Nosocomial infections in acute leukemia: comparison between younger and elderly patients

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SUMMARY

The progressive decline in immune functions render elderly individuals more susceptible to infections than younger patients. To evaluate potential age-related differences in nosocomial infections between younger (<60 yr) and elderly (≥60 yr) patients with acute leukemia, we retrospectively reviewed 161 consecutive febrile episodes.

All neutropenic patients with an absolute neutrophil count (ANC) less than 500/µl were examined during the different phases of intensive chemotherapy and hospitalized until fever and neutropenia resolved.

Fever was recorded in 66% of younger and in 64% of elderly patients and occurred respectively in 45% and in 51% during induction, in 32% and in 36% during consolidation, in 23% and in 13% during relapse/ refractory treatment (P=0.01). A central venous catheter (CVC) was present in 68% and in 42% of patients (P=0.001). Febrile episodes during severe neutropenia with ANC <100/µl were recorded in 47% and in 22% respectively, during neutropenia with ANC >100/µl in 53% and in 78% respectively (P=0.002). No significant difference was documented in the overall incidence of infections, type of febrile episodes, nosocomial pattern, defervescence-time, median duration of antimicrobic therapy and in overall outcome.

Elderly patients do not seem to be more susceptible to infections than younger ones, although the lower frequency of some risk factors must be taken into account.

KEY WORDS: Nosocomial infections, Acute leukemia, Younger leukemia, Elderly leukemia

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INTRODUCTION

The immune system undergoes a complex and continuous remodelling as a result of aging and the progressive decline renders elderly individuals more susceptible to infections, cancer and autoimmune disorders than younger subjects (Bohemer *et al*., 2004).

The most important changes occur in B and T cell subpopulations. Moreover with aging there is an alteration of the receptor-driven function of human neutrophils, such as superoxide anion production, chemotaxis and apoptosis (Hakim *et al.*, 2004; Fulop *et al*., 2004). The clinical consequences of these changes are not well defined, except for their extremely negative impact on defence against infections (Fulop *et al*., 2004) mainly in severely immunocompromised patients such as patients with hematologic malignancies, who develop prolonged neutropenia after receiving chemotherapy and are traditionally susceptible to serious infections (Girmenia *et al*., 2003; Offidani *et al.,* 2004) However, direct comparisons between younger and elderly patients stratified for risk have been made in very few experiences (Garcia-Suarez *et al*., 2003).

To evaluate potential age-related differences in a selected high-risk population, also stratified for underlying disease, we focused on infectious complications in younger and elderly patients with acute leukemia undergoing intensive chemotherapy.

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MATERIALS AND METHODS

Patient selection

The study was carried out in our Department in patients admitted between January 2003 and December 2005.

We examined younger (<60yr) and elderly patients (≥60 yr) with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) during induction, consolidation and relapse or refractory treatment. Eligibility criteria were: fever (a single measurement >38.5°C on one occasion or >38°C on two or more occasions within 12 h, not related to underlying disease, chemotherapy or blood infusion). Neutropenia was defined a WBC count <1000/µl or absolute neutrophil count (ANC) less than 500/µl or WBC count >1000/µl but expected to decrease <1000/µl within 24-48 h. Severe neutropenia was defined as ANC less than 100/µl >10 days. Infections were classified as nosocomial if they were detected only after at least 72 hours of hospitalization.

Antineoplastic regimen

At admission all patients were monitored for routine biochemistry, chest radiography and cardiac investigation.

Patients treated with oral therapy (i.e. hydroxyurea) or with low-dose chemotherapy because of severe coexisting medical conditions (e.g. renal failure, liver or cardiac disease) were excluded from this analysis.

Younger AML patients in remission-induction therapy, were treated with FLAG-Ida: fludarabine 25 mg/m^2 day 1 to 4; cytarabine 2 g/m^2 day 1 to 4, idarubicin 12 mg/m^2 day 2 to 4, followed by granulocyte colony stimulating factor; in consolidation with FLAG course. Elderly AML patients in remission-induction therapy were treated with the same regimen as the younger patients for five days, without Idarubicin (FLAG) and in consolidation, with idarubicin 10 mg/ m^2 plus vepesid 175 mg/ mq both for two days. Younger resistant or relapsed patients were treated with the HAM protocol (Buchner *et al*., 2003), while only a minority of the elderly ones received an aggressive regimen in this phase. All patients were treated with conventional protocols (Vitale *et al*., 2005).

Clinical and microbiological evaluation

Antibiotic prophylaxis was performed with oral quinolones in patients free from signs of infection and not taking antibiotics and was stopped upon onset of fever. Antifungal prophylaxis was performed with oral azoles and stopped when antifungal therapy was started.

At the onset of fever, at least two blood cultures were performed before starting antibiotic treatment. If the patient had an indwelling venous catheter (CVC), blood cultures were taken from each lumen as well as from a peripheral vein.

Specimens of blood were inoculated into Bactec Plus A/F and Bactec Plus Anaerobic/F vials. The bottles were placed in the instrument (Bactec 9240) and processed according to the manufacturer's recommendations. All strains were identified and tested for their antimicrobial susceptibility (MICs) with the automated Vitek system (Biomerieux, Marcy l'Etoile, France). MIC range (NCCLS-M7) was ≤8-≥32 mg/L when testing *Pseudomonas aeruginosa* and all other gram-negative bacteria. The identification of fungi was obtained by AMS Vitek 2 (USA); the susceptibility test was performed using Yeast One System (Biomedical).

Febrile episodes were classified according to EORTC criteria. In the case of isolation of skin saprophytes, 2 positive blood cultures were required.

Documented infections (DI) were defined as being either microbiologically or clinically evident. Fever of undetermined origin (FUO) was diagnosed when early clinical and microbiological evaluation failed to reveal a site or microbial isolate to which the patient's fever might be attributed. Fungal infections were defined according to established criteria (Ascioglu *et al*., 2002).

Treatment strategies

Broad spectrum antibiotic therapy (third generation cephalosporin plus an aminoglycoside or an antipseudomonas semi-synthetic penicillin with a betalactame inhibitor such as piperacillin-tazobactam) was initiated when pyrexia was greater than 38°C after cultures had been taken. Glycopeptide (vancomycin or teicoplanin) was added later if Gram-positive bacteria were isolated in culture or if after 72 hours no response was obtained from the initial antibiotics. Antifungal therapy was started if fever persisted despite antibiotics or in the case of suspected or documented fungal infections.

All patients were evaluated for their clinical and microbiological outcome according to others (Freifeld *et al.*, 1995). Patients were clinically evaluated twice: early into (72 hours) and at the end of antibiotic therapy or at the recovery of each episode of neutropenia.

The overall outcome occurred either at resolution of the neutropenia for patients with FUO, or after appropriate antibiotic therapy for patients with DI.

Episodes were classified into one of three categories:

1) Success without modification - referring to episodes in which the patient successfully recovered from fever and neutropenia without modifications in the original regimen.
2) Success with modification - episodes in which the patient successfully recovered from fever and neutropenia, but required antimicrobic modification.
3) Failure - death resulting from a documented or presumed infection during neutropenia.

All patients were hospitalized until fever and neutropenia were resolved.

Statistical methods

Differences between groups of patients were analysed by a Pearson Chi-Square or, when appropriate, Fisher's Exact Test and a P-value of 0.05 (two-sided) was considered the significant limit. All analyses were performed using the Statistical Package For The Social Sciences (SPSS) for Windows software, version 12.0 (SPSS, Chicago, IL, USA).

RESULTS

During the study period, febrile episodes occurred in 128 of 196 examined patients (65%): in 63 of 95 younger patients (66%), median 45 years and in 65 of 101 elderly patients (64%), median 71 years. Febrile episodes were documented in 69% of AML (119/172) and in 37% of ALL (9/24). Characteristics of the 128 patients with febrile episodes are shown in Table 1.

The total of assessable febrile episodes was 161: 90 in <60 yr, 71 in ≥60 yr, occurring respectively in 45% and in 50% during induction treatment, in

TABLE 1 - *Characteristics of the patients with febrile episodes.*

Patients	*<60 years (n=63)*	*≥60 years (n=65)*	*P-value*	*Total (n=128)*
Underlying disease:				
AML	57	62		119
ALL	6	3		9
Age (median, years)	45	71		
Sex (male/female), n	31/32	36/29		67/61
Febrile episodes, n	90	71		161
Disease status:				
First induction	40 (45%)	36 (51%)		76
Consolidation	21 (32%)	26 (36%)	0.01	47
Relapse/Refractory	29 (23%)	9 (13%)		38
Central venous catheter, n	61 (68%)	30 (42%)	0.001	91
ANC (µl)				
≤100	42 (47%)	16 (22%)		58
101-500	48 (53%)	55 (78%)	0.002	103
Antimicrobial prophylaxis	69 (77%)	58 (77%)	ns	107
Antifungal prophylaxis	68 (75%)	56 (78%)	ns	108

AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; ANC: absolute neutrophil count/mL.

TABLE 2 - *Classification of febrile episodes.*

Variable	*<60 years*	*≥60 years*	*Total*
MDI	48 (53%)	31 (44%)	79
CDI	11 (12%)	15 (21%)	26
Pneumonia	7	11	
Gastrointestinal tract	2	1	
Subcutaneous tissue	2	3	
FUO	31 (35%)	25 (35%)	56

MDI: microbiologically documented infections; CDI: clinically documented infections; FUO: fever of undetermined origin. P-value: ns.

32% and in 36% during consolidation, in 23% and in 13% during relapse (P=0.01). CVC (Groshong) was present in 68% and in 42% respectively (P=0.001).
No significant comorbidity was documented (only transient elevation levels of plasma AST and ALT in two older patients).
Febrile episodes during severe neutropenia with ANC <100/µl was recorded in 47% of younger and in 22% of elderly; during neutropenia with ANC >100/µl in 53% of younger and in 78% of elderly (P=0.002).
No significant difference was documented in antimicrobial and antifungal prophylaxis. As shown in Table 2, no significant differences were recorded in microbiologically documented infections with and without bacteraemia, in clinically documented infections (mainly pneumonia) and in FUO. Microbiologically documented infections were the cause of 53% and 44% respectively and there were no differences in the overall distribution rates of the organisms (Table 3).
Among the 102 organisms isolated in mono and polymicrobial infections, 64 were recorded in

TABLE 3 - *Comparison of organisms causing documented infections.*

	<60 years				*≥60 years*			
	I	*C*	*R*	*Tot.*	*I*	*C*	*R*	*Tot.*
GRAM POS	**22**	**12**	**16**	**50**	**11**	**2**	**13**	**26**
CNS	11	10	12	33	8	2	9	19
Staphylococcus aureus	0	2	1	3	0	0	1	1
Streptococcus spp.	3	0	3	6	0	0	0	0
Enterococcus spp.	3	0	0	3	2	0	2	4
Others	5	0	0	5	1	0	1	2
GRAM NEG	**1**	**6**	**4**	**11**	**7**	**1**	**3**	**11**
Escherichia coli	1	0	2	3	2	0	1	3
Pseudomonas aeruginosa	0	1	2	3	4	0	0	4
Serratia marcescens	0	1	0	1	0	0	0	0
Klebsiella pneumoniae	0	0	0	0	0	0	1	1
Enterobacter spp.	0	2	0	2	0	1	1	2
Others	0	2	0	2	1	0	0	1
FUNGI	**0**	**0**	**3**	**3**	**0**	**0**	**1**	**1**
Non-*albicans Candida* spp.	0	0	1	1	0	0	1	1
Aspergillus fumigatus	0	0	2	2	0	0	0	0
TOTAL	**23**	**18**	**23**	**64**	**18**	**3**	**17**	**38**

I: first induction; C: consolidation; R: relapse/refractory. Polymicrobial infections: 6. *P-value:* ns.

TABLE 4 - *Outcome of febrile episodes.*

	<60 years (n=90)	*≥60 years (n=71)*
Days of neutropenia*	18 (11-45)	19 (11-50)
Time to defervescence, days*	8 (3-30)	7 (3-25)
Duration of antimicrobic therapy, days*	9 (4-28)	10 (5-32)
Outcome, n.		
Success without modification	33 (37%)	24 (34%)
Success with modification	41 (45%)	32 (45%)
Failure	16 (18%)	15 (21%)

*median (range); *P-value:* ns.

younger and 38 in elderly patients. Microbiologically documented infections without bacteraemia were two pneumonia due to *Aspergillus fumigatus*.

Gram-positive cocci were responsible for 81% and 68% respectively of bloodstream infections (P: ns), namely coagulase-negative staphylococci (66% and 73%), frequently responsible for CVC related infections due to strain slime producer. Streptococci were isolated only in younger patients (during induction and during relapse HAM treatment); in addition three of these patients had severe oral mucositis.

All enterococci were HLAR (high level aminoglycoside resistance) strains, while a VRE (vancomycin resistant enterococcus, van A type) was documented in a younger patient during induction treatment.

Gram-negative infections were documented in 18% and in 29% of sepsis (mainly *E. coli* and *P. aeruginosa*); fungi were recorded in 5% and 3% of documented infections (P: ns). Proven fungal in-

TABLE 5 - *Organism responsible for death.*

Organism	*<60 years*	*≥60 years*
GRAM POS COCCI	*3/50 (6%)*	*2/26 (8%)*
S. aureus	1	0
Enterococci	1	2
Streptococci	1	0
GRAM NEG BACILLI	*5/11 (45%)*	*4/11 (36%)*
P. aeruginosa	2	2
E. coli	1	1
Enterobacter	0	1
Others	2	0
FUNGI	*2/3 (66%)*	*1/1 (100%)*
C. krusei	1	0
C. tropicalis	0	1
A. fumigatus	1	0
	0	0
TOTAL	**10/64 (16%)**	**7/38 (18%)**

p-value: ns.

fections were 2 candidemia (1 *C.krusei* in a younger patient and 1 *C. tropicalis* in an elderly one) and 2 aspergillosis (*A.fumigatus* in two younger patients) during the course of relapse.

Outcome

Severe mucositis (grade III and IV) was found in 21% of 90 episodes in younger and in 13% of 71 episodes in elderly (P: ns).

The median duration of neutropenia, the median time to defervescence and the duration of antibiotic therapy were similar between the two groups. The overall success rate and failure (death for documented and presumed infection) was also not significantly different (Table 4).

Overall mortality rate of microbiologically documented infection was 13% (17/128 patients). The overall rate of organisms responsible for death was 17% (17/102 organisms): 16% in younger and 18% in elderly patients (P: ns). In no case was death due to polymicrobial sepsis.

Gram-positive bacteria included one *S. aureus* MRSA, three Enterococci (one of which a VRE Van A, despite Linezolid therapy), all responsible for sepsis and one *Streptococcus mitis*, causing sepsis and concomitant ARDS.

Other microorganisms responsible for death were mainly multiresistant *P. aeruginosa* in both groups, all causing sepsis. Fungal mortality was due to 2 systemic candidemia (from *Candida krusei* and *Candida tropicalis*) and one pneumonia due to *Aspergillus fumigatus* (Table 5).

DISCUSSION

The intensive chemotherapy used to induce remission in patients with acute leukemia, causes prolonged periods of neutropenia, increasing the patient's susceptibility to infectious complications, mainly bacterial and fungal. Moreover, the progressive decline in immune function that develops with age is an additional risk factor. In several clinical trials patients have been stratified according to risk of infections (Freifeld *et al.,* 1999; Kern *et al*., 1999; Chernobelski *et al.,* 2006; Sung *et al.*, 2007) without a comparison between older and non-elderly patients.

Therefore, because it is important to identify potential age-related differences in clinical outcome and death among high-risk patients, the present study compared the incidence and management of nosocomial infections between younger and elderly acute leukemia. All patients were examined during aggressive intravenous antineoplastic therapy and all had prolonged neutropenia (>10 days); the two groups were also comparable in duration of neutropenia. Severe neutropenia with ANC <100/ul was recorded more frequently in younger patients and the difference was related to more intensive courses of chemotherapy. A difference was also recorded in disease status, with a number of febrile episodes during relapse/refractory disease, a phase traditionally associated with high morbidity and mortality rates, significantly lower in elderly patients. This difference was not unexpected, because only rarely were elderly patients treated with aggressive chemotherapy during this phase.

Severe mucositis was recorded more frequently in younger patients, although there was no statistical difference. No difference was documented in the defervescence-time, in median duration of antimicrobic therapy and in overall outcome. Nor was any difference recorded in the overall incidence of infections between the two groups, particularly in type of febrile episodes (documented infections and FUO) and in the nosocomial infection pattern (gram-positive, gram-negative and fungi). Both subgroups had a trend of more gram-positive infections than gram-negative ones, although in elderly the frequency of important risk factors for these infections, such as CVC, was significantly lower than the in younger patients.

Coagulase-negative staphylococci represented the major cause of septicemia, frequently due to strain slime producer in patients with indwelling CVC (Groshong), without significant differences between elderly and younger patients. In our bacteremic patients only the younger subgroup had viridans streptococci, very likely related to the high dose of cytarabine and to oral mucositis, recently emerged as important risk factors for these infections in severe immunocompromised patients (Bochud *et al.,*1994; Richard *et al*., 1995; Falcone *et al*., 2004). No differences were documented in enterococcal bacteraemias and in antimicrobial susceptibility; in fact, all strains were HLAR.

Even if mortality due to gram-positive was lower than gram-negative bacteria, pathogens such as *S. aureus* MRSA, viridans streptococci re-

sponsible for ARDS and multiresistant enterococci mainly VRE type, can be still responsible for severe nosocomial sepsis in patients with acute leukaemia, despite adequate antimicrobial therapy (Falcone *et al*., 2004; Fanci *et al*., 1999).
In regard to gram-negative infections, although we documented a decline of these infections compared to our previous experiences, *P. aeruginosa* remains the most important factor of morbidity and mortality in both subgroups, very likely related to multidrug resistance, as documented in our center and in other studies (Fanci *et al*., 2001; Fanci *et al.*, 2003; Rolston *et al*., 1999).
Incidence of documented fungal infections and mortality rate were similar, but the number was too low to reach definitive conclusions. As reported by others, mortality attributable to fungi remains very high in severely immunocompromised patients despite antifungal strategies (Mavor *et al.,* 2005; Brakkage, 2005).
In conclusion, elderly patients with acute leukemia do not seem to be more susceptible to infections than younger ones, as reported in a similar experience in which haematological patients were stratified for risk and age (Garcia-Suarez *et al.,* 2003). However in our study, performed in a population also stratified for underlying disease, the lower frequency of some risk factors such as CVC and severe neutropenia, related to the chemotherapy regimen, must be taken into account.

REFERENCES

Ascioglu S., Rex J.H., De Pauw B., Bennet J.E., Bille, J., Crokaert F., Denning D.W., Donnelly J.P., Edwards J.E., Friavec Z., Fiere D., Lortholary O., Maertens J., Meis J.F., Patterson T.F., Ritter J., Selleslag D., Shah P.M., Stevens D.A., Walsh T.J. Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer; Mycoses Study Group of the National Institute of Allergy and Infectious Diseases. (2002). Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin. Infect. Dis.* **34** (1), 7-14.

Bochud P.Y., Eggiman P., Calandra T., Van Melle G., Saghafi G., Francioli P. (1994). Bacteremia due to *viridans streptococcus* in neutropenic patients with cancer: clinical spectrum and risk factors. *Clin. Infect. Dis.* **18** (1), 25-31.

Boehmer E.D., Goral J., Faunce D.E., Kovacs E.J. (2004). Age - dependent decrease in Toll-like receptor 4-mediated proinflammatory cytokine production and mitogen-activated protein kinase expression. *J. Leucoc. Biol.* **75** (2), 342-349.

Brakhage AA. (2005). Systemic fungal infections caused by Aspergillus species: epidemiology, infection progress and virulence determinants. *Curr. Drug Targets.* **6** (8), 875-876.

Buchner T., Hiddemann W., Berdel W.E., Wormann B., Schoch C., Fonatsch C., Loffler H., Haferlach T., Ludwig W.D., Maschmeyer G., Staib P., Aul C., Gruneisen A., Lengfelder E., Frickhofen N., Kern W., Serve H.L., Mesters R.M., Sauerland M.C., HeinecKe A. German A.M.L. Cooperative Group et al. (2003). Thioguanine, cytarabine and daunorubicin (TAD) and high-dose cytarabine and mitoxantrone (HAM) for induction, TAD for consolidation, and either prolonged maintenance by reduced montly TAD or TAD-HAM-TAD and one course of intensive consolidation by sequential HAM in adult patients at all ages with de novo acute myeloid leukemia (AML): a randomized trial of the German AML Cooperative group. *J. Clin. Oncol.* **15**, **21** (24), 4496-4504.

Chernobelski P., Lavrenkov K., Rimar D., Riesenberg K., Schlaeffer F., Ariad, S., Mermershtain, W. (2006). Prospective study of empiric monotherapy with ceftazidime for low-risk grade IV febrile neutropenia after cytotoxic chemotherapy in cancer patients. *Chemotherapy.* **52** (4), 185-189.

Falcone M., Micozzi A., Pompeo M.E., Baiocchi P., Fabi F., Penni A., Martino P., Venditti, M. (2004). Methicillin-resistant staphylococcal bacteraemia in patients with hematologic malignancies: clinical and microbiological retrospective comparative analysis of *S. haemoliticus*, *S. epidermidis* and *S. aureus J. Chemother*. **16** (6), 540-548.

Fanci R., Pecile P., Fabbri A., Paci C., Martinez R.L., Longo G. (1999). Emerging infections due to enterococci in patients with acute leukemia. *Haematologica*. **84** (7), 662-664.

Fanci R., Paci C., Pecile P. (2001). Isolation frequency and antimicrobial susceptibility of *Pseudomonas aeruginosa* bloodstream infections in neutropenic patients with acute leukemia. *J. Chemother.* **13** (2), 213-215.

Fanci R., Paci C., Anichini P., Pecile P., Marra G., Casini C., Nicoletti P. (2003). Incidence and molecular epidemiology of *Pseudomonas aeruginosa* bacteremia in patients with acute leukemia: analysis by pulsed-field gel electrophoresis. (2003). *New Microbiol*. **26** (4), 353-361.

Freifeld A., Walsh T., Marshall D., Gress J., Steinberg S.M., Hathorn J., Rubin M., Jarosinski P., Gill V., Young R.C., Pizzo P.A. (1995). Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. *J. Clin. Oncol.* **13** (1), 165-176.

FREIFELD A., MARCHIGIANI D., WALSH T., CHANOCK S., LEWIS L., HIEMENZ J., HIEMENZ S., HICKS J.E., GILL V., STEINBERG S.M., PIZZO P.A. (1999). A double–blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *New Engl. J. Med*. **341** (5), 305-311.

FULOP T., LARBI A., DOUZIECH N., FORTIN C., GUERARD K.P., LESUR O., KHALIL A., DUPUIS G. (2004). Signal transduction and functional changes in neutrophils with aging. *Aging Cell.* **3** (4), 217-226.

GARCIA-SUAREZ J., KRSNIK I., REYES E., DE MIGUEL D., HERMANZ N., BARR-ALÌ M., BURGALETA C. (2003). Elderly haematological patients with chemotherapy-induced febrile neutropenia have similar rates of infection and outcome to younger adults: a prospective study and risk-adapted therapy. *Br. J. Haematol*. **120** (2), 209-216.

GIRMENIA C., LO COCO F., BRECCIA M., LATAGLIATA R., SPADEA A., D'ANDREA M., GENTILE G., MICOZZI A., ALIMENA G., MARTINO P., MANDELLI F. (2003). Infectious complications in patients with acute promyelocitic leukemia treated with the AIDA regimen. *Leukemia* **17** (5), 925-930.

HAKIM F.T., FLOMERFELT F.A., BOYADZIS M., GRESS R.E. (2004). Aging, immunity and cancer. *Curr Opin Immunol*. **16** (2), 151-156.

KERN W.V., COMETTA A., DE BOCK R., LANGENAEKEN J., PAESMANS M., GAYA H. (1999). Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy intravenous International. Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *New Engl. J. Med.* **341** (5), 312-318.

MAVOR A.L., THEWES S., HUBE B. (2005). Systemic fungal infections caused by Candida species: epidemiology, infection progress and virulence attributes. *Curr. Drug Targets*. **6** (8), 863-874.

OFFIDANI M., CORVATTA L., MALERBA L., MARCONI M., LEONI P. (2004). Infectious complications in adult acute lymphoblastic leukemia (ALL): experience at one single center. *Leuk Lymphoma.* **45** (8), 1617-1621.

RICHARD P., AMADOR DEL VALLE G., MOREAU P., MILPIED N., FELICE M.P., DAESCHLER T., HAROUSSEAU J.L., RICHET H. (1995). Viridans streptococcal bacteraemia in patients with neutropenia. *Lancet*. **345**, (8965) 1607-1609.

ROLSTON K.V., TARRAND J.J. (1999). *Pseudomonas aeruginosa* - still frequent pathogen in patients with cancer: 11-year experience at a comprehensive cancer Center. *Clin. Infect. Dis.* **29** (2), 463-464.

SUNG L., LANGE B.J., GERBING R.B., ALONZO T.A., FEUSNER J. (2007). Microbiologically documented infections and infections-related mortality in children with acute myeloid leukaemia. Blood **27** (Epub ahead of print).

VITALE A., GUARINI A., ARIOLA C., MANCINI M., CUNEO A., PANE F., SAGLIO G., CIMINO G., TAFURI A., MELONI G., FABBIANO F., RECCHIA A., KROPP M.G., KRAMPERA M., CASCAVILLA N., FERRARA F., ROMANO A., MAZZA P., FOZZA C., PAOLONI F., VIGNETTI M., FOÀ R. (2006). Adult T-cell acute lymphoblastic leukemia: biologic profile at presentation and correlation with response to induction treatment in patients enrolled in the GIMEMA LAL 0496 protocol. *Blood*. **107** (2), 473-479.