Etiology, clinical course and outcome of healthcare-associated bloodstream infections in patients with hematological malignancies: a retrospective study of 350 patients in a Finnish tertiary care hospital

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healthcare

ORIGINAL ARTICLE: CLINICAL

Etiology, clinical course and outcome of healthcare-associated bloodstream infections in patients with hematological malignancies: a retrospective study of 350 patients in a Finnish tertiary care hospital

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Abstract

This retrospectively collected laboratory-based surveillance data includes 575 healthcare-associated bloodstream infections (BSIs) in 350 patients with hematological malignancy in Tampere University Hospital, Finland, during 1999–2001 and 2005–2010. The most common underlying diseases were acute myelogenous leukemia ($n = 283$, 49%), followed by myeloma ($n = 87$, 15%) and acute lymphocytic leukemia ($n = 76$, 13%). The overall rate was 9.1 BSIs per 1000 patient-days. Gram-positive BSIs predominated and the most common pathogens were coagulase-negative staphylococci (23%), viridans streptococci (11%), enterococci (9%) and *Escherichia coli* (9%). Fungi caused 2% of BSIs. The 7-day and 28-day case fatalities were 5% and 10% and were highest in BSIs caused by *P. aeruginosa* (19% and 34%, respectively). The median age of patients with BSI has increased; it was 55.0 years during 1999–2001, compared to 59.0 years in 2005–2007 and 59.0 years in 2008–2010 ($p < 0.0001$). Gram-positive bacteria predominated in this material. Case fatalities were low as compared to previous reports although the median age of patients increased.

Keywords: Bacteraemia, healthcare-associated, hematological, incidence density

Introduction

Healthcare-associated bloodstream infections (BSI) are associated with an excess length of hospital stay, mortality and extra costs in hematological patients [1]. The presence of central venous catheters (CVC) increase the risk of BSI [2]. Hematological malignancy itself alters immune response and immunosuppression may also be therapy-related.

Patients with hematological malignancies have been identified with a changing spectrum of pathogens as a cause of BSIs in the last three decades. At the beginning of the 1980s, gram-negative bacteria were responsible for approximately two thirds of the infections in most centers. At the end of the 1980s the trend changed; gram-negative pathogens accounted for one third of BSIs [3] and gram-positive pathogens dominated [4]. In the 1990s and in the twenty-first century, gram-positive cocci have dominated [5,6]. Interestingly, some reports indicate that gram-negative infections would re-emerge [7,8].

To provide the best empirical antimicrobial coverage, knowledge of general and local trends in microbiological etiology is important. The Finnish Hospital Infection Program was started at the end of 1997. The program includes hospital-wide surveillance for healthcare-associated BSIs. The aim of this study was to identify etiology, clinical course and outcome of BSI in patients with hematological malignancies. We report results of a large tertiary-care hospital in Tampere, Finland, which participated in the national surveillance program for healthcare-associated BSIs among hematological patients during 1999–2001 and 2005–2010.

Methods

Pirkanmaa hospital district (HD) is a joint municipal authority comprising 22 municipalities and is responsible for the healthcare services of about 482 631 inhabitants (population in year 2010). The overall population of Finland in 2009 was 5 351 427. Thus, the HD covers the health care of 9% of the total Finnish population [9]. Tampere University Hospital (TAUH) is a tertiary care hospital with 942 beds in the HD, covering the need of specialized healthcare for more than one million Finns.

Setting

This retrospectively collected surveillance data includes all healthcare-associated BSIs in patients with hematological

malignancy in TAUH from 1 January 1999 to 31 December 2001 and from 1 January 2005 to 31 December 2010. One hematological ward in TAUH takes care of all patients with hematological malignancies in the HD. TAUH is not performing allogeneic, but performs autologous hematopoietic cell transplantations (HCT). Therefore acute allogeneic post-transplantation periods are not included in our data. There are five university hospital areas in Finland but allogeneic HCTs are centralized in two of them (Helsinki and Turku). The material represents all hematological healthcare-associated BSIs treated in Tampere University hospital in 1999–2001 and 2005–2010.

BSI surveillance was not conducted during 2002–2004 in the hospital due to limited resources.

Standard care

The standard antimicrobial treatment in neutropenic fever during the study years was a third generation cephalosporin alone or in combination with a new generation fluoro-quinolone. There were no major changes in antimicrobial practices or diagnostic procedures during the study period. No routine antibacterial prophylaxis has been used in this hematological center. Antifungal prophylaxis, fluconazole, was used in acute leukemia patients with neutropenia ($< 0.5 \times 10^9$/l) lasting for > 7 days.

Diagnostics

Finnish guidelines recommend that blood samples should be obtained for culture if the body temperature of a patient is $> 38°$C and/or a patient has other symptoms or signs that are compatible with BSI (e.g. hypothermia or hypotonia). No routine surveillance cultures are performed on samples from asymptomatic patients.

Definitions

Surveillance of healthcare-associated bloodstream infections has been conducted as a part of Finnish Hospital Infection Program (SIRO) since 1999, using the "old" CDC definition for BSIs [10,11]. The CDC definition of healthcare-associated BSIs was used. It means that the BSI is either a consequence of previous hospitalization or invasive procedure or related to the present hospitalization (the onset of BSI is associated with present hospitalization). BSI was defined as isolation of a bacterial or fungal pathogen from at least one blood culture [11]. The criterion for BSI in SIRO were that a potential pathogenic bacteria was isolated at least once in a blood culture or a potential skin contaminant was isolated at least twice. If a potential skin contaminant was isolated only once, the definition required that the clinician had initiated antimicrobial therapy. Primary BSI was defined as a condition in which there was no identifiable infection focus and secondary BSI as a condition in which there was an identifiable infection focus. According to national surveillance criteria, BSI was categorized as central venous catheter (CVC)-associated if there was no identifiable infection focus and the patient had a CVC inserted. Polymicrobial bacteremia was an infection with > 1 organism detected in a 48-h period.

An infection-control nurse reviewed the laboratory database for positive blood culture results in 1999–2001 and

2005–2010. The BACTEC 9240 (BD Diagnostic Systems, Sparks, MD, USA) blood culture system was used until 2007, and from 2007 BacT/ALERT 3D (bioMerieux SA, Mercy L'Etoile, France). Patient-days (years 1999–2001 and 2005–2010) and diagnoses of the patients were obtained from the hospital administration of TAUH. Data about the allogeneic HCT were obtained from the register of the HD in Helsinki, Uusimaa and data about autologous HCTs from the European group for blood and marrow transplantation database. The outcome at 7 and 28 days following the date of the first positive blood culture result for a particular patient was obtained from the national population registry by use of unique person identifiers. The day 7 and 28 mortalities represent crude mortality. A bacteremia episode in one patient was considered as a new episode, if the time interval between the two positive blood culture dates were more than 1 week and the patient had no positive blood cultures less than 7 days between these dates.

Statistics

An SPSS package (version 20) was used for statistical analyses and a two-sided p-value < 0.05 was taken as a cut-off for statistical significance. Categorical data were analyzed by χ^2 test or Fisher's exact test when appropriate, nonparametric data by Mann-Whitney U-test or Kruskal-Wallis test.

Results

The study comprised 350 patients with hematological malignancies. These patients had 575 BSI episodes during the 9-year study period in TAUH. The overall rate was 9.1 BSIs per 1000 patient-days and it peaked in 2006 (11.2/1000 patient-days) and 2010 (10.7/1000 patient-days) (Figure 1). The median age of patients during the whole study period was 58 years at the time of the positive blood culture (range 17–83 years). The median age of patients has increased; it was 55 years in 1999–2001, compared to 59 years in 2005–2007 and 59 years in 2008–2010 ($p < 0.0001$). Fifty four percent of patients were male. The main characteristics of the patients are given in Table I.

The most common underlying diseases were acute myelogenous leukemia (AML) ($n = 283$, 49%), followed by myeloma (MM) ($n = 87$, 15%) and acute lymphocytic leukemia (ALL) ($n = 76$, 13%). A total of 210 (37%) of patients underwent an allogeneic or autologous HCT, 232 (66%) patients had
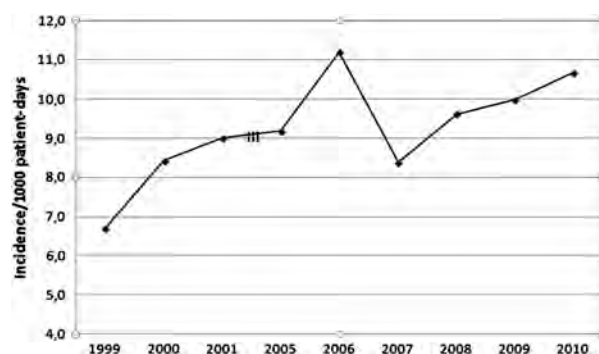

Figure 1. The overall incidence of healthcare-associated bloodstream infections in patients with hematological malignancy, Tampere University Hospital, Finland, 1999–2001 and 2005–2010.

Table I. Demographic characteristics and underlying conditions of patients with hematological malignancy and healthcare-associated bloodstream infections, Tampere University Hospital, Finland, in 1999–2001, 2005–2007 and 2008–2010.

Characteristic	Number (%)	1999–2001 n = 197	2005–2007 n = 199	2008–2010 n = 179
Age, median (range)	58 (17–83)	55 (18–81)	59 (17–83)	59 (17–79)
Male sex	308 (53.6)	113 (57.4)	94 (47.2)	101 (56.2)
Hematological malignancy				
Acute myelogenous leukemia	283 (49.2)	94 (47.7)	113 (56.8)	76 (42.5)
Acute lymphocytic leukemia	76 (13.2)	14 (7.1)	28 (14.1)	34 (19.0)
Myeloma	87 (15.1)	26 (13.2)	26 (13.1)	35 (19.6)
Non-Hodgkin lymphoma	59 (10.3)	19 (9.6)	26 (13.1)	14 (7.8)
Chronic lymphocytic leukemia	31 (5.4)	14 (7.1)	4 (2.0)	13 (7.3)
Chronic myelogenous leukemia	20 (3.5)	20 (10.2)	0	0
Hodgkin lymphoma	4 (0.7)	2 (1.0)	0	2 (1.1)
Myelodysplastic syndrome	5 (0.9)	4 (2.0)	1 (0.5)	0
Other	10 (1.7)	4 (2.0)	1 (0.5)	5 (2.8)
Bone marrow transplantation				
Autologous	110 (19.1)	30 (15.2)	40 (20.1)	40 (22.3)
Allogeneic	91 (15.8)	30 (15.2)	35 (17.6)	26 (14.5)
Both	9 (1.6)	4 (2.0)	2 (1.0)	3 (1.7)
Coexisting conditions				
Chronic hemodialysis	3 (0.5)*	2 (1.0)	0	1 (0.6)
Central venous catheter	325 (58.7)†	191 (97.0)	75 (39.1)	59 (35.8)
ICU stay	7 (1.2)‡	4 (2.0)	2 (1.0)	1 (0.6)

*Data available 570.
†Data available 554.
‡Data available 574.

a single BSI episode, 58 (17%) had two, and 60 (17%) had three or more episodes. Median time to the BSI onset was 13 days after hospitalization (range, 0–132). Overall, 79 (14%) of the BSIs occurred ≤ 7 days after hospitalization and 314 (55%) ≤ 14 days after hospitalization. *Candida albicans*, *P. aeruginosa* and enterococci species BSIs appeared late after hospital admission (17, 16.5 and 19 days, respectively) as compared to *S. aureus* BSIs, which appeared a median of 11 days after hospital admission. Gram-positive organisms accounted for 54% of all BSIs in years 1999–2001, 61% in 2005–2007 and 51% in 2008–2010, and gram-negative organisms accounted for 36%, 24% and 29% of all BSIs during the years, respectively (Figure 2). Anaerobes were rarely isolated (n = 11, 2% of all isolates), *Candida albicans* (n = 6) and non-*albicans* fungi (n = 6) accounted for 2.1% of all BSI episodes.

The total number of polymicrobial BSIs was 72 (13%) with 25 different isolated pathogens.

A total of 71 different pathogens were isolated. The most common causative organism was coagulase negative staphylococci (CoNS) (n = 130) followed by viridans streptococci (n = 66), enterococci (n = 53) and *Escherichia coli* (n = 49) (Figure 3). Most CoNS (n = 101, 78%) were *Staphylococcus*

Figure 3. Most common pathogens causing healthcare-associated bloodstream infection in patients with hematological malignancy, Tampere University Hospital, Finland, 1999–2001 and 2005–2010[a].
[a]Coagulase-negative staphylococci include *S. epidermidis* (101), caprae (1), hominis (6), haemolyticus (18), lugdulensis (2), warneri (1), xylosus (1), Enterococci include *Enterococcus faecalis* (13), casseliflavus (1), avium (1), faecium (37) and spp. (1), Enterobacter species include *Enterobacter cloacae* (17), aerogenes (1), agglomerans (1), sakazii (3), Viridans streptococci include milleri-group (5), gordonii (1), cristatus (1), salivarius (1), parasanguis (1), oralis (13), mitis (7), mitis-group (23), viridans-group (2), sp. (2) Klebsiella species include pneumonia (32), oxytoca (11), Candida species include albicans, clabrata (1), tropicalis (1), krusei (1), Candida sp. (3), other gram positive aerobes include *Corynebacterium jeikeium* (5), Bacillus sp. (1), Streptococcus sp. (5), *Bacillus cereus* (3), Leuconostoc sp. (1), Micrococcus sp. (2), Corynebacterium sp (6), *Rothia mugilacinosa* (4), *Listeria monocytogenes* (1), *Lactococcus lactis* (1).
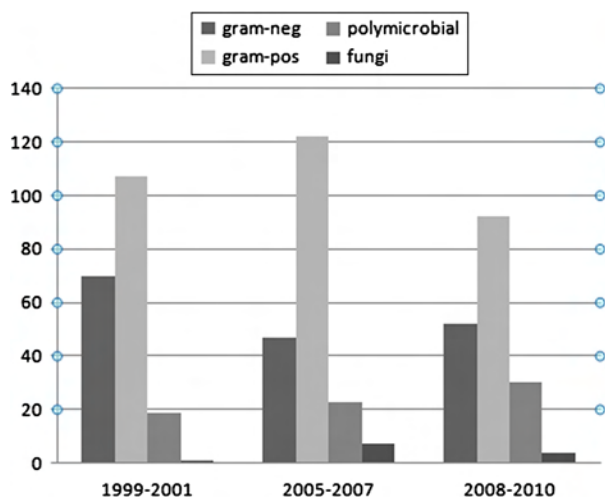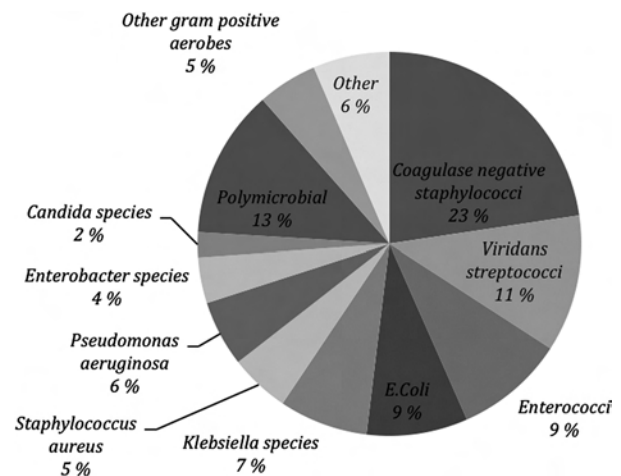
Figure 2. Gram-negative and gram-positive bacteremias, fungemias, and polymicrobial bloodstream infection in patients with hematological malignancy, Tampere University Hospital, Finland, 1999–2001 and 2005–2010.

epidermidis. Of viridans streptococci, 30 (45%) belonged to the *Streptococcus mitis*-group. Of the enterococci, 13 (25%) were *Enterococcus faecalis* and 37 (70%) were *Enterococcus faecium.* The proportion of BSIs due to CoNS showed a reduction during the study period. CoNS accounted for 28% of all BSIs in the years 1999–2001, 23% in 2005–2007 and 17% in 2008–2010 ($p = 0.071$). The number of enterococcal BSIs (all enterococcal species) varied during the study period, from 5% in 1999–2001 to 15% in 2005–2007 and 8% in 2008–2010 ($p = 0.003$). The proportion of polymicrobial BSIs was 10% in 1999–2001, 12% in 2005–2007 and 17% in 2008–2010 ($p = 0.095$).

In 57% of BSIs, patient had a CVC (data available on 96% of BSIs). BSI was CVC-associated in 50% (285/575) of cases. The proportion of CoNS in BSIs with CVC was 30% compared to 14% in BSIs without CVC ($p < 0.0001$). During 1999–2001, almost all the patients had CVC (97%). During 2005–2007 and 2008–2010, the proportions were 39% and 36%, respectively ($p < 0.001$). The infection focus was reported only in 4% of BSIs. The most common foci were urinary tract, gastrointestinal tract and respiratory tract (all less than 1% of BSIs). In 428 (74%) episodes the isolated bacteria was a potential pathogen, in 97 (17%) episodes it was a potential skin contaminant but it was isolated at least twice and in 50 (9%) episodes it was a potential skin contamination isolated only once but the clinician had initiated antimicrobial therapy. BSI was associated with earlier hospitalization in 7% (40/575) of cases and 1.7% of cases were associated to a previous outpatient procedure.

In patients with autologous HCT the most common causative organism was CoNS (36%) and it was significantly more common as compared to those with no autologous HCT ($p = 0.001$). Viridans streptococci accounted for 15% and *E. coli* 10% in patients with autologous HCT. The proportion of enterococci was less than in those with no autologous HCT (3% vs. 11%, $p = 0.064$). Among the patients with allogeneic HCT the most common causative organism were viridans streptococci (18%) followed by *Klebsiella species* (15%) and CoNS (15%). The relative proportion of viridans streptococci (18%) and *Klebsiella species* (15%) was high as compared to patients without allogeneic HCT (10% and 6%, $p = 0.064$ and $p = 0.005$, respectively). The proportion of *E. coli* was 5% in patients with allogeneic HCT. CoNS appeared less common than in those with no allogeneic HCT (15% vs. 24%, $p = 0.035$). Of 12 fungal isolates, one BSI caused by *Candida*

albicans occurred in a patient with the history of autologous HCT, but there was none in patients with allogeneic HCT. The distribution of pathogens in the different diagnosis groups are presented in Table II.

Altogether 139 patients of the total 350 died during the study period and the crude mortality was 40%. Of these patients, 5% (31/575) died within 7 days and 10% (59/575) died within 28 days of positive blood culture. The 7-day and 28-day case fatalities were 4% and 8% in gram-positive, 6% and 11% in gram-negative, 8% and 14% in polymicrobial BSIs and 8% and 33% in fungal BSIs, respectively. The case fatality within 7 and 28 days after the positive blood culture was highest for BSIs caused by *P. aeruginosa*, *Enterococcus faecium*, Candida species and polymicrobial infections. In patients ≥ 60 years (43% of the study population), the case fatality within 7 days was 10%, whereas in patients ≤ 35 years (14% of the study population), death occurred within 7 days in 4% of BSIs. The 7-day and 28-day case fatalities were 7% and 12%, 7% and 13% and 3% and 6% during 1999–2001, 2005–2007 and 2008–2010, respectively ($p = 0.179$ and $p = 0.088$, respectively). The case fatality in BSIs in relation to hematological malignancy and causative micro-organism are given in Table III. Antimicrobial resistances of some key pathogens are presented in Table IV. The proportion of meropenem- and ceftazidime-resistant strains of *P. aeruginosa* were 0% and 21% in 1999–2001, 17% and 0% in 2005–2007 and 63% and 17% in 2008–2010, respectively. In 2010, there was an outbreak of meropenem-resistant *P. aeruginosa* in the hematological ward. In 2010, there was an outbreak of multi-drug resistant *P. aeruginosa* in the hematological ward. Altogether three cases of multi-drug resistant (both meropenem- and ceftatzidime-resistant) strains were detected. This outbreak was managed with strict hygiene measures and screening of resistant strains by a rectal swap sample.

None of the enterococcal isolates were resistant to vancomycin in this material.

Discussion

The present study found that the median age of patients with hematological BSIs has increased over the years studied. However, case fatality did not increase. The overall rate of BSIs was 9.1 BSIs per 1000 patient-days and it peaked in 2006 (11.2/1000 patient-days) and 2010 (10.7/1000 patient-days). The overall rate was lower than in some previous reports

Table II. Gram-positive and gram-negative bacteremias, fungemias and polymicrobial bloodstream infections (BSI) in patients with hematological malignancies in Tampere University Hospital, Finland, 1999–2001 and 2005–2010 (Number (%)).

Hematological malignancy	Gram-positive bacteremia	Gram-negative bacteremia	Fungemia	Polymicrobial BSI
Acute myelogenous leukemia	153 (54.3)	85 (30.1)	5 (1.8)	39 (13.8)
Chronic myelogenous leukemia	10 (50.0)	8 (40.0)	0 (0)	2 (10.0)
Acute lymphocytic leukemia	46 (60.5)	18 (23.7)	2 (2.6)	10 (13.2)
Chronic lymphocytic leukemia	15 (48.4)	13 (41.9)	0 (0)	3 (9.7)
Hodgkin lymphoma	3 (75.0)	0 (0)	0 (0)	1 (25.0)
Non-Hodgkin lymphoma	36 (61.0)	14 (25.4)	4 (6.8)	4 (6.8)
Myeloma	51 (58.6)	24 (27.6)	1 (1.1)	11 (12.6)
Myelodysplastic syndrome	3 (60.0)	1 (20.0)	0 (0)	1 (20.0)
Other	4 (40.0)	5 (50.0)	0 (0)	1 (10.0)
	321 (55.8)	169 (29.4)	12 (2.1)	72 (12.5)

Table III. Case fatalities at 7 and 28 days after positive blood culture in patients with hematological malignancy and healthcare-associated bloodstream infections, Tampere University Hospital, Finland, 1999–2001 and 2005–2010.

Character	7-day case fatality, n (%)	28-day case fatality, n (%)
Hematological malignancy		
Acute myelogenous leukemia	8/283 (2.8)	18/283 (6.4)
Acute lymphocytic leukemia	0/76 (0.0)	6/76 (7.9)
Myeloma	9/87 (10.3)	14/87 (16.1)
Non-Hodgkin lymphoma	4/59 (6.8)	7/59 (11.9)
Chronic lymphocytic leukemia	5/31 (16.1)	9/31 (29.0)
Chronic myelogenous leukemia	0/20 (0.0)	0/20 (0.0)
Hodgkin lymphoma	0/4 (0.0)	0/4 (0.0)
Myelodysplastic syndrome	2/5 (40.0)	2/5 (40.0)
Other	3/10 (30.0)	3/10 (30.0)
Autologous hematopoietic cell transplantation	2/119 (1.7)	4/119 (3.4)
Allogeneic hematopoietic cell transplantation	1/100 (1.0)	3/100 (3.0)
Pathogen		
*Coagulase-negative staphylococci**	3/130 (2.3)	13/130 (10.0)
S. aureus	1/29 (3.4)	1/29 (3.4)
E. coli	1/49 (2.0)	1/49 (2.0)
Enterococcus[†]	5/53 (9.4)	7/53 (13.2)
Enterobacter species[‡]	1/22 (4.5)	1/22 (4.5)
Viridans streptococci[§]	4/66 (6.1)	4/66 (6.1)
Klebsiella species[#]	1/43 (2.4)	1/43 (2.3)
P. aeruginosa	6/32 (18.8)	11/32 (34.4)
Candida albicans	0/6 (0.0)	2/6 (33.3)
Non-albicans yeast[^]	1/6 (16.7)	2/6 (33.3)
Other grampositive aerobes+	1/29 (3.4)	1/29 (3.4)
Anaerobes[$]	0/11 (0.0)	2/11 (18.2)
Polymicrobial	6/72 (8.3)	10/72 (13.9)

*Including *S. epidermidis* (101), caprae (1), hominis (6), haemolyticus (18), lugdulensis (2), warneri (1), xylosus (1).
[†]Including *Enterococcus faecalis* (13), casseliflavus (1), avium (1), faecium (37) and spp. (1) [‡]Including *Enterobacter cloacae* (17), aerogenes (1), agglomerans (1), sakazii (3).
[§]Including milleri-group (5), gordonii (1), cristatus (1), salivarius (1), parasanguis (1), oralis (13), mitis (7), mitis-group (23), viridans-group (2), sp. (2).
[#]Including pneumonia (32), oxytoca (11).
[^]Including *Candida clabrata* (1), tropicalis (1), krusei (1), Candida sp. (3).
[+]Including Corynebacterium jeikeium (5), Bacillus sp. (1), Streptococcus sp. (5), *Bacillus cereus* (3), Leuconostoc sp. (1), Micrococcus sp. (2), Corynebacterium sp (6), *Rothia mugilacinosa* (4), *Listeria monocytogenes* (1), *Lactococcus lactis* (1).
[$]*Clostridium perfringens* (1), Clostridium species other than perfringens (4), *Bacteroides fragilis* group (3), other gram negative anaerobes (3).

[12,13]. The most common underlying disease in our hematological patients with healthcare-associated BSIs was AML followed by myeloma and acute lymphocytic leukemia. Distribution of diagnoses is in accord with previous studies in hematological patients [5,6,14], although some have reported contrary findings [15]. Interestingly, the relative proportion of acute lymphocytic leukemia and myeloma increased during the study period. The most common causative organism in autologous HCT was CoNS and *Klebsiella* species in allogeneic HCT. Interestingly, our patients with autologous HCT had a low proportion of enterococci. It should be noted, that allogeneic HCT are not performed in our hospital, thus early

Table IV. Antimicrobial resistance in *Escherichia coli*, *Klebsiella* species, *P. aeruginosa* and *Staphylococcus aureus* causing healthcare-associated bloodstream infections in patients with hematological malignancy, Tampere University Hospital, Finland, 1999–2001 and 2005–2010.

Antimicrobial	Number of resistant isolates/all tested (%)			
	Staphylococcus aureus	*Klebsiella species*	*P. aeruginosa*	*Esherichia coli*
Ampicillin		47/49 (96%)		29/63 (46%)
Cefotaxime		1/18 (6%)		0/19 (0%)
Ceftatzidime		2/50 (4%)	5/30 (17%)	0/63 (0%)
Cefuroxime		5/52 (10%)		0/63 (0%)
Ciprofloxacin			21/32 (66%)	
Clindamycin	1/29 (3%)			
Erytromycin	1/29 (3%)			
Fucidin acid	1/29 (3%)			
Levoflocacin	2/28 (7%)	1/50 (2%)	19/31 (61%)	8/63 (13%)
Meropenem/imipenem		0/51 (0%)	9/33 (27%)*	0/63 (0%)
Oxacillin/methicillin	1/28 (4%)			
Piperacillin-tazobactam		3/50 (6%)	20/33 (61%)	0/63 (0%)
Rifampin	0/27 (0%)			
Tobramycin/netilmycin	1/29 (3%)	1/37 (3%)	21/33 (64%)	1/63 (2%)

*Proportion of MDRPA was 2/33 (6%).

post-transplantation BSIs in allogeneic patients were not included in our study.

In our study the most common pathogens were gram-positive organisms, and they varied from 54% of all BSIs in years 1999–2001, 61% in 2005–2007 and 51% in 2008–2010. The most common causative organism was CoNS, followed by viridans streptococci, enterococci and *E. coli*. There are previous studies that are in line with our results [3,5,6] and also those showing different distribution of pathogens [7,15,16]. The proportion of fungi was only 2%, which is low compared to earlier studies [2,5,6]. Several studies have shown that BSIs in patients with hematological diseases are most frequently caused by the above-mentioned pathogens (CoNS, viridans streptococci, enterococci and *E. coli*), in various rank orders [5,6,13,17–19]. Different causative agents appear in different time points as regards to hospital stay. *S. aureus*, *E. coli* and *Klebsiella* species appear earlier than enterococci and fungi. Their results might be explained by the fact that most severely ill patients stay longer in hospital and are prone to infections caused by fungi and enterococci. Chemotherapy-related immunosuppression and neutropenia appears most often weeks after hospital admission and beginning of the chemotherapy-cycle.

There is ongoing discussion about the Central Line-Associated Bloodstream Infection (CLABSI) definitions and different centers have used varying definitions [20–22]. We found the decreasing proportion of CoNS as a causative organism of healthcare-associated bacteremia and a significant decrease in the use of CVC during the study years. This might indicate that decreased use of CVCs would result in a decrease in BSIs caused by CoNS. However, we did not have data on CVC days, which is a prequisite for the definition of CVC-related infections. Thus, conclusions about the effect of decreased CVC usage in relation to BSIs cannot be made. If a patient has a bacteremia and has concomitant CVC this does not absolutely mean that the bacteremia is due to CVC. Enterococcal, polymicrobial and *E. coli* bacteremias in our study are a good example of this. Enterococcal, *E. coli* and polymicrobial bacteremias reflect the mucosal barrier injury in most patients [20,21]. One recent Swedish study found *E. coli* to be the most common pathogen in patients with hematological malignancy (data collected during 2002–2008) and healthcare-associated BSI and CoNS only constituted 15% of all BSIs [23]. The proportion of CoNS in our study during the last period (2008–2010) was almost the same as in this Swedish study but the proportion of *E.coli* in our study was much lower throughout the study period.

Antimicrobial susceptibility testing showed that methicillin-resistant *S. aureus* (MRSA) caused only one BSI in patients with hematological malignancy, although there has been a large ongoing MRSA epidemic in the Pirkanmaa HD [24]. This finding may be due to strict hygiene measures and screening policies in the hematological unit. Almost every third of *P. aeruginosa* isolates were resistant to imipenem and/or meropenem and carbapenem resistance was more common than resistance to ceftatzidime. The increasing resistance against carbapenems is worrisome. Due to this, in a case of suspicion of *P. aeruginosa* sepsis (septic shock), ceftatzidim-based empirical therapy has been chosen. Meropenem is more used than ceftazidime in Tampere University Hospital, and the selection pressure seems to be higher for meropenem-resistant strains. In 2013, 14.5% of all *P. aeruginosa* bloodstream isolates were resistant or intermediate resistant to meropenem in Finland [25]. Increasing genetic resistance of *P. aeruginosa* is increasing in Europe [26]. One recent report indicated that 27% of *P. aeruginosa* isolates were doripenem-non-susceptible in Sweden in 2011 as compared to the year 2009, when only 4% of isolates were doripenem-non-susceptible [26]. The large genome of *P. aeruginosa* provides a tremendous amount of flexibility and the metabolic capability in addition to mediator activation via release of endotoxin, *P. aeruginosa* possesses a repertoire of exotoxins and enzymatic products designed to evade host defences. It has also an array of chromosomal and plasmid-mediated antibiotic resistance factors, making antibiotic treatment difficult. The present findings are in concordance with previous studies indicating that *P. aeruginosa* more easily develops resistance towards imipenem than to ceftatzidime [27]. In 2010, there was an outbreak of multi-drug resistant *P. aeruginosa* in the hematological unit of TAUH resulting in an increase in the proportion of resistant *P. aeruginosa* BSI isolates. The outbreak was managed with screening and strict hygiene measures. None of the enterococcal isolates were resistant to vancomycin in this study.

According to the Finnish treatment guidelines for neutropenic fever, the antimicrobial therapy should start immediately after the blood cultures have been obtained. The international guidelines recommend that febrile neutropenic patients should receive initial doses of empirical antibacterial therapy within an hour [28]. The empirical coverage (a third generation cephalosporin with or without an aminoglycoside) is broad. However, *P. aeruginosa*, CoNS and enterococci may not always be covered with these recommended empirical antibiotics, as is seen in our study. The primary empirical choice in febrile neutropenia is third generation cephalosporine in combination with or without fluoroquinolone.

In our study, 5% died within 7 days after the onset of the BSI and 10% died within 30 days. These figures are low compared to other studies [2,12,15,29]. This may result from the differences in patient materials but also reflect the low antimicrobial resistance of pathogens in this unit. The case fatality was lowest in BSIs due to gram-positive pathogens. The 7-day and 28-day case fatalities were 4% and 8% in gram-positive, 6% and 11% in gram-negative, 8% and 14% in polymicrobial BSIs and 8% and 33% in fungal BSIs, respectively. In accord with previous studies the case fatality was highest for infections caused by *P. aeruginosa* and *Enterococcus faecium* [6,16].

No antibacterial prophylaxis is used in neutropenic patients in our center. The international guidelines advocate the use of antimicrobial prophylaxis in severe neutropenia, which lasts 1 week or longer [28]. Antifungal prophylaxis with fluconazole has been used during the neutropenic periods

in acute leukemias. Fungemia was rare in the present material. This does not support the idea of prolonged prophylactic use of antifungals or the use of more broad-spectrum antifungals.

Some limitations must be conceded here. Healthcare-associated BSI surveillance was not conducted during the years 2002–2004 due to limited resources. Thus, these years are not presented in the present study. The rates of healthcare-associated BSI during the years 2002–2004 are unknown in TAUH. Also we have no information about neutropenic days as a denominator and hospitalization days according to hematological diagnosis. It would also be interesting to know the total utilization rate of CVCs; the present data is only concerns the patients with BSI.

In summary, this large retrospectively collected cohort study among hematological patients in a tertiary care hospital in Finland showed that gram-positive organisms predominate in BSIs and CoNS is the most common pathogen. The median age of patients with healthcare-associated BSI rose during the study years but the case fatality remained low. This may reflect the general trends of modern medicine. However, micro-organisms causing healthcare-associated BSIs and antimicrobial resistance may change rapidly. This warrants the implementation of new empirical treatment schemes in hematological patients. Thus, continuous surveillance is necessary.

Acknowledgements

Funding

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