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Blood stream infections throught the entire course of acute lymphoblastic leukemia treatment

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The incidence, type and mortality of bacteremias were evaluated in a pediatric patient cohort, during the entire course of treatment for acute lymphoblastic leukemia (ALL).

Eighty-six patients with newly diagnosed ALL were studied. A bacteremic episode was defined as blood isolation of a pathogen in the presence of clinical symptomatology of septicaemia. Bacteremias were analyzed according to the treatment element being delivered and the degree of neutropenia. A central venous catheter (CVC) was inserted at diagnosis in all patients.

Fifty-two episodes of bacteremias were encountered in 38/86 (44%) patients, while 48/86 patients had no positive blood culture. Three out of the 38 patients had bacteremia and CVC area infection, simultaneously. Most blood stream infections (29/52, 56%) were documented during the induction phase. Isolated Gram-positive organisms were 48%, Gram-negative 50% and 2% of the positive blood cultures represented fungaemias. The most common Gram-positive isolates were Staphylococcus species (N=22) and the commonest Gram-negative isolated pathogens were Escherichia coli and Pseudomonas aeruginosa. The majority of bacteremias (75%) occurred during neutropenia. The initial antibiotic treatment was ceftazidime or piperacillin/tazobactam and amikacin or tobramycin. CVC was not removed in the majority of bacteremias (94%). No infection related fatality was recorded. Bacteremias constituted a severe and common complication in our patient cohort. However, infection-related fatality rate was negligible, most probably due to the prompt initiation of broad coverage antimicrobial therapy.

Key words: bacteremia, acute lymphoblastic leukemia, childhood, central venous catheter, Staphylococcus

Among patients with malignancy, blood stream infections are a prominent cause of morbidity, and in some cases even of mortality. Patients with lymphoid malignancy are susceptible to blood stream infections related to the underlying immune dysfunction, to the use of myelosuppressive regimens, to the high colonization rate with pathogenic organisms and to the frequent use of invasive procedures [1,2].

The spectrum of bacteria isolated from bacteremias patients has changed overtime. An increase in Gram-positive infections is evident, in the last decades. The widespread use of indwelling central venous catheters (CVC) and the use of prophylactic antibacterial agents with gram-positive coverage have contributed to this change [3, 4].

Central venous catheters provide a consistent venous access to cancer patients. However, the most common problem associated with these devices is catheter related infection [5, 6]. The relative risk of infection is estimated to be high in children having a CVC in place during chemotherapy treatment [6]. Thus, differentiating catheter related from non-catheter related blood stream infections prevents unnecessary removal of surgically placed CVCs and helps in the therapeutic decisions.

The aim of this retrospective study is to report the incidence, type and mortality of bacteremias in a pediatric patient cohort with acute lymphoblastic leukemia (ALL), during the entire course of treatment. Furthermore, the study of the epidemiologic pattern of bacteremias in specific ALL populations will help in the management of infectious episodes with effective evaluations and interventions.

Materials and methods

The incidence and type of bacteremias were evaluated retrospectively in 86 patients (47 boys and 39 girls) with newly diagnosed ALL and initiation of chemotherapy treatment, from April 1994 to February 2000. Median and mean age at diagnosis was 5.9 and 6.3 years, respectively (range, 0.3 to 14.9

years). All patients received treatment according to a modified ALL-BFM 90 and ALL-BFM 95 protocol [7, 8]. The treatment and dosage schedules have been described in detail elsewhere [7-9]. Among the patients studied, 69 received median risk (MR) ALL treatment and 17 received high-risk (HR) treatment. Out of these 17 patients, 15 received HR treatment due to the presence of an absolute neutrophil count of more than 1000 /mm^3 in the peripheral blood, on the 8th day of induction treatment and 2 patients due to no remission on the 33rd day of induction. Patients' characteristics are given in Table 1.

An indwelling central venous catheter (CVC) of the Hickman-Broviac type was inserted in all patients, at diagnosis, and it was planned to be removed at the beginning of oral maintenance chemotherapy. CVCs were inserted surgically under strict aseptic conditions, via external or internal jugular vein cutdown. Maintenance procedures, such as daily change of the dressing of the CVC with provodine solution, were applied at the exit site. Additionally, at least every 3 days heparinization with a 10U/ml heparin solution was prescribed. The long-term vascular access was used for blood sampling and blood transfusions, as well as, for the administration of chemotherapeutic regimens, antibiotics and total parenteral fluids.

In the present study, all the documented episodes of bacteremias, verified with positive blood cultures, were collected and evaluated. Microbiologic diagnosis confirmed the clinically documented infections. Time of patient follow up for susceptibility for bacteremia was calculated from diagnosis to the end of maintenance treatment in first remission (76 patients), from diagnosis to death (2 patients) or first relapse while on treatment (8 patients), whatever came first.

A bacteremic episode was defined as isolation of a pathogen from blood in the presence of clinically significant symptomatology suggesting septicemia. Clinical signs of inflammation at the exit site and/ or the CVC tunnel and a positive site culture established a CVC tunnel infection. Fever was defined as an oral temperature of 38°C or higher taken twice over a 12-hour interval. Blood cultures were drawn at the beginning and during the course of each febrile episode. Furthermore, during the investigation of a suspected blood stream infection, blood cultures were drawn from peripheral veins and via the CVCs, with standard aseptic techniques and analyzed with qualitative methods.

The patients were classified as having very severe, severe or moderate degree of neutropenia, when the absolute neutrophil count (ANC) was less than 0.1 K/uL, 0.1-0.5 K/uL and between 0.5 to 1.0 K/uL, respectively. Patients were considered not neutropenic if the ANC was more than 1.0 K/uL [10]. Bacteremias were analyzed and categorized according to *a)* the component of the antineoplastic treatment being delivered (induction, consolidation, reinduction, maintenance) and *b)* the degree of neutropenia (ANC, in the peripheral blood).

Patients received *Pneumocystis jiroveci* prophylaxis with oral co-trimoxazole three times per week, for the entire treatment duration. Patients with contraindications to receive co-trimoxazole received pentamidine. Infection prophylaxis also included intensive daily oral mucosa hygiene and nystatin application. Fluconazole was given systematically during the intensive part of treatment (excluding maintenance).

Table 1. Patients' Characteristics

	No. of patients	BFM- 90	BFM- 95
Patients	86	29	57
Male	47	17	30
Female	39	12	27
Mean Age yrs.	6.3	5.9	6.3
Range	0.3-14.9	0.3-14.1	2.0-14.9
Risk group of ALL			
MRG	69	21	48
HRG	17	8	9

MRG, median risk group
HRG, high risk group

The initial antibiotic treatment consisted of ceftazidime or the combination of piperacillin/tazobactam and an aminoglycoside (amikacin or tobramycin). In a few cases, a specific antistaphylococcal agent (vancomycin or teicoplanin) was given without a proven Staphylococcal species infection upon admission, due to the patient's clinical condition. The antibiotic treatment was changed and modified later based on the results of the blood cultures and the in vitro sensitivity results.

Results

Fifty-two episodes of bacteremias were encountered in 38/86 patients (44%). To the contrary, 48/86 (56%) patients had no positive blood culture. Twenty-six patients out of the 38 had a single episode, 9 patients had two and 3 patients had more than two episodes of bacteremia. The time that the patients had a CVC of Hickman-Broviac type in place was 79 to 721 days (mean, 309 days). The total risk period was 26590 patients * days.

Most of those bacteremias were documented during the induction phase of ALL treatment (29/52 episodes, 56%). During the consolidation phase, 13/52 episodes (25%) were encountered, the majority of them (12/13) in patients receiving HR ALL treatment and a single episode in a patient receiving MR ALL treatment. During reinduction and maintenance ALL treatment phases, 2/52 (4%) and 8/52 (15%) episodes of bacteremias were identified, respectively. The distribution of bacteremias per treatment phase, based on the patients' risk group is presented in Figure 1.

Among the organisms that were isolated, 25/52 were Gram positive (48%), 26/52 were Gram negative (50%) and 1/52 was fungus (2%). The most common Gram positive isolates were *Staphylococcus* species (N=22), particularly *coagulase-negative Staphylococci* (17/22), followed by *Streptococcus viridans* (N=2) and *Enterococcus* (N=1). *Escherichia coli* (N=6), *Pseudomonas aeruginosa* (N=6) and *Klebsiella species* (N=5) were

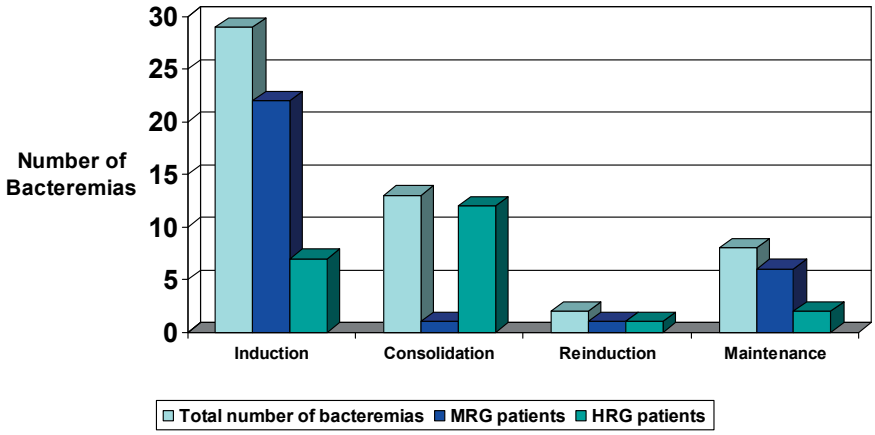

Figure Legend: Distribution of the number of bacteremias per treatment phase, based on the patients' ALL treatment risk group. MRD Median Risk Group. HRG High Risk Group

the most commonly isolated Gram negative organisms. The rest of the Gram negative isolates were *Enterobacter cloacae* (N=3), *Serratia* (N=1), *Salmonella species* (N=2), *Acinetobacter calcoaceticus* (N=3), *Aeromonas hydrophila* (N=1) and one non further identified Gram negative bacterium. The isolated fungus was *Candida cruzei* in a patient receiving total parenteral nutrition. The isolated microorganisms from the positive blood cultures in relation to the treatment element are summarized in Table 2.

Considering the bacteremias during maintenance, six (6/8 bacteremias noted during maintenance) were due to Gram positive organisms (5 *Staphylococci* and 1 *Corynobacterium species*). All the 5 *Staphylococcal* infections were diagnosed in patients in the CVC place, during the first two months of maintenance treatment and only two of them with concurrent moderate degree of neutropenia. The rest 2/8 bacteremias in maintenance were due to Gram negative organisms (1 *Enterobacter* and 1 *Aeromonas*). The Gram negative infections occurred early into the maintenance treatment with catheter in place, both without concomittant neutropenia.

Twenty, 10 and 9 positive blood cultures were documented during very severe, severe and moderate degree of neutropenia, respectively. Only 13 (25%) episodes of bacteremias were encountered in patients without neutropenia. The dis-

Table 2. Isolated bacteria from positive blood cultures in relation to the treatment element

	Total	INDUCTION	CONSOLIDATION		REINDUCTION	MAINTENANCE
			MRG	HRG		
BACTERIA	**52**					
Gram-positive	**25**					
Staphylococcus		13	-	3	1	5
Streptococcs		-	-	1	-	1
Enterococcus		1	-	-	-	-
Gram-negative	**26**					
Klebsiella species		3	-	2	-	-
Pseudomonas aeruginosa		2	1	1	1	1
E.coli		2	-	4	-	-
Enterobacter cloacae		3	-	-	-	-
Serratia		-	-	1	-	-
Salmonella species		2	-	-	-	-
Acinetobacter calcoaceticus		3	-	-	-	-
Aeromonas hydrophila		-	-	-	-	-
Gr –negative non specified		1	-	-	-	-
Fungi	**1**		-	-	-	-
Candida cruzei		1	-	-	-	-

tribution and the frequency of the isolated microorganisms according to the degree of neutropenia are presented in Table 3.

Blood stream and CVC infection, simultaneously, was identified in 3/38 patients. Removal of the CVC was necessary in all these 3 cases, due to increased infection related morbidity and cardiovascular instability. CVC was not removed in the majority of the cases of bacteremias (49/52 cases, 94%).

Infection related fatality was negligible in this patient cohort. None of the patients had a life-threatening infection requiring transfer to the intensive care unit and none of the patients succumbed during a bacteremic episode.

Table 3. Type and number of blood culture isolates in relation to the absolute neutrophil count (ANC)

		ANC			
	TOTAL	**< 0.1**	**0.1-0.5**	**0.5-1.0**	**> 1.0**
BACTERIA					
Gram-positive	**25**				
Staphylococcus		5	4	6	7
Streptococcus		1	-	-	1
Enterococcus		1	-	-	
Gram-negative	**26**				-
Klebsiella species		3	2	-	-
Pseudomonas aeruginosa		2	2	-	2
E.coli		4	-	-	-
Enterobacter cloacae		2	1	-	-
Serratia		-	-	1	-
Salmonella species		-	-	1	1
Acinetobacter calcoaceticus		1	1	-	1
Aeromonas hydrophila		-	-	-	1
Gr- negative non specified		1	-	-	-
Fungi	**1**				
Candida cruzei		-	1	-	-

Discussion

Bacteremias are a severe and common complication in children with cancer during their treatment and particularly at the most intensive part of it. For patients with ALL the most intensive treatment is the induction phase. During induction treatment, patients are immunosuppressed and neutropenic, with newly placed indwelling catheters and not in well consolidated leukemic remission [11, 12]. Additionally, the use of a CVC poses a higher risk of severe blood stream infection for the patient, even in cases without neutropenia [6, 13]. The individual practices in maintaining and accessing the catheters might also be of significance, although there are contradicting practices and the need of well designed studies is strongly indicated [14].

Searching the related literature, several studies have indicated that the majority of the serious bacterial infections occur during the induction treatment in leukemia [1, 15, 16]. In our series, more than half of bacteremias (56%) occurred during the induction phase, particularly in MR patients (22 of total 30 bacteremias). It is worth noticing that, 75% (39/52) bacteremias occurred while the patients were neutropenic and particularly with severe degree of neutropenia (51%, 20/39). In HR patients most of the bacteremias were encountered during consolidation phase (12 of the total 32 bacteremias). *Graubner et al* also reported in their recent analysis that the distribution of the total infectious complications during consolidation was higher among patients with high risk than low risk ALL. However, in the same study and in contrast to our study, infectious complications during induction almost equal for both low risk and high risk patients [17].

Despite the fact that bacteremias with concurrent neutropenia, constitute a significant factor of morbidity, mortality rates have decreased dramatically. This is most probably due to the prompt initiation of broad spectrum antimicrobial therapy and overall improvements in supportive care. In the present study, none of the patients succumbed to bacteremia.

Over the past decade, the nature of bacteremia in febrile neutropenic patients with cancer has changed, with a reduction in Gram negative infections and a shift toward Gram positive bacterial predominance [3, 4, 17]. The cause of this change from Gram negative to Gram positive organisms is not absolutely clear and is most probably multifactorial. Important considerations include different types of aggressive chemotherapeutic regimens, increased use of central venous access devices and the use of prophylactic antibacterial agents with relatively weak activity against Gram positive organisms [3]. *Staphylococcus aureus* is second only to coagulase negative *Staphylococcus* as the most common isolated Gram positive bacterium in patients with cancer [18, 19] and catheter is the most commonly identified source of bacteremia [20, 21].

According to our experience and based on a previous study of our Department, Gram negative organisms were the predominant isolates during 1972-1981. In this study, *Pseudomonas* and *Klebsiella* species were the most common isolated pathogens. During the next decade, in a second study of our Department, predominance of Gram positive organisms prevailed. Over the time course of the present study, there was no change in pathogens' resistance patterns.

In the present study, slight increase in the incidence of Gram negative bacteremias is observed, during 1994-2000. In recently published studies in pediatric patients, increase in Gram negative bacteremias is reported [22].

We analyzed the episodes of bacteremias in a pediatric patient cohort with ALL, during the entire course of treatment. Bacteremias constituted a significant factor of morbidity in this cohort. However, it is significant that fatality was negligible. Surveillance and prompt investigation of each febrile episode, together with prompt and timely initiation of antimicrobial treatment, tailored to the locally encountered pathogens and sensitivity resistance patterns is expected to improve patient outcome overall and minimize morbidity and mortality.

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