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Infectious complications in pediatric acute myeloid leukemia: analysis of the prospective multi-institutional clinical trial AML-BFM 93

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Infections still remain a major cause of therapy-associated morbidity and mortality in children with acute myeloid leukemia (AML). To improve supportive care measurements, detailed information on frequency and characteristic features of infectious complications is needed. We retrospectively analyzed the medical charts of 304 children, treated in 30 hospitals according to the multi-institutional clinical trial AML-BFM 93. Overall, 855 infectious complications occurred in 304 patients (fever without identifiable source ($n=523$; 61.2%), clinically ($n=57$; 6.7%) and microbiologically documented infections ($n=275$; 32.1%)). Neutropenia was present in 74.1% of the infectious episodes. In all, 20 patients died of infection-associated complications (15/276 (5.4%) patients without and 5/28 (17.9%) with Down syndrome), most of them during early induction therapy ($n=11$). Blood stream infections occurred in 228 episodes (Gram-positive ($n=202$) and Gram-negative ($n=42$) pathogens). Invasive fungal infection was probable or proven in 15 patients. In 113 out of the 855 infectious episodes (13.3%), pneumonia was radiologically diagnosed. Better strategies of supportive care might help to improve overall survival in children undergoing chemotherapy for AML. Therefore, children with AML should be treated in specialized pediatric centers, and there should be a very low threshold to readmit patients, in particular patients with pulmonary symptoms.
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Introduction

Acute myeloid leukemia (AML) accounts for approximately 20% of acute leukemias in children. Significant progress in improving outcome for AML patients has been achieved over the last two decades and is mainly attributed to intensification of chemotherapy. For example, the introduction of high-dose cytarabine and mitoxantrone significantly increased the 5-year event-free survival of high-risk patients treated according to the clinical trial AML-BFM 93 compared with the previous trial AML-BFM 87 (44 *vs* 31%; $P=0.01$).[1] Intensive chemotherapy, however, also increased the risk of infectious complications, which are a substantial cause of morbidity and mortality in this patient population.[2] Recently, the clinical trial CCG-2961 was suspended because of a high number of therapy-related toxic deaths (Feusner *et al*. *Blood* 2002; **100**: 332a; abstract). Surprisingly, published data about the incidence and characteristics of infectious complications in patients undergoing therapy for AML are limited.[3,4] This prompted us to perform a retrospective study in children undergoing therapy for AML according to the multi-institutional clinical trial AML-BFM 93. The objectives of this study were to identify the incidence, main pathogens and sites, as well as risk factors of infectious complications. The results of this analysis may help to improve supportive care strategies in patients undergoing therapy for AML, to decrease morbidity and mortality, and thus, to improve overall survival.

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Patients and methods

The medical records of 304 patients enrolled in the prospective multi-institutional clinical trial AML-BFM 93 were reviewed. These 304 patients consisted of 276 patients officially enrolled as protocol patients, and 28 patients with Down syndrome who were not registered as protocol patients, but were treated according to AML-BFM 93 and were therefore subjects of this retrospective report. All data regarding infectious complications occurring during intensive treatment were gathered by two of the authors (DV and JK) in the hospital where the patient had been treated. Infectious complications were defined as fever requiring antibiotic therapy and/or clinical signs and symptoms associated with the isolation of a pathogen or an identifiable site of infection by physical examination or imaging study. One cycle of chemotherapy was defined as the time from the start of chemotherapy (eg induction therapy) until the day before the start of the next cycle of chemotherapy (eg consolidation). Fever was documented if one axillary temperature was greater than 38.5°C or two measurements of 38–38.5°C were taken within a 4-h interval. Neutropenia was defined as an absolute neutrophil count $\leqslant 500/\mu l$. Infectious episodes were categorized as microbiologically or clinically documented infections or as fever without an identifiable source (FUO). Bacteremia was defined as fever with a positive blood culture for bacteria (peripheral blood or from the central venous indwelling catheter). If the bloodstream isolate was a potential skin contaminant (eg coagulase-negative staphylococci (CoNS), *Propionibacterium* spp, *Bacillus* spp), the presence of an intravascular catheter was required for the diagnosis of a bloodstream infection.[5] The diagnosis of infection of the gastrointestinal (GI) tract was made when clinical symptoms could be attributed to a pathogen (such as *Clostridium difficile* or rotavirus). Diarrhea alone or the recovery of a pathogen in the stool without clinical symptoms did not fulfill the criteria of GI tract infection. Similarly, the diagnosis of pneumonia was based on pathological chest X-ray and/or CT scan accompanied by clinical symptoms of lower respiratory infection. The diagnosis of an infection of the central venous line (CVL) was only made when a pathogen could be isolated from the tip of the CVL or from the insertion site combined with clinical symptoms such as erythema and/or exudate. Fungal infection were defined as proven invasive infection (positive histopathologic findings or positive culture) or probable invasive infection (at least one host factor criterion, such as neutropenia for more than 10 days or persistent fever refractory to broad-spectrum antibacterial

treatment in high-risk patients; and one microbiological criterion, such as a positive result of culture for *Aspergillus* spp from sputum or brochoalveolar lavage fluid samples or a positive result for *Aspergillus* antigen in at least two blood samples; and one major (or two minor) clinical criterion such as halo-sign or air crescent sign on pulmonary CT imaging), according to criteria published recently.[6]

Nearly all patients (92.4%) had an indwelling central venous catheter. G-CSF was individually administered in some patients, but was not a study objective in this clinical trial. Most patients (82.9%) were receiving thrice-weekly prophylaxis for *Pneumocystis carinii* with thrimethroprim-sulfamethoxazole.

Treatment

All patients were treated according to the clinical trial AML-BFM 93.[7] Briefly, the patients were randomized at diagnosis to receive the 8-day induction with either daunorubicin (ADE: cytarabine 100 mg/m^2/day continuous infusion on days 1 and 2 followed by a 30 min infusion every 12 h on days 3–8, daunorubicin 30 mg/m^2 every 12 h on days 3–5 and etoposide (VP-16) 150 mg/m^2 on days 6–8) or with idarubicin (AIE: idarubicin 12 mg/m^2 every 24 h, days 3–5 instead of daunorubicin, cytarabine, and VP-16 as in ADE). After induction, patients were treated according to risk groups.[7] High-risk patients were randomized to receive either HAM (high-dose cytarabine 3 g/m^2 every 12 h for 3 days and mitoxantrone 10 mg/m^2 on days 4 and 5) followed by consolidation (early HAM) or consolidation followed by HAM (late HAM). Consolidation therapy consisted of seven different drugs as follows: 6-thioguanine 60 mg/m^2/day, days 1–43 orally; prednisolone 40 mg/m^2/day, days 1–28 orally; vincristine 1.5 mg/m^2/day, days 1, 8, 15, 22; cytarabine 75 mg/m^2/day, days 3–6, 10–13, 17–20, 24–27, 31–34, 38–41; intrathecal cytarabine days 1, 15, 29, 43; cyclophosphamide 500 mg/m^2/day, days 29, 43. Standard risk patients received consolidation without HAM. Children with Down syndrome were treated according to the protocol AML-BFM 93, but were not included as protocol patients in the clinical trial AML-BFM 93. Until 1996, most patients with Down syndrome received the same therapy as patients without Down syndrome. However, in October 1996, the intensity of chemotherapy was reduced in patients with Down syndrome because of the high toxicity: HAM was omitted and the dosage of anthracyclines was reduced to two-thirds of the original dosage.[8] For all patients, intensification was given with one block of high-dose cytarabine and etoposide (HAE). Intensive treatment was followed by cranial irradiation and maintenance therapy for a total of 18 months.

Statistical analysis

The anonimyzed patients' data were collected using Microsoft Access (version 2000 for Windows 95/NT). The comparison of different groups was performed using a χ^2 test or Fisher's exact test, when applicable. The *P*-values reported are two-tailed, and *P*-values less than 0.05 were considered to be significant. All statistical calculations were carried out with the statistical software package BiAS (version 7.07 for Windows 95/NT).

Results

Overall, 304 patients (165 boys, 139 girls) treated according to the clinical trial AML-BFM 93 were reviewed. In all, 28 of the patients were diagnosed with Down syndrome. These 28 patients constituted 51.9% of all the 54 patients with Down syndrome treated according to the trial AML-BFM 93; however, patients with Down syndrome were not officially enrolled as protocol patients. In contrast, the 276 patients without Down syndrome represented 58.6% of all 471 patients officially registered as protocol patients in the clinical trial AML-BFM 93. In total, 30 centers were included in the analysis (4–23 patients per center). The median age of the patients was 5 years 10 months (range 1 month to 17 years 9 months). The distribution of FAB morphology was as follows (patients with Down syndrome excluded): 13 patients with M0, 33 with M1, 71 with M2, 14 with M3, 50 with M4/M4Eo, 64 with M5, 13 with M6, and 18 with M7. Among the 28 patients with Down syndrome, 23 patients had M7 morphology, two patients could not be classified, and one patient each had M3, M5, and M6 morphology. In all, 90 patients were treated according to standard risk and 186 according to high risk (early HAM and late HAM: 67 and 119 patients, respectively). Overall, 855 infections were seen in 304 patients (2.8 infectious complications per patient during intensive treatment). Out of these 855 infectious episodes, 523 (61.2%) were classified as FUO, 57 (6.7%) as clinically documented, and 275 (32.1%) as microbiologically documented (Table 1). The overall findings did not differ significantly from the findings in 28 patients with Down syndrome (FUO 34/68 infectious episodes (50%), clinically and microbiologically documented infections 6/68 (8.8%), and 28/68 infectious episodes (41.2%), respectively). Neutropenia was present in almost three-quarters of infectious episodes (634 episodes (74.1%)), but the distribution of FUO, clinically, and microbiologically documented infections did not differ between neutropenic and non-neutropenic episodes (59.8, 5.7, and 34.5%, and 65.2, 9.5, and 25.3%, respectively) (data not shown). Only three patients experienced no single infectious episode. Out of the 304 patients, 55 had one infectious episode, 70 patients suffered from two infections, 84 from three, 61 from four, 24 from five, five from six, and two from seven infections. When analyzing the first, the second up to the seventh infectious episode, the distribution of FUO, clinically, and microbiologically documented infections did not differ from the overall distribution.

Bloodstream infections occurred in 228 out of the 275 microbiologically documented infections. In 24 episodes (10.5%), more than one pathogen was recovered. Of a total of 252 isolates, 203 (80.6%) were Gram-positive and 49 (19.4%) were Gram-negative (Table 2). Out of a total of 203, 163 Gram-positive organisms (80.3%) and 42 (85.7%) out of a total of 49 Gram-negative organisms were recovered in neutropenic patients, whereas 40 Gram-positive (19.7%) and seven Gram-negative organisms (14.3%) were isolated in non-neutropenic

Table 1 Classification of infectious episodes according to chemotherapy

	Induction[a]	*Consolidation*	*HAM*	*HAE*
Patients	285	265	156	202
Episodes of infection	295	249	144	167
FUO	180 (61.0b)	149 (59.8)	86 (59.7)	108 (64.7)
Clin. documented	30 (10.2)	15 (6.0)	5 (3.5)	7 (4.2)
Microb. documented	85 (28.8)	85 (34.2)	53 (36.8)	52 (31.1)

[a]No significant difference between ADE and AIE.
[b]Percent of episodes of infection.
FUO fever without identifiable source.

Table 2 Distribution of Gram-positive and Gram-negative bloodstream isolates according to chemotherapy

	Number (% of all pathogens isolated)						
	Neutrophils/μl			*Chemotherapy*			
Pathogen	*Total* 252 (100)	*⩽500* 205 (81.3)	*>500* 47 (18.7)	*Induction* 68 (27.0)	*Consolidation* 72 (28.6)	*HAM* 58 (23.0)	*HAE* 54 (21.4)
Gram-positive organisms							
All	203 (80.6)	163 (64.7)	40 (15.9)	57 (22.6)	58 (23.0)	50 (19.9)	38 (15.1)
Staphylococci							
All	94 (37.3)	68 (67.7)	26 (15.9)	28 (11.1)	36 (14.3)	19 (7.5)	11 (4.4)
CoNS	80 (31.7)	60 (23.8)	20 (7.9)	21 (8.3)	33 (13.1)	16 (6.3)	10 (4.0)
S. aureus	6 (2.4)	4 (1.6)	2 (0.8)	3 (1.2)	2 (0.8)	0	1 (0.4)
Streptococci							
All	80 (31.7)	71 (28.2)	9 (3.5)	20 (8.0)	16 (6.3)	24 (9.5)	20 (8.0)
VGS[a]	56 (22.2)	49 (19.4)	7 (2.8)	12 (4.8)	13 (5.2)	18 (7.2)	13 (5.2)
Enterococcus spp	7 (2.8)	7 (2.8)	0	2 (0.8)	1 (0.4)	3 (1.2)	1 (0.4)
Corynebacterium spp	6 (2.4)	5 (2.0)	1 (0.4)	0	2 (0.8)	1 (0.4)	3 (1.2)
Other[b]	16 (6.3)	12 (4.8)	4 (1.6)	7 (2.8)	3 (1.2)	3 (1.2)	3 (1.2)
Gram-negative organisms							
All	49 (19.4)	42 (16.6)	7 (2.8)	11 (4.4)	14 (5.5)	8 (3.2)	16 (6.3)
Klebsiella spp	8 (3.2)	8 (3.2)	0	1 (0.4)	3 (1.2)	0	4 (1.6)
P. aeruginosa	10 (4.0)	8 (3.2)	2 (0.8)	1 (0.4)	5 (2.0)	1 (0.4)	3 (1.2)
E. coli	13 (5.2)	12 (4.8)	1 (0.4)	0	3 (1.2)	4 (1.6)	6 (2.4)
Other[c]	18 (7.2)	14 (5.6)	4 (1.6)	8 (3.2)	4 (1.6)	3 (1.2)	3 (1.2)

[a]Includes *S. mitis* (29), *S. viridans* (11), *S. sanguis* (9), *S. oralis* (5), and *S. salivarius* (2).
[b]Includes unspecified Gram-positive cocci (8) and rods (4), *Bacillus* spp (2), *Micrococcus* spp (1) and *Morganella* spp (1).
[c]Includes unspecified Gram-negative cocci (3) and rods (3), *Enterobacter* spp (3), *Acinetobacter* spp (3), *Neisseria* spp (2), *Citrobacter* spp (2), *Xantomonas* spp (1), and *Bramhanella* spp (1).
CoNS coagulase-negative staphylococci, VGS viridans group streptococci.

patients (Table 2). The incidence of Gram-positive and Gram-negative bacteremia did not differ significantly between the cycles of chemotherapy, whereas the incidence of sepsis due to viridans group streptococci (VGS) was significantly higher in cycles of chemotherapy that included high-dose cytarabine (31 episodes of sepsis due to VGS out of 358 cycles of HAM or HAE (8.7%) *vs* 25 episodes of sepsis due to VGS out of 550 cycles of induction/consolidation (4.6%) ($P=0.027$)). Whereas the proportion of Gram-negative organisms showed a great variation with a peak of 29.2% in 1996 and a nadir of 12.8% in 1997, the incidence of infections due to VGS remained stable throughout the study period (21–24%).

In 113 out of the 855 infectious episodes (13.3%), pneumonia was radiologically diagnosed (Table 3). Pneumonia occurred significantly more often during induction therapy compared to the other cycles of chemotherapy ($P=0.0007$). In 14 out of these 113 episodes, a pathogen was recovered in the bloodstream (CoNS (2), VGS (4), Gram-negative organisms (8)). In another 24 patients, sputum culture was positive for a possible pathogen for pneumonia (*Staphylococcus aureus* (one), VGS (9), Enterococci (2), *Corynebacterium* spp (1), *Haemophilus influenzae* (2), *Klebsiella* spp (2), *Escherichia coli* (1), *Enterobacter* spp (4), and respiratory syncytial virus (2)). Pulmonary aspergillosis was proven in five patients and suspected in another five children, whereas invasive candidiasis was proven in two and suspected in three patients (Table 4). Four patients suffered from meningitis caused by *Streptococcus sanguis* (1), *Propionibact* spp (2), and *Acinetobacter* spp (1), one patient from urinary tract infection caused by *Enterococcus* spp. *S. aureus* was recovered from an abscess in one patient. A causative organism of diarrhea was identified in the stool of 43 patients (*C. difficile* (26), rotavirus (14), *Salmonella* spp (2), and adenovirus (1)), whereas viral infection with cytomegalovirus was seen in four patients, and infection due to herpes simplex virus in one patient.

Table 3 Sites of infection according to chemotherapy

	Number (percent of episodes of infection)				
	Total	*Induction*	*Consolidation*	*HAM*	*HAE*
Blood	228 (26.6)	66 (22.4)	62 (24.9)	45 (31.2)	50 (29.9)
GI	43 (5.0)	12 (4.1)	21 (8.4)	4 (2.8)	6 (3.6)
Liver	5 (0.6)	2 (0.7)	2 (0.8)	1 (0.7)	0
Lung	113 (13.2)	54 (18.3)	27 (10.8)	17 (11.8)	15 (9.0)
CNS	4 (0.5)	3 (1.0)	1 (0.4)	0	0
UTI	1 (0.1)	1 (0.3)	0	0	0
Skin	9 (1.1)	3 (1.0)	3 (1.2)	2 (1.4)	1 (0.6)
CVL	12 (1.4)	3 (1.0)	4 (1.6)	2 (1.4)	2 (1.2)

GI, gastrointestinal tract; CNS, central nervous system; UTI, urinary tract infection; CVL, central venous line.

Table 4 Suspected or proven invasive fungal according to chemotherapy

	Total number (proven/suspected invasive fungal infection)			
	Induction	*Consolidation*	*HAM*	*HAE*
Aspergillosis	5 (1/4)	1 (1/0)	3 (2/1)	1 (1/0)
Candidiasis	1 (0/1)	2 (1/1)	2 (1/1)	0

Overall, 20 out of the 304 patients (6.6%) died because of infection-associated complications (Table 5). No trend of mortality was observed throughout the study period. Compared to children without Down syndrome, patients with Down syndrome were significantly over-represented among children with infection-associated fatal complications (5/28 (17.9%) *vs*

Table 5 Infection-related death during intensive treatment for AML

Patient ID	*Age (years)*	*Sex*	*DS*	*FAB*	*Chemotherapy*	*Death (day)*	*Blasts BM (day 15)*	*Radiologic finding*	*Organism identified*[a]
12	1	F	Yes	7	Induction	15–42	NA	Pneumonia	*Streptococcus* spp
35	18	F	No	3	Induction	<15	NA	Pneumonia	
46[a]	9	F	No	0	Induction	15–42	NA		*Enterobacter* spp
68	10	F	No	7	Induction	>42	>5%	Pneumonia	CoNS
82[b]	2	F	Yes	7	Induction	15–42	NA	Pneumonia	
106	1	F	No	0	Induction	15–42	>5%	Pneumonia	
114	3	M	No	5	Induction	15–42	<5%	Pneumonia	Gram-neg. cocci
143	8	M	No	5	Induction	15–42	<5%		*P. aeruginosa*
144[c]	15	M	Yes	NS	Induction	<15	NA	Pneumonia	
218	1	M	No	5	Induction	15–42	<5%	Pneumonia	
246	14	F	No	2	Induction	15–42	<5%	Pneumonia	
Patient ID	*Age (years)*	*Sex*	*DS*	*FAB*	*Chemotherapy*	*Neutropenia*	*Remission*	*Radiologic finding*	*Organism identified*[a]
4	13	F	No	4	HAM	Present	No	Pneumonia	
201	4	F	Yes	3	HAM	Present	No	Pneumonia	*P. aeruginosa* *Asp*. spp (lung biopsy)
222	7	M	No	7	HAM	Present	No	Pneumonia	*Asp*. spp (BAL)
232	15	M	No	6	HAM	Present	Yes	Pneumonia	*Streptococcus* spp *Asp*. spp (lung biopsy)
236	17	M	No	5	HAM	Present	Yes	Pneumonia	*Streptococcus* spp
13	10	F	No	2	Consolidation	Present	No	Pneumonia	*P. aeruginosa* *Asp*. spp (lung, autopsy)
47	3	F	Yes	7	Consolidation	Present	No	Pneumonia	*Streptococcus* spp
105	15	M	No	1	Consolidation	Present	No	Pneumonia	*Enterococcus* spp
253	4	F	No	3	Consolidation	Present	Yes	Pneumonia	

[a]All pathogens were identified in the blood, except when indicated otherwise.
[b]In this patient, pulmonary alveolar proteinosis was found during autopsy.
[c]This patient experienced massive pulmonary hemorrhage.
[d]This patient died after diagnosis, but before receiving chemotherapy
DS, Down syndrome; BM (15), bone marrow (day 15); NS, not specified; NA, not available; CoNS, coagulase-negative stapylococci.

15/276 (5.4%) ($P=0.04$, Fisher's exact test)). One patient with Down syndrome (ID 144) died soon after diagnosis of AML due to infection-related complications without having received chemotherapy, whereas two patients each had received intensive treatment (ID 82 and ID 201) or chemotherapy with reduced intensity (ID 12 and ID 47) (Table 5). In all, 11 patients (55.0%) died due to infections within the first 6 weeks after diagnosis. In total, 18 patients (90.0%) had radiologic signs of pneumonia. Streptococci were recovered from four patients, Gram-negative organisms from five patients, and invasive Aspergillosis was proven in four patients (Table 5). Notably, six out of nine patients, who died during HAM or consolidation, had not reached complete remission.

Discussion

Infectious complications are a major cause for morbidity and mortality in patients undergoing therapy for cancer. Hematologic malignancies, in particular AML, are associated with more infections than solid tumors.[2–4,9] Comparable to our findings, other authors report that pediatric and adult patients undergoing various intensive treatments for AML experience an average number of three infectious episodes throughout therapy and that less than 3% of all patients remain without any infectious complication.[3,4,10] In contrast, the reported infection-related mortality varied between 5 and 31%, which might be explained by different age groups, different treatment regimens, and different supportive care strategies (Feusner *et al*. *Blood* 2002; **100**: 332a; abstract).[3,10] We observed that roughly three-quarters of infections occurred during severe neutropenia, which is considered as a sentinel risk factor for the development of serious infections.[4,11] On the other hand, one-quarter of patients experienced infections without a significant loss of neutrophils, underlining the importance of therapy-induced alterations of other arms of the immune system, such as lymphocytes, natural killer cells, or innate immunity.[12]

Although Gram-positive organisms represented the majority of bloodstream isolates, we did not find an increasing incidence of Gram-positive isolates throughout the study period, as recently reported by Wisplinghoff *et al*.[5] This study, however, focused on adult patients with a wide variety of underlying malignancies, whereas we looked at children with AML. CoNS and VGS accounted for more than half of Gram-positive bloodstream isolates (67%), which is consistent with previous reports (Feusner *et al*. *Blood* 2002; **100**: 332a; abstract).[4] The incidence of VGS was significantly higher after therapeutic regimens that included high-dose cytarabine ($P=0.027$). Furthermore, VGS bacteremia occurred more often during episodes of neutropenia (49/205 (23.9%) *vs* 7/47 (14.9%) in non-neutropenic episodes), although the difference did not reach statistical significance. Both treatment with high-dose cytarabine and severe neutropenia have been implicated to predispose individuals to develop VGS bacteremia.[13] Other risk factors for VGS bacteremia, however, such as the use of colistin or female sex, were not associated in our analysis with a higher incidence of VGS.[13,14] Unfortunately, it was not possible to determine the role of antimicrobial prophylaxis in the development of VGS sepsis, since most of the children received trimethroprim-sulfamethoxazole, whereas fluoroquinolones were rarely administered. In contrast to other reports,[13,15] we did not find an increasing incidence of VGS, which is probably

due to the fact that modalities of cytotoxic therapy and supportive care remained unchanged throughout the study period. Notably, prophylaxis with penicillin was not routinely recommended at that time. Acute respiratory distress syndrome has been observed in VGS sepsis in as many as 25% of patients,[16] whereas in our population only four out of 56 patients with VGS (7.1%) had to be ventilated. This might reflect the early initiation of appropriate therapy.

Gram-negative organisms accounted for only 49 out of 252 bloodstream isolates (19.4%). Similar results were reported by Feusner *et al*. (*Blood* 2002; **100**: 332a; abstract), whereas in an early study, Woods *et al*[17] observed an equal incidence of Gram-positive and Gram-negative sepsis in children with AML. The difference might be explained, at least in part, by the shift towards Gram-positive organisms over the last decade, which in turn is due to factors such as the wide use of indwelling central catheters.[18] Corroborating previous reports, *Pseudomonas aeruginosa*, *E. coli*, and *Klebsiella* spp were the predominant isolates among the Gram-negative organisms in our analysis (63.3%) (Feusner *et al*. *Blood* 2002; **100**: 332a; abstract).[3] Interestingly, 42 out of the 49 Gram-negative isolates (85.7%) were found during episodes of neutropenia. Eight out of these 42 patients (19%) had to be ventilated and/or experienced septic shock, reflecting the high pathogeneity of these organisms.

It is important to note that the lung was the second most common site of infection. In contrast to children with solid tumors, a high incidence of lower respiratory tract infections has been observed in children with hematologic malignancies.[3,4,9] We are unable to explain why pneumonia significantly occurred more often during induction therapy compared to other cycles of therapy.

We recognize that the low frequency of probable or proven fungal infections most likely represents an underestimation of the true incidence and might reflect insufficient diagnostic procedures, such as a low number of imaging studies (data not shown). On the other hand, we applied rather stringent criteria defining invasive fungal infections,[6] whereas the definitions used by other authors are not detailed and might account for a higher incidence of invasive mycoses (Feusner *et al*. *Blood* 2002; **100**: 332a; abstract).[19] Unlike patients undergoing bone marrow or stem cell transplantation, children receiving chemotherapy for AML are not routinely tested for viral infections during febrile neutropenic episodes. Therefore, the low incidence of viral infection in our study population is not surprising.

The overall infection-related mortality of 6.6% was comparable to two recent studies (Feusner *et al*. *Blood* 2002; **100**: 332a; abstract).[10] However, neither of these two studies included patients with Down syndrome in the analysis, whereas in our study, patients with Down syndrome constituted five out of the 20 infection-associated deaths. Zubizarreta *et al*[20] reported on a particular high toxicity of intensive chemotherapy in children with AML and Down syndrome; six of the 11 patients died of sepsis or pulmonary infection. On the other hand, myeloblasts from children with Down syndrome and AML have increased *in vitro* sensitivity to cytarabine and daunorubicine.[21] Therefore, since October 1996, patients with Down syndrome treated according to the clinical trials AML-BFM 93 and AML-BFM 98 received anthracyclines in a reduced dosage and consolidation without HAM. According to preliminary data, this strategy results in a better outcome in patients with Down syndrome compared with treatment strategies with palliative or very intensive chemotherapeutic regimens (manuscript in preparation). It has to be speculated whether in a subgroup of patients, an improved overall survival can be achieved by a reduction of the intensity of chemotherapy. On the other hand, better strategies of supportive care might help to improve overall survival in children with AML. According to preliminary results of the national Phase III study CCG-2961, the institution of improved infection management strategies significantly lowered the nonleukemic deaths (Feusner *et al*. *Blood* 2002; **100**: 332a; abstract).

In conclusion, infection-associated morbidity and mortality of children undergoing chemotherapy for AML is substantial. Therefore, children with AML should be treated in specialized pediatric cancer centers, and there should be a very low threshold to readmit patients, including not only those who are febrile but also those who have nonspecific symptoms, in particular regarding the lung. Further considerations have to include the prophylactic use of antifungal agents, the improvement of diagnostic procedures in suspected invasive fungal disease, and the empirical use of vancomycin in children with fever and neutropenia, all of which will be implemented in the new clinical multicenter trial AML-BFM 2003.

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References

1 Creutzig U, Ritter J, Zimmermann M, Reinhardt D, Hermann J, Berthold F *et al*. Improved treatment results in high-risk pediatric acute myeloid leukemia patients after intensification with high-dose cytarabine and mitoxantrone: results of Study Acute Myeloid Leukemia–Berlin–Frankfurt–Munster 93. *J Clin Oncol* 2001; **19**: 2705–2713.
2 Feusner JH, Hastings CA. Infections in children with acute myelogenous leukemia. Concepts of management and prevention. *J Pediatr Hematol Oncol* 1995; **17**: 234–247.
3 Tobias JS, Wrigley PF, O'Grady F. Bacterial infection and acute myeloblastic leukaemia: an analysis of two hundred patients undergoing intensive remission induction therapy. *Eur J Cancer* 1978; **14**: 383–391.
4 Madani TA. Clinical infections and bloodstream isolates associated with fever in patients undergoing chemotherapy for acute myeloid leukemia. *Infection* 2000; **28**: 367–373.
5 Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. *Clin Infect Dis* 2003; **36**: 1103–1110.
6 Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F *et al*. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; **34**: 7–14.
7 Creutzig U, Ritter J, Zimmermann M, Hermann J, Gadner H, Blütters-Sawatzki D *et al*. Idarubicin improves blast cell clearance during induction therapy in children with AML: results of study AML-BFM 93. AML-BFM Study Group. *Leukemia* 2001; **15**: 348–354.
8 Creutzig U, Ritter J, Vormoor J, Ludwig WD, Niemeyer C, Reinisch I *et al*. Myelodysplasia and acute myelogenous leukemia in Down's syndrome. A report of 40 children of the AML-BFM Study Group. *Leukemia* 1996; **10**: 1677–1686.
9 Auletta JJ, O'Riordan MA, Nieder ML. Infections in children with cancer: a continued need for the comprehensive physical examination. *J Pediatr Hematol Oncol* 1999; **21**: 501–508.
10 Riley LC, Hann IM, Wheatley K, Stevens RF. Treatment-related deaths during induction and first remission of acute myeloid leukaemia in children treated on the Tenth Medical Research Council acute myeloid leukaemia trial (MRC AML10). The MCR

Childhood Leukaemia Working Party. *Br J Haematol* 1999; **106**: 436–444.
11 Pizzo PA, Robichaud KJ, Wesley R, Commers JR. Fever in the pediatric and young adult patient with cancer. A prospective study of 1001 episodes. *Medicine (Baltimore)* 1982; **61**: 153–165.
12 Lehrnbecher T, Foster C, Vazquez N, Mackall CL, Chanock SJ. Therapy-induced alterations in host defense in children receiving chemotherapy. *J Pediatr Hematol Oncol* 1997; **19**: 399–417.
13 Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. *Clin Infect Dis* 2002; **34**: 1524–1529.
14 Cordonnier C, Buzyn A, Leverger G, Herbrecht R, Hunault M, for the Club de Réflexion sur les Infections en Onco-Hématologie *et al.* Epidemiology and risk factors for Gram-positive coccal infections in neutropenia: toward a more targeted antibiotic strategy. *Clin Infect Dis* 2003; **36**: 149–158.
15 Rieske K, Handrick W, Spencker FB, Gunther E. Infection caused by viridans streptococci in children with malignant hematologic diseases. *Klin Padiatr* 1997; **209**: 364–372.
16 Shenep JL. Viridans-group streptococcal infections in immunocompromised hosts. *Int J Antimicrob Agents* 2000; **14**: 129–135.
17 Woods WG, Ruymann FB, Lampkin BC, Buckley JD, Bernstein ID, Srivastava AK *et al.* The role of timing of high-dose cytosine arabinoside intensification and of maintenance therapy in the treatment of children with acute nonlymphocytic leukemia. *Cancer* 1990; **66**: 1106–1113.
18 Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. *Clin Infect Dis* 1999; **29**: 239–244.
19 Ritter J, Roos N. Special aspects related to invasive fungal infections in children with cancer. In: F. Meunier (ed) *Invasive Fungal Infections in Cancer Patients*. London, Philadelphia, Sydney, Tokyo, Toronto: Balliere Tindall, 1995, pp 179–204.
20 Zubizarreta P, Felice MS, Alfaro E, Fraquelli L, Casak S, Quinteros R *et al.* Acute myelogenous leukemia in Down's syndrome: report of a single pediatric institution using a BFM treatment strategy. *Leukemia Res* 1998; **22**: 465–472.
21 Taub JW, Stout ML, Buck SA, Huang X, Vega RA, Becton DL *et al.* Myeloblasts from Down syndrome children with acute myeloid leukemia have increased *in vitro* sensitivity to cytosine arabinoside and daunorubicin. *Leukemia* 1997; **11**: 1594–1595.