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Bloodstream infections and invasive mycoses in children undergoing acute leukaemia treatment: A 13-year experience at a single Italian institution

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Abstract

The incidence rate (IR) of bloodstream infections (BI) and invasive mycoses (IM) during chemotherapy for paediatric acute lymphoblastic (ALL) or non-lymphoblastic leukaemias (AnLL) was evaluated for 153 BI and 22 IM diagnosed during 143,668 patient-days at risk from January 1988 to December 2000. IR, the number of episodes/100 days at risk, was 0.315 for AnLL and 0.092 for ALL ($P < 0.001$) with significant changes reflecting the intensity of anti-ALL chemotherapy. IR was 0.097 for first-line less intensive, 0.136 during first-line intensive, 0.261 during second-line therapy ($P < 0.001$), and 0.021 during maintenance. During intensive chemotherapy, the IR for BI was 0.134 in ALL with 0.087 for first-line less intensive therapy, 0.110 for first-line intensive, 0.230 for second-line intensive therapy ($P < 0.001$) and 0.274 in AnLL ($P = 0.001$). IR was 0.021 in ALL and 0.048 in AnLL ($P = 0.034$) for IM. In conclusion, there is a correlation between intensity of chemotherapy and rate of infections in paediatric acute leukaemias.

Keywords: Leukaemia; Pediatrics; Bacteraemia; Fungemia; Invasive mycosis

1. Introduction

Infections are an important cause of morbidity and mortality for patients undergoing cancer treatment. Reported incidence of infections varies between institutions and among patients treated with similar protocols due to different local environmental factors and/or prophylactic measures. Recently, many studies have evaluated infection incidence in children/adults receiving chemotherapy for acute leukaemia both lymphoblastic and non-lymphoblastic [1–10]. However, most of these studies used the percentage of observed events in the given population as a measure of the burden of infection and/or focused only on infections during neutropenia.

Since the risk of infection in cancer patients is multifactorial, with different risk factors simultaneously or consecutively present in the same patient [11], it is likely to be present throughout the entire period of chemotherapy. In this study, we have evaluated the incidence rate of bloodstream infections (BI) and invasive mycoses (IM) during the entire period of antileukaemic chemotherapy in a cohort of children treated in a single Italian tertiary care centre from 1988 to 2000.

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2. Patients and methods

2.1. Patients

To be eligible for this study, subjects should have been diagnosed before 15 years of age with acute lymphoblastic leukaemia (ALL), or acute non-lymphoblastic leukaemia (AnLL), and should have been admitted for treatment at the Division of Paediatric Haematology and Oncology of the G. Gaslini Institute (IGG) teaching hospital between January 1, 1988, and December 31, 2000. Patients admitted at IGG for counselling and those with incomplete medical records were excluded from the study. First-line treatment protocols used during the study period were those officially adopted by the Italian Association of Paediatric Haematology and Oncology (AIEOP). In particular, patients with ALL were treated according to AIEOP ALL-88, ALL-91 and ALL-95, BFM-based protocols [12], while patients with AnLL received AIEOP LAM-87 and LAM-92 [13,14] protocols. Salvage protocols used in relapsing patients were more heterogeneous and, in general, more intensive than first-line protocols.

Information on all cancer patients observed at least once at IGG either for counseling or treatment has been stored since 1985 in an electronic data set that registers demographics, type of neoplasia, date of diagnosis and first visit at IGG with dates and type of antileukaemic treatment (*i.e.*, for leukaemia patients and for each therapeutic program: start of therapy, start of maintenance, end of therapy and relapse, if any). Data on bloodstream infections and invasive mycoses (*i.e.*, etiology, localisation and date of diagnosis) have been collected retrospectively before 1989, and then prospectively. In 2002, after publication by Ascioglu and collegues [15] of the first comprehensive shared definition of invasive fungal infections, all the episodes were retrospectively evaluated and classified according to these internationally approved criteria. Bone marrow transplant patients were not included in this analysis.

Treatment periods were subdivided according to the type and phase of disease: induction/consolidation/reintensification for first-line therapy, reinduction after relapse for second-line therapy and maintenance therapy. First-line treatment for ALL were further divided into: those for low-intermediate risk ALL (that received ''less'' intensive therapy) and those for high risk ALL. Patients were arbitrary assigned to one of these risk groups according to the criteria used in the different antileukaemic protocols adopted. For this reason, each subject may have contributed to different categories of treatment periods: ''first-line intensive'' (high risk ALL and any AnLL); ''first-line less intensive'' (low/intermediate risk ALL); ''second-line intensive'' (any relapse) and ''maintenance'' (ALL and promyelocytic AnLL).

The duration of the various treatment periods was calculated from the start date of the first aggressive treatment period after IGG admission to: the beginning of another type of treatment period (*e.g.*, a maintenance therapy), to the first elective end of therapy, to the last visit at IGG, to the end of the follow-up period (31/12/2000) or finally, to the date of bone marrow transplantation or death. If a relapse occurred after the end of therapy, another treatment period was calculated using the same criteria as before, starting from the date of relapse. If an intensive treatment period was the last therapeutic procedure, the end of therapy date was arbitrarily postponed by 30 days. The date and type of any bloodstream infection or invasive mycosis was recorded for each patient. Deaths occurring within 15 days after diagnosis of a BI or within 90 days after an IM were defined as infection-related.

2.2. Definitions of infectious episodes

Single-agent bacteraemia was defined as the isolation of a single pathogen (bacteria or fungus) from blood culture. For coagulase-negative staphylococci, corynebacteria other than *Corynebacterium jeikeium* and other skin contaminants, at least two sets of positive blood cultures were required unless the same pathogen was simultaneously isolated from the blood and another site of infection. Polymicrobial bacteraemia was defined as the isolation of more than one pathogen from the same blood sample or from two consecutive samples obtained within 24 h. A febrile illness occurring with isolation of fungal organisms in one or more blood cultures, without evidence of visceral involvement, was defined as fungemia [16]. Invasive fungal infections were classified as documented, probable and possible, according to internationally standardised definitions [15]. An infectious episode was defined as neutropenia-related if documented in the presence of an absolute granulocyte count below 1.0×10^{-6}/L [16,17]. Any Hickman–Broviac catheter (CVC) related infections were defined according to our previously published criteria [16].

2.3. Standard of care during the study period

Antibacterial or antifungal prophylaxis was not routinely administered, except low dose cotrimoxazole for *P. jiroveci* pneumonia prophylaxis. A combination of a beta-lactam and an aminoglycoside was always used as initial empirical antibacterial therapy of febrile neutropenia [18]. Modifications to initial treatment were performed on the basis of bacterial sensitivity tests or clinical criteria, by adding or replacing antibacterials or empirical antifungals as clinically requested. All patients were fitted if possible, with CVC from diagnosis of leukaemia or admission to IGG until the end of therapy. Maintenance procedures of CVC were always

performed according to international recommendations [19]. Unless specifically recommended by the antileukaemic protocols (*i.e.*, high risk ALL-95 and FLAG and IDA–FLAG for relapsed AnLL) neither granulocyte (G-CSF) nor other colony stimulating factors were routinely administered because of uncertainties about their effectiveness as prophylaxis for severe infections in leukaemia children [20].

2.4. Statistical analysis

Descriptive statistics were performed and reported as absolute frequencies or percentages for qualitative data, in medians and range or means and standard deviations (SD) for quantitative data. Comparison of frequency distribution was analysed by the χ^2 test. Fischer's exact test was used in case of at least one expected frequency less than five.

IR of bloodstream infections and IM were calculated as the number of events divided by the person-days by different levels of categorical explanatory variables (*e.g.*, diagnosis, type of treatment period). IR was expressed as episodes/100 person-days at risk (pdr) and reported with 95% Confidence Intervals (95%CI).

Person-time data of different groups of patients were compared by means of the log-rank test or by means of the test for trend in case of three or more ordered levels of any explanatory variable. A P value less than 0.05 was considered to be statistically significant. The statistical software "Statistica" (release 6.0, StatSoft Corporation, Tulsa, OK) and the software "Stata" (release 7.0, StataCorp 2001, College Station, TX, USA) have been used.

Table 1
Etiology and localisation (for invasive mycoses) of infections in children treated for acute leukaemia at the G. Gaslini Institute Teaching Hospital between 1988 and 2000

Pathogens from bloodstream infections		162[a]	
Gram-positives		84	
Coagulase-negative staphylococci			26
S. aureus			19
Viridans streptococci			25
Other Gram-positives			14
Gram-negatives		70	
P. aeruginosa			14
Other *Pseudomonadaceae*			6
E. coli			15
Klebsiella Enterobacter Serratia group			19
Other Gram-negatives			16
Fungi		8	
C.albicans			1
Candida non-*albicans*			7
Documented invasive mycoses			10
Yeasts		2	
Hepatosplenic candidiasis	Not identified		2
Filamentous fungi		8	
Pneumonia	Not identified		3
	Aspergillus sp.		1
Disseminated	Not identified		2
	Aspergillus sp.		2
Probable invasive mycoses		2	
Pneumonia	Positive galactomannan antigen		2
Possible invasive mycoses		10	
Pneumonia			10

[a] One sixty two isolated pathogens from 153 episodes. Nine strains were isolated from five polymicrobial bloodstream infections.

3. Results

During the study period, 436 patients were admitted at the IGG due to acute leukaemia; 39 came only for counselling and 45 had incomplete medical records. This left 352 patients (204 males, 148 females; 270 ALL, 82 AnLL) eligible and evaluable for this study. Their mean age at first observation was 7.0 years (SD: 4.1 years). Overall, 175 infectious episodes were documented in 127 patients (36%), since 36 children had more than one episode, with a maximum of four episodes observed in two. BI, with 153 episodes (87%), were the most frequently reported type of infectious episode, while IM accounted for 22 episodes (13%). Among the 153 bloodstream infections, single-agent Gram-positive bacteraemia accounted for 79 episodes (52%); single-agent Gram-negative bacteraemia for 64 (42%), polymicrobial bacteraemia for 5 (3%) and isolated fungemia for 5 (3%) episodes, respectively. The 22 IM were classified as documented in 10 (46%), probable in 2 (9%) and possible in the remaining 10 (46%) episodes. Table 1 details the etiology and the localisation (for IM) of the infectious episodes. The outcome of infectious episodes was favourable in 172 (98.3%). Three patients died because of the infection, two of the patients had BI (1.3%) and one IM (4.5%).

3.1. Overall infection rates according with type of leukaemia and intensity of treatment

In Table 2, patients' underlying disease and contribution in terms of number and types of treatments cycles, person-days at risk and number and rates of infectious episodes have been documented. Overall, 608 treatment courses were given for a total of 143,668 pdr and due to the 175 infectious episodes observed, an overall IR (BI and IM) of 0.122 (95%CI 0.105–0.141) was calculated. The respective contributions were 0.106 (95%CI 0.091–0125) for BI and 0.015 (95%CI 0.010–0.023) for IM. The overall IR was different according to the type of the underlying disease; it was 0.092 for ALL and 0.315 for AnLL ($P < 0.001$, log-rank test). Moreover, amongst ALL cases, the IR varied according to treatment

Table 2
Rates of infectious complications in children treated for acute leukaemia at the G. Gaslini Institute Teaching Hospital between 1988 and 2000

Type of cancer	Number of patients at study entry	Total number of treatments	Person-days	Number of infectious episodes	IR (95%CI)
Total ALL	270	495	124 599	115	0.092 (0.077–0.111)
First-line less intensive	138	138	27 725	27	0.097 (0.067–0.142)
First-line intensive	62	62	11 812	16	0.136 (0.083–0.221)
Second-line intensive	70	151	22 620	59	0.261 (0.202–0.337)
Maintenance	0	144	62 442	13	0.021 (0.012–0.036)
Total AnLL	82	113	19 069	60	0.315 (0.244–0.405)
First-line intensive	73	73	13 002	45	0.346 (0.258–0.464)
Second-line intensive	9	38	5647	15	0.266 (0.160–0.441)
Maintenance (APL)	0	2	420	0	0
Total	352	608	143 668	175	0.122 (0.105–0.141)

ALL, acute lymhoblastic leukaemia; AnLL, acute non-lymphoblastic leukaemia; APL, acute promyelocytic leukaemia; IR, infection rate $\times 10^{-2}$ patient-days.

intensity (Table 2) and increased from 0.097 among children treated with first-line less intensive chemotherapy to 0.136 among those receiving first-line intensive therapy and to 0.261 among those receiving second-line therapy ($P < 0.001$, test for trend). As expected, the lowest IR (0.021) was observed during maintenance treatment for ALL and no further analysis was performed on the 13 episodes (all BI) observed during this period. Among patients with AnLL (Table 2), no difference in IR was observed between patients receiving first-line therapy (0.346) and those receiving treatment for relapse (0.266 $P = 0.43$, log-rank test). Finally, no infectious episodes were observed during maintenance chemotherapy for AnLL and no further analysis was conducted during this treatment period.

3.2. Rates of bloodstream infection and invasive mycoses reflects treatment intensity

For this analysis, only the 140 episodes of BI and the 22 episodes of IM observed during intensive antileukemic treatments were considered (Table 3). The overall IR for BI occurring during any intensive treatment for ALL or AnLL was 0.143 and 0.274, respectively ($P = 0.001$, log-rank test). If only ALL cases were considered, the treatment-specific bloodstream IR was 0.087 for first-line less intensive therapy, 0.110 for first-line intensive and 0.230 for second-line intensive therapy ($P < 0.001$, test for trend). On the contrary, no significant differences were observed in bloodstream IR between first-line (IR = 0.308) and second-line (IR = 0.195) therapies among AnLL patients ($P = 0.21$, log-rank test). The IR for IM (Table 3) was 0.021 in ALL and 0.048 in AnLL ($P = 0.034$, log-rank test), with no significant differences in rates observed during different intensive treatments among ALL or AnLL patients.

3.3. Role of risk factors in determining the infection rate

Neutropenia at diagnosis of infectious complication was documented in 79.4% of episodes ($n = 139$; 121 BI and 18 IM). In particular, it was present in 74% (85/115) of the episodes observed in patients with ALL and in 90% ($n = 54/60$) of those observed in patients

Table 3
Infection rate for blood stream infections and invasive mycoses in leukemic patients by type of aggressive treatment

Underlying disease	Days at risk	No. of bloodstream infections	Bloodstream infections IR (95%CI)	No. of invasive mycoses	Invasive mycoses IR (95%CI)
ALL first-line less intensive	27 725	24	0.087 (0.058–0.129)	3	0.011 (0.004–0.034)
ALL first-line intensive	11 812	13	0.110 (0.064–0.190)	3	0.025 (0.008–0.079)
ALL second-line intensive	22 620	52	0.230 (0.175–0.302)	7	0.031 (0.015–0.065)
Total ALL intensive	62 157	89	0.143 (0.116–0.176)	13	0.021 (0.12–0.036)
AnLL first-line intensive	13 002	40	0.308 (0.226–0.419)	5	0.039 (0.016–0.092)
AnLL second-line intensive	5 647	11	0.195 (0.108–0.352)	4	0.071 (0.027–0.189)
Total AnLL intensive	18 649	51	0.274 (0.208–0.360)	9	0.048 (0.025–0.093)
Total intensive	80 806	140	0.173 (0.147–0.205)	22	0.027 (0.018–0.041)

ALL, acute lymhoblastic leukaemia; AnLL, acute non-lymphoblastic leukaemia; IR, infection rate $\times 10^{-2}$ patient-days.

with AnLL. All the neutropenia-related episodes were documented during intensive phases of treatment. Since information on the total number of days of neutropenia was not available the neutropenia-related infection rates were not calculated. For CVC, the exact dates of insertion and removal of each device were not available for all patients, and therefore CVC related IR was not calculated. The overall proportion of CVC-related BI was 29.4% (45/153) and in particular 34.3% (35/102) with ALL and 19.6% (n = 10/51) in AnLL patients. Interestingly, the 13 episodes of BI observed during ALL maintenance were all CVC-related. Finally, 10 episodes (5.7%) were neither CVC nor neutropenia-related: eight occurred among ALL and two in AnLL patients.

4. Discussion

This study, which analysed 352 children with leukaemia treated at a single centre with uniform supportive care and followed-up with uniform criteria, gave an estimation of the rate of severe infections occurring in leukaemia children undergoing treatment in a tertiary care centre. We believe that the estimates we calculated should not be used to evaluate the risk of severe infection in a given patient and in a peculiar clinical condition. These data can be used to compare the burden of infection among ALL and AnLL patients during the different intensive phases of their antileukemic treatments. They could also represent a baseline for the comparison of toxicities for new antileukaemia protocols and in the planning of strategies for the management of infections in children with leukaemia.

Descriptive studies of infectious complications in patients with leukaemia usually employ percentages of observed events in the study population to measure infection burden [2,9,10]. With this approach, each patient contributes to the denominator independently from the length of the course of the disease (*e.g.*, a patient that died after 2 weeks from diagnosis contributes similarly to another one who completed his treatment plan and was treated for many months). We believe that the use of incidence rates (number of episodes/duration of observation) gives a more accurate estimate of the impact of infectious complications in cancer patients that allows for a more reliable comparison between different protocols or studies.

Only few other papers [3,21] report on rates of infection, although using different types of stratifications (*e.g.*, underlying disease) or different time measurement (*e.g.*, every 100 or 1000 days at risk). Our overall bloodstream IR of 0.122 (95%CI 0.105–0.141) is similar to the IR of 0.13 that can be easily calculated from the data on 51 children with leukaemia or lymphoma reported by Auletta and colleagues [3] (40 BI observed during 31,282 days at risk). On the contrary, Velasco and colleagues [21] in a study on 110 episodes of BI in 82 patients aged 1–78 years with different haematological malignancies reported a rate of 1.024 episodes per 100 days at risk. This discrepancy can not be easily explained but could in part be from differences in infectious complications observed between adults and children as previously suggested by the International Antimicrobial Therapy Cooperative Group of the European Organisation for Research and Treatment of Cancer [22] and/or by the different number of patients included in the studies or finally by local differences.

Our data confirm that the rate of severe infectious complications in leukaemia children is strictly related with the type of leukaemia-with AnLL having a higher rate than ALL-and that in patients with ALL the rate of severe infection increase with higher treatment intensity. The role of aggressiveness of therapy as a risk factor for the development of infectious complication is confirmed by the observation that during maintenance chemotherapy the rate of infectious complications is low and mainly related to the presence of CVC. Other series have already documented that the intensity of chemotherapy is a risk factor for the development of infectious complications in children with ALL [2] (n = 59, single centre) and in adults [9] (n = 89, single centre) or children [10] (n = 304, multicentre) with AnLL. All these studies however, analysed the incidence of phase-specific (induction or consolidation) infections and did not consider the duration of treatment in calculating the rate of severe infectious complications. This aspect was considered in the already mentioned study by Auletta and colleagues [3], in which a higher infection rate among patients with active disease was documented, as compared to those in remission. Unfortunately these authors did not stratify the type of underlying disease and used different and, in our opinion, more arbitrary methods for the calculation of the length of periods at risk.

We have also documented that the rate of IM during antileukaemic treatment is more than seven times lower than that of BI (IR = 0.106 *vs.* 0.015) confirming that IM, although often lethal, are infrequent at least in the paediatric populations. We believe that the overall rate of 0.122 (0.092 for ALL and 0.135 for AnLL) for IM is the first reliable estimation of the impact of these complications during treatment for acute leukaemia in children. In fact, due to the relative rarity of this complication, epidemiological data on invasive fungal infections in children with cancer are scarce, with reported percentages ranging between 5% and 28% [10,23–26] and with even less information on the duration of the periods at risk.

In our series approximately 80% of the severe infections were diagnosed in the presence of neutropenia. The importance of neutropenia as a risk factor for infectious complications is well known as reported by many investigators [1–10,24,26]. However, none of these

studies had data on the duration of neutropenic periods and so IR calculations were not possible. In our study, no information was available on the exact duration of periods of neutropenia for each patient but a rough estimation of the neutropenia-related IR was calculated using the entire length of aggressive treatment, including the periods of "normal" granulocyte counts that are obviously present between phases of antileukaemia treatment. With this calculation (data not shown) it was possible to estimate a neutropenia-related IR 0.172 (0.137 in ALL and 0.290 in AnLL, $P < 0.0001$, conditional test). In this case, the calculated rate of severe infections correlated to neutropenia is, in our opinion, an underestimation. We believe that only a prospective study that will consider all the episodes of neutropenia observed during a given period will allow an accurate estimation of the risk of severe infectious complications during different phases of cancer treatment.

Conflict of interest statement

None declared.

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References

1. Paganini H, Bologna R, Debbag R, *et al*. Fever and neutropenia in children with cancer in one pediatric hospital in Argentina. *Pediatr Hematol Oncol* 1998, **15**, 405–413.
2. Rahiala J, Perkkio M, Riikonen P. Infections occurring during the courses of anticancer chemotherapy in children with ALL: a retrospective analysis of 59 patients. *Pediatr Hematol Oncol* 1998, **15**, 165–174.
3. 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.
4. Wehl G, Allerberger F, Heitger A, *et al*. Trends in infection morbidity in a pediatric oncology ward, 1986–1995. *Med Pediatr Oncol* 1999, **32**, 336–343.
5. Yoshida M, Tsubaki K, Kobayashi T, *et al*. Infectious complications during remission induction therapy in 577 patients with acute myeloid leukemia in the Japan Adult Leukemia Study Group studies between 1987 and 1991. *Int J Hematol* 1999, **70**, 261–267.
6. Madani TA. Clinical infections and bloodstream isolates associated with fever in patients undergoing chemotherapy for acute myeloid leukemia. *Infection* 2000, **28**, 367–373.
7. Lex C, Korholz D, Kohlmuller B, *et al*. Infectious complications in children with acute lymphoblastic leukemia and T cell lymphoma a rationale for tailored supportive care. *Support Care Cancer* 2001, **9**, 514–521.
8. Meir HM, Balawi IA, Meer HM, *et al*. Fever and granulocytopenia in children with acute lymphoblastic leukemia under induction therapy. *Saudi Med J* 2001, **22**, 423–427.
9. Girmenia C, Lo Coco F, Breccia M, *et al*. Infectious complications in patients with acute promyelocytic leukaemia treated with the AIDA regimen. *Leukemia* 2003, **17**, 925–930.
10. Lehrnbecher T, Varwig D, Kaiser J, *et al*. Infectious complications in pediatric acute myeloid leukemia: analysis of the prospective multi institutional clinical trial AML BFM 93. *Leukemia* 2004, **18**, 72–77.
11. Viscoli C, Castagnola E. Factors predisposing cancer patients to infections. *Cancer Treat Res* 1995, **79**, 1–30.
12. Conter V, Aricò M, Valsecchi MG, *et al*. Long term results of the Italian Association of Paediatric Hematology and Oncology (AIEOP) Acute Lymphoblastic Leukemia Studies, 1982–1995. *Leukemia* 2000, **14**, 2196–2204.
13. Amadori S, Ceci A, Comelli A, *et al*. Therapy of childhood acute myelogenous leukemia: an update of the AIEOP/LAM 8204 study. Italian Pediatric Hematology–Oncology Association. *Haematol Blood Transfus* 1990, **33**, 222–225.
14. Amadori S, Testi AM, Arico M, *et al*. Prospective comparative study of bone marrow transplantation and postremission chemotherapy for childhood acute myelogenous leukemia. The Associazione Italiana Ematologia ed Oncologia Pediatrica Cooperative Group. *J Clin Oncol* 1993, **11**, 1046–1054.
15. Ascioglu S, Rex JH, de Pauw B, *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.
16. Viscoli C, Castagnola E, Giacchino M, *et al*. Bloodstream infections in children with cancer: a multicentre surveillance study of the Italian Association of Paediatric Haematology and Oncology Supportive Therapy Group Infectious Diseases Section. *Eur J Cancer* 1999, **35**, 770–774.
17. Wisplinghoff H, Seifert H, Wenzel RP, *et al*. 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.
18. Viscoli C. EORTC International Antimicrobial Therapy Group. Management of infection in cancer patients. Studies of the EORTC International Antimicrobial Therapy Group (IATG). *Eur J Cancer* 2002, **38**(Suppl. 4), S82–S87.
19. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000, **132**, 391–402.
20. Pui CH, Boyett JM, Hughes WT, *et al*. Human granulocyte colony-stimulating factor after induction chemotherapy in children with acute lymphoblastic leukemia. *New Eng J Med* 1997, **336**, 1777–1781.
21. Velasco E, Byington R, Martins CAS, *et al*. Prospective evaluation of the epidemiology, microbiology, and outcome of bloodstream infections in hematologic patients in a single cancer center. *Eur J Clin Microbiol Infect Dis* 2003, **22**, 137–143.
22. Hann I, Viscoli C, Paesmans M, *et al*. A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC). *Br J Haematol* 1997, **99**, 580–588.
23. Gozdasoglu S, Ertem M, Buyukkececi Z, *et al*. Fungal colonization and infection in children with acute leukemia and lymphoma during induction therapy. *Med Pediatr Oncol* 1999, **32**, 344–348.

24. Groll AH, Kurz M, Schneider W, *et al*. Five year survey of invasive aspergillosis in a paediatric cancer centre. Epidemiology, management and long term survival. *Mycoses* 1999, **42**, 431–442.
25. Haupt R, Romanengo M, Fears T, *et al*. Incidence of septicaemias and invasive mycoses in children undergoing treatment for solid tumours: a 12-year experience at a single Italian institution. *Eur J Cancer* 2001, **37**, 2413–2419.
26. Abbasi S, Shenep JL, Hughes WT, *et al*. Aspergillosis in children with cancer: a 34-year experience. *Clin Infect Dis* 1999, **29**, 1210–1219.