phase were recorded. An infection was only classified as being nosocomial if there was clear evidence that—at the point of admission to the ward—the infection had been neither active nor incubating. In addition, an infection was considered to be nosocomial if symptoms appeared at any time on or after the second day after the onset of neutropenia up to 2 days after the end of neutropenia.

During the neutropenic phase parameters and characteristics of the patients such as age, gender, underlying disease, relapse of disease, devices, transplantation, and type of transplantation were collected during their hospital stays.

Intervention

After the first 18 months of surveillance (May, 2001–October, 2002) the nosocomial incidence rates for CA-BSI were calculated. Compared with reference data the rates were presented to the healthcare workers in the ward. Within the following weeks an intensive training course was conducted for the clinical staff to improve the prevention measures concerning the handling of central venous lines according to national and international guidelines [12, 13].

Instead of gauzes only transparent semi-permeable dressings were used consequently and changed at least every 7 days or when it became damp, soiled, or loosened. All other recommended prevention measures were reinforced and improved consequently by education, particularly hand disinfection before donning or after removing gloves.

In addition, an improved standard operating procedure protocol for dealing with central venous lines was worked out and introduced into the routine nursing care of the ward. The formerly used non-impregnated central venous catheters were replaced by chlorhexidine-silversulfadiazine impregnated catheters (first generation) which were coated on the outer catheter surface.

Data analysis

The data were entered into Microsoft Excel (Microsoft, Redmond, WA, USA). Incidences (episodes per 100 patients) and incidence densities of nosocomial bloodstream infections per 1,000 neutropenic days were calculated [10]. Incidence densities were compared using the exponential maximum likelihood estimation test. Categorical variables were compared using chi-square or Fisher's exact test as appropriate.

To identify risk factors for CA-BSI a multivariate analysis was done by sequential backward stepwise elimination. All statistical tests were considered significant if the p-value was ≤ 0.05. Statistical analyses were performed using SAS software (SAS Institutes, Cary, NC).

Results

Patients

Throughout the 36 months of observation from May, 2001 to April, 2004, altogether 268 patients were treated on the HSCT unit at the Hannover Medical School during 10,013

patient days which included 4,286 (42.8%) neutropenic days. A total number of 280 neutropenic episodes were observed among these 268 patients. The mean length of stay on the unit of the study group was 37.4 days (median, 33.0 days; range, 7–168 days).

A total of 202/268 (75.4%) patients underwent transplantations. Of these, 157 (76.6%) patients received allogeneic and 48 (23.4%) patients obtained autologous transplantations. The duration of neutropenic episodes varied among different types of transplantation and in comparison to those patients without any transplantation (see Table 1).

Throughout the study period no changes in the anti-infective prophylaxis protocols were noticed.

Bloodstream infections

Eighty-eight CA-BSIs were recorded in 87 patients, i.e. one patient suffered two episodes of CA-BSI during his hospital stay on the ward. For further data evaluation only the first sepsis episodes were taken into account in the risk factor analysis. The mean length of stay on the unit of these BSI-patients was 41.1 days (median, 35.0 days; range, 9–127 days).

During the neutropenic phase, central venous lines were present in 97.8% (262/268) of the neutropenic patients. A non-tunneled central venous catheter was used in 258 patients of whom 86 (33.3%) suffered a sepsis. An existing totally implantable port system was used in four patients of whom one patient suffered an episode of CA-BSI. Six patients did not have any central venous access during neutropenia phase and they did not suffer from any sepsis.

The average time from the beginning of neutropenia to the first positive blood culture was 9.8 days (median 7 days, range 1 to 82 days). Of the 87 relevant bacterial isolates, 66 (75.9%) were gram-positive bacteria, 13 (14.9%) were gram-negative bacteria, four (4.6%) were yeasts, two (2.3%) were other cocci, one (1.1%) was *Corynebacterium* spp., and one (1.1%) was an anaerobe pathogen. Polymicrobial bacteremia was found in 14 patients.

No differences in the kind of infections concerning gram-positive and gram-negative bacteria were noticed between pre- and post-intervention period.

Intervention and reference data

The calculated incidence rates are presented in Table 2. In comparison with the reference data of ONKO-KISS—18 hospitals were participating in this module at the date of analysis—the rate of 24.3 for nosocomial CA-BSIs per 1,000 neutropenic days showed an outlier position above the 75th percentile (20.3) to the reference rate with a median of 17.7 in the first study period (period A) [10]. After intervention the rate decreased to 16.2 nosocomial CA-BSIs per 1,000 neutropenic days and showed a position below the median (17.7) compared to the reference data. This reduction was significant (OR 0.58; 95% CI 0.34–0.99) (see Table 3).

Risk factor analysis

The characteristics of the study population and the results of the univariate risk factor analysis are presented in Table 3. During multivariate analysis, variables independently associated with a CA-BSI were transplantation (OR 2.11; 95% CI, 1.10–4.26) and acute myeloid leukemia (AML) (OR 1.92; 95% CI, 1.12–3.32).

Discussion

The recently published article of Pronovost et al. has demonstrated that an evidence-based intervention resulted in a large and sustained reduction up to 66% in rates of catheter-associated BSIs in ICUs [14]. Several other studies described reduction rates of 14% to 71% on ICUs, e.g. surgical ICUs, neonatological ICUs, and hospital-wide. The authors of all these studies performed a surveillance with feedback and education programs [15–21]. Reduction rates of 41% to 100% in CA-BSIs were discussed in further studies [22–24]. The elimination of CA-BSIs was achieved with continuous training programs which included lectures, posters, fact sheets, self-study programs for health care workers, and a review with pre- and post-tests [24]. The duration of 4 years needed for the introduction of these measures as well as their evaluation is one characteristic of the latter.

Table 1 Duration of neutropenic episodes according to the different types of transplantation or to no transplantation

Type of transplantation	Total no. of patients	Total no. of neutropenic days	Duration of neutropenic phase			
			Mean	Min	Median	Max
Allogeneic transplant recipients	154	2,764	17.2	2.0	15.0	85.0
Autologous transplant recipients	48	508	10.6	4.0	8.0	99.0
Patients without transplantation	66	1,014	15.4	2.0	11.0	57.0
Total	268	4,286	16.0	2.0	13.0	99.0

Table 2 Comparison of the two study periods (A = basic period and B = after intervention) among all patients

Interventions	Period A Before	Period B After	Total
Duration (month)	18	18	36
Patients	138	130	268
Neutropenic days	2,184	2,102	4,286
Bloodstream infections (BSI)	53	34	87
Incidence density, BSI episodes per 1,000 neutropenic days	24.3	16.2	20.3
Rate, BSI episodes per 100 patients	38.4	26.2	32.5

To our knowledge, our study is the first to show a reduction of infection rates in patients with hematological malignancies after the implementation of surveillance with feedback and following training. Due to the implementation of these prevention measures during a time as short as 18 months, we achieved a significant reduction of 35.8% of CA-BSI episodes per 1,000 neutropenic days at the end of this observation period. Our successful efforts were not as impressive as described by Beerenholtz et al. [24]. Therefore, it is probably possible to achieve even much better reduction rates. However, the question remains whether this infection rate can be reduced to a sustained zero-rate in this high-risk patient group.

The duration of neutropenic phases caused by chemotherapy represents an important risk factor for acquiring nosocomial infections independently of undergoing a HSCT [25–27]. In our study we demonstrated that the main significant risk factors for nosocomial CA-BSI acquired during neutropenia are transplantation and the diagnosis and treatment for an AML. With 42.2%, patients with this underlying disease represent the main patient population of our study group. The recently published article of Meyer et al. shows similar results in patients with advanced AML who had an increased risk of CA-BSI [28]. However, patients with the diagnosis and treatment for

Table 3 Frequency of nosocomial catheter-associated bloodstream infection (CA-BSI) depending on patient characteristics and intrinsic risk factors in the study group (n=268)

Factor	Total no. of patients	No. of patients with CA-BSI		OR (95% CI)	p on univariate analysis	Multivariate analysis[a] OR (95% CI)
	No.	No.	(%)			
Age≥49	141	48	(34.0)	1.17 (0.70–1.95)	0.60	
Gender, male	152	53	(34.9)	1.29 (0.77–2.17)	0.36	
Underlying disease						
Acute myeloid leukemia	113	44	(38.9)	1.66 (0.99–2.78)	0.06	1.92 (1.12–3.32)
Acute lymphocytic leukemia	40	16	(40.0)	1.47 (0.74–2.95)	0.28	
Plasmacytoma	36	9	(25.0)	0.66 (0.30–1.47)	0.34	
Chronic myeloid leukemia	31	6	(19.4)	0.46 (0.18–1.17)	0.11	
Non-Hodgkin lymphoma	20	4	(20.0)	0.50 (0.16–1.53)	0.32	
Myelodysplastic syndrome	3	2	(66.7)	4.24 (0.38–47.4)	0.25	
Other	25	6	(24.0)	0.63 (0.24–1.64)	0.38	
Treatment of relapse	90	33	(36.7)	1.32 (0.77–2.26)	0.34	
Transplantation[b]	202	72	(35.6)	1.88 (0.99–3.58)	0.07	2.11 (1.10–4.26)
Bone marrow transplant						
Autologous	1	0	(0.0)	–	1.00	
Allogeneic sibling donor	5	1	(20.0)	0.52 (0.06–4.67)	1.00	
Matched unrelated donor	17	7	(41.2)	1.50 (0.55–4.07)	0.43	
Peripheral blood stem cells						
Autologous	47	11	(23.4)	0.58 (0.28–1.21)	0.17	
Allogeneic sibling donor	58	24	(41.4)	1.65 (0.90–3.00)	0.11	
Matched unrelated donor	77	31	(40.3)	1.63 (0.94–2.82)	0.09	
Central venous catheter	258	86	(33.3)	4.50 (0.56–36.1)	0.17	
Portsystem	4	1	(25.0)	0.69 (0.07–6.73)	1.00	
Without central device	6	0	(0.0)	–	0.10	
Study period B	130	34	(26.2)	0.57 (0.34–0.96)	0.04	0.58 (0.34–0.99)

[a] Significance level=0.05 for entry into the model and stay in the model after stepwise variable selection; basis odds=0.2574 c-index=0.623
[b] Two patients received more than one transplantation during their hospital-stay

advanced disease did not represent a significant number in our patient group.

The study has several limitations. First, the observation period of catheter-associated bloodstream infections was only restricted to neutropenic episodes in each patient. Hence, we did not know how many CA-BSIs were missed during the whole hospital stay and we did not observe patients without a neutropenic episode which had to occur at least on two consecutive days. Another aspect of this restriction is the unavailable comparison with published international CA-BSI rates because these rates refer to the common catheter-days. However, over 70% to 80% of nosocomial infections occur during neutropenic episodes [4, 29]. Hence, due to the restriction to high risk days—the neutropenic days—it is a time-saving effective method for surveillance of nosocomial infections among neutropenic patients. Meanwhile, 24 hospitals with bone marrow transplantation units from Germany, Suisse, and Austria participated in the ONKO-KISS module and provided their data to the national reference centre for surveillance of nosocomial infections (http://www.nrz-hygiene.de), which proves that the module i.e. the surveillance method is very well accepted.

Second, we did not evaluate compliance with the several trained procedures after intervention. Thus, we could not evaluate the relative importance of individual components of the multifaceted intervention.

The recently published systematic review of Niel-Weise et al. have shown that available scientific evidence to prevent CA-BSI by the use of antiseptic-treated CVCs in patients receiving chemotherapy is not sufficient as a basis to recommend their use [30]. A decade ago, Logghe et al. have demonstrated no statistically significant difference between the overall rates of BSI for impregnated and non-impregnated catheters in patients with hematologic malignancy by a randomized controlled trial [31]. Therefore, our introduction of chlorhexidine-silversulfadiazine impregnated catheters could not be solely responsible for the significant reduction of CA-BSI rates.

Many studies have shown successful reduction rates of CA-BSI due to multifaceted interventions in several patient groups [14, 19, 23, 24]. A systematic review has even shown that studies investigating multi-module program, however, found a substantial reduction in CA-BSIs. Simple interventions are often useful for reducing CA-BSI rates and the opportunities to decrease CA-BSI rates appear to be greatest when multi-module programs are applied [32]. Hence, we could confirm these statements with our data in a vulnerable high-risk patient group.

However, the aim of this study was to improve prevention measures which could be demonstrated with a significant reduction. More reports on successful interventions will be needed to promote a continuous prospective surveillance of nosocomial CA-BSIs in this high-risk patient group and to motivate clinical staff to improve prevention measures [33].

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