The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study

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Background and Objectives. The aim of this study was to evaluate the incidence and outcome of invasive fungal infections (IFI) in patients with hematologic malignancies.

Design and Methods. This was a retrospective cohort study of patients admitted between 1999 and 2003 to 18 hematology wards in Italy. Each participating center provided information on all patients with newly diagnosed hematologic malignancies admitted during the survery period and on all episodes of IFI experienced by these patients.

Results. The cohort was formed of 11,802 patients with hematologic malignacies: acute leukemia (myeloid 3012, lymphoid 1173), chronic leukemia (myeloid 596, lymphoid 1104), lymphoma (Hodgkin's 844, non-Hodgkin's 3457), or multiple myeloma (1616). There were 538 proven or probable IFI (4.6%); 373 (69%) occurred in patients with acute myeloid leukemia. Over half (346/538) were caused by molds (2.9%), in most cases *Aspergillus spp*. (310/346). The 192 yeast infections (1.6%) included 175 cases of candidemia. Overall and IFI-attributable mortality rates were 2% (209/11802) and 39% (209/538), respectively. The highest IFI-attributable mortality rates were associated with zygomycosis (64%) followed by fusariosis (53%), aspergillosis (42%), and candidemia (33%).

Interpretation and Conclusions. Patients with hematologic malignancies are currently at higher risk of IFI caused by molds than by yeasts, and the incidence of IFI is highest among patients with acute myeloid leukemia. *Aspergillus spp* are still the most common pathogens, followed by *Candida spp*. Other agents are rare. The attributable mortality rate for aspergillosis has dropped from 60-70% to approximately 40%. Candidemia-related mortality remains within the 30-40% range reported in literature although the incidence has decreased.

Key words: fungal infection, aspergillus, Candida, epidemiology, hematologic malignancies.

Haematologica 2006; 91:1068-1075

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The percentage of patients who develop invasive fungal infections (IFI) has increased dramatically in recent decades. Most of these infections occur in patients with hematologic malignancies.[1-3] This increase is attributed to host defense impairment due to intensive cytotoxic chemotherapies, hematopoietic stem cell transplantation, ablative radiation therapy, use of corticosteroids, cyclosporine, and new immunosuppressive agents.[3-8] *Candida spp.* have been the main cause of IFI, but recent autopsy and epidemiological findings indicate that an increasing number of infections are being caused by molds.[9-11] Most are attributed to *Aspergillus spp.*, and such infections have become a prime cause of death in patients with hematologic malignancies. During the last 20 years, other opportunistic fungal pathogens, such as *Fusarium spp.* and *Zygomycetes*, have also emorged[12-15] whereas infections caused by other fungi are still rare.[16-19] The true incidence of IFI among patients with hematologic malignancies remains obscure since data in the literature are based largely on reports from single institutions or analyses of selected subgroups of patients (e.g., those with acute leukemia or following stem cell transplantation).[7-8] The aim of the present study was to investigate current incidence and mortality rates for IFI in patients with hematologic malignancies in Italy.

Design and Methods

This retrospective cohort study was conducted in hematology wards of tertiary care centers or university hospitals located throughout Italy, between January 1999 and December 2003. Enrollment was limited to adult patients (aged over 16 years) with newly diagnosed acute myeloid or lymphoid leukemia (AML and ALL, respectively), chronic myeloid or lymphoid leukemia (CML and CLL, respectively), Hodgkin's or non-Hodgkin's lymphoma (HL and NHL, respectively), or multiple myeloma. Seven centers contributed data only on patients with acute leukemia. Patients with other types of hematologic malignancies (e.g., myelodysplastic syn-

Table 1. Incidence of mold and yeast infections in patients with different types of hematologic malignancies.

HM	No. of patients	No. of IFI (incidence)	Molds		Yeasts	
			No. cases	Incidence %	No. cases	Incidence %
AML	3012	373 (12%)	239	7.9	134	4.4
ALL	1173	77 (6.5%)	51	4.3	26	2.2
CML	596	15 (2.5%)	14	2.3	1	0.2
CLL	1104	6 (0.5%)	5	0.4	1	0.1
NHL	3457	54 (1.6%)	30	0.9	24	0.7
HD	844	6 (0.7%)	3	0.35	3	0.35
MM	1616	7 (0.5%)	4	0.3	3	0.2
Total	11802	538 (4.6%)	346	2.9	192	1.6

HM: hematologic malignancies; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; CML: chronic myeloid leukemia; CLL: chronic lymphoid leukemia; NHL: non-Hodgkin's lymphoma; HD: Hodgkin's disease; MM: multiple myeloma; IFI: invasive fungal infection.

Table 2. Species distribution of invasive fungal infections in patients with hematologic malignancies.

Infections caused by	No. of cases (%)	Incidence %
Molds	**346 (100)**	**2.9**
Aspergillus spp.	310 (90)	2.6
Zygomycetes	14 (4)	0.1
Fusarium spp.	15 (4)	0.1
Others*	7 (2)	0.06
Yeasts	**192 (100)**	**1.6**
Candida spp.	175 (91)	1.5
Cryptococcus spp.	8 (4)	0.07
Trichosporon spp.	7 (4)	0.06
Others°	2 (1)	0.02

**Scedosporium spp. (n=3) , Acremonium spp. (n=2) , Cladosporium spp.(n=1) , Penicillium spp. (n=1); °Rhodotorula spp 1, Hansenula (n=1).*

dromes) or non-malignant hematologic disorders (hemolytic anemia; thrombocytopenias, aplastic anemia, etc) were excluded from this analysis, as were those patients undergoing autologous or allogeneic HSCT.

Each participating center completed a form which included information on all patients with newly diagnosed hematologic malignancies admitted during the survey period and on all episodes of IFI experienced by these patients. The consensus criteria proposed by the EORTC/ MSG were used to define IFI,[20] and analysis was restricted to infections classifiable as *proven* or *probable*. For each episode, additional information was requested: date of first positive identification, fungal species isolated, microbiological and histological findings (*in vivo* and *post mortem*), and outcome (assessed 30 days after diagnosis). Multiple episodes in the same patient were counted as separate infections unless they were caused by the same fungal agent. Overall and attributable mortality rates were estimated in the study population. Information was specifically requested on the antifungal prophylaxis protocols used in each center. Because the majority of the participating centers were members of the GIMEMA-Infection, their diagnostic work-ups were almost identical. These diagnostic works-ups include collection of blood cultures at the onset of fever, nasal, pharyngeal, and rectal swabs, serological tests for IFI, and computed tomography (CT) scans on the 4-7th day of fever. Additional examinations (e.g., abdominal sonography, sinus or brain CT, skin biopsy, bronchoalveolar lavage, fundus examination) were performed as indicated.[3,21]

Antifungal prophylaxis was administered in 13 centers. The use of itraconazole for this purpose increased (six departments in 1999, nine in 2000, and ten in 2002) with parallel reductions in fluconazole use. The therapeutic protocols used by the centers during the

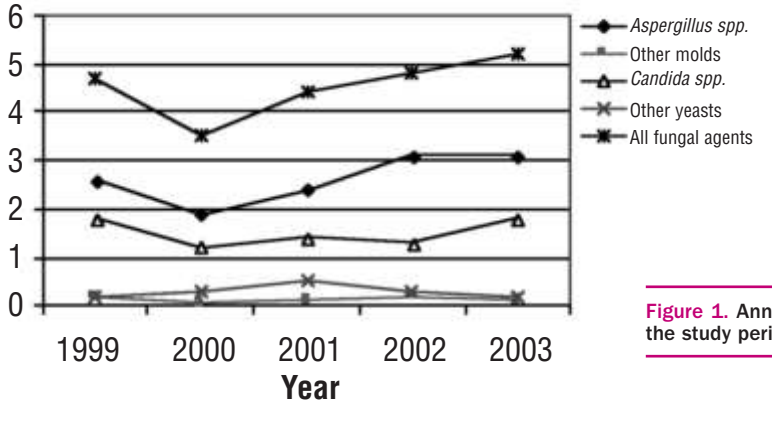

Figure 1. Annual incidence rates for IFI subgroups during the study period. RR 1.1 (95% CI 0.86-1.42; *p*= 0.452)

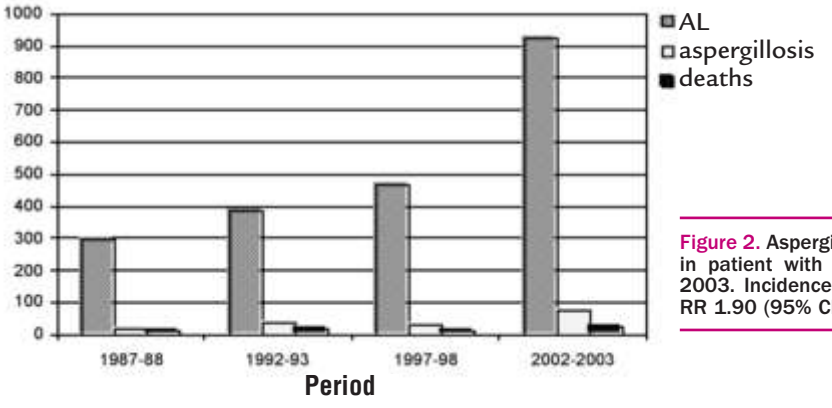

Figure 2. Aspergillosis and aspergillosis-related deaths in patient with acute leukemia between 1987 and 2003. Incidence: RR 0.81 (95% CI 0.50-1.30). AMR: RR 1.90 (95% CI 1.17-3.09).

Table 3. Molds infections in patients with different types of hematologic malignancies.

HM	*No. of patients*	*Aspergillus spp.*			*Zygomycetes*			*Fusarium spp.*		
		Cases (%)	*Deaths (AMR%)*	*Mortality (%)*	*Cases (%)*	*Deaths (AMR%)*	*Mortality (%)*	*Cases (%)*	*Deaths (AMR%)*	*Mortality (%)*
AML	3012	213 (69)	80 (38)	2.6	9 (64)	6 (66.7)	0.2	13 (87)	7 (47)	0.2
ALL	1173	44 (14)	19 (43)	1.6	4 (29)	2 (50)	0.08	1 (6.5)	1 (100)	0.08
CML	596	14 (4.5)	7 (50)	1.2	0	0	0	0	0	0
CLL	1104	5 (1.5)	4 (80)	0.4	0	0	0	0	0	0
NHL	3457	27 (9)	14 (52)	0.4	1 (7)	1 (100)	0.03	1 (6.5)	0	0
HD	844	3 (1)	2 (67)	0.2	0	0	0	0	0	0
MM	1616	4 (1)	3 (75)	0.2	0	0	0	0	0	0
Total	11802	310 (100)	129 (42)	1.1	14 (100)	9 (64)	0.07	15 (100)	8 (53)	0.07

HM: hematologic malignancy; AMR: attributable mortality rate; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; CML: chronic myeloid leukemia; CLL: chronic lymphoid leukemia; NHL: non-Hodgkin's lymphoma; HD: Hodgkin's disease; MM: multiple myeloma.

study period were also similar and reflected current IDSA guidelines.[22,23] Six institutions had participated in a previous study on filamentous fungi infections in acute leukemia patients during the period 1987-1998,[3] and IFI incidence and mortality rates registered in these centers during the two study periods were thus compared.

Statistical methods

Associations between variables were evaluated using the χ^2 and Fisher's exact tests. Regression analysis with ANOVA was used to determine trends in incidence, while the Cochran-Armitage trend test was used to evaluate mortality trends. p values <0.05 were considered statistically significant. Statistical analyses were performed using SAS version 8.02.

Results

During the study period, 11,802 patients with newly diagnosed hematology malignancies were admitted to the 18 participating centers for treatment other than hematopoietic stem cell transplantation. Their underlying malignancies are reported in Table 1. Five hundred and thirty-eight proven or probable IFI were documented. The overall incidence of IFI, 4.6%, remained stable (RR=1.1; 95%CI=0.86-1.42; p=0.452), and no significant shifts were observed in the incidence of infections caused by individual pathogen subgroups (Figure 1). Molds were held responsible for 346/538 episodes (2.9%) and yeasts for 192 infections (1.6%) (Table 2). The incidence of IFI in the different subsets of patients ranged from 0.5% among patients with

Table 4. Yeast infections in patients with different types of hematologic malignancies.

UHM	No. of patients	Candida spp.			Cryptococcus spp.			Trichosporon spp.		
		Cases (%)	Deaths (AMR%)	Mortality (%)	Cases (%)	Deaths (AMR%)	Mortality (%)	Cases (%)	Deaths (AMR%)	Mortality (%)
AML	3012	124 (71)	44 (35.5)	1.4	5 (62.5)	2 (40)	0.1	5 (71)	2 (40)	0.1
ALL	1173	22 (12.5)	8 (36)	0.7	2 (25)	1 (50)	0.08	2 (29)	0	0
CML	596	1 (0.5)	0	0	0	0	0	0	0	0
CLL	1104	1 (0.5)	0	0	0	0	0	0	0	0
NHL	3457	21 (12)	4 (19)	0.1	1 (12.5)	1 (100)	0.03	0	0	0
HD	844	3 (1.5)	0	0	0	0	0	0	0	0
MM	1616	3 (1.5)	1 (33)	0.05	0	0	0	0	0	0
Total	11802	175 (100)	57 (33)	0.5	8 (100)	4 (50)	0.04	7 (100)	2 (29)	0.02

HM: hematologic malignancy; AMR: attributable mortality rate; AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; CML: chronic myeloid leukemia; CLL: chronic lymphoid leukemia; NHL: non-Hodgkin's lymphoma; HD: Hodgkin's disease; MM: multiple myeloma.

multiple myeloma to 12% in those with AML (Table 1). The overall mortality rate for fungal infections was 2% (209/11,802), and the IFI-attributable mortality rate (AMR) was 39% (209/538).

Molds infections

The majority of the mold infections (310/346; 90%) were caused by *Aspergillus spp.*, and these infections accounted for 58% of the IFI analyzed. Forty-one percent of the *Aspergillus* isolates were identified at the species level, and *A. fumigatus* was the main pathogen (68/310 episodes, 53%) (Table 3). Non-significant variations were observed in the annual incidence of IFI caused by the different *Aspergillus* species. An increasing trend was observed for *A. flavus* infections (5 cases in 1999 versus 14 cases in 2003), although this was also not statistically significant (RR 2.10, 95%CI 0.8-5.49; p=0.117). *Zygomycetes* and *Fusarium spp.* were responsible for 14 and 15 episodes (0.1%), respectively. The remaining six infections were due to *Scedosporium spp.*, *Acremonium spp.*, *Penicillium spp.*, or *Cladosporium spp.* Aspergillosis was most common in patients with acute leukemia (Table 3).

Almost half of these infections (43%; 111/259 evaluable cases) emerged during the first course of induction chemotherapy; 20 others (8%) occurred during consolidation chemotherapy in patients who were obviously in complete remission, and 73 (28%) emerged during a second or third course of induction chemotherapy for relapse of the hematopoietic malignancy. The remaining 55 patients (21%) were resistant to first-line chemotherapy and had received salvage therapy. The diagnosis of aspergillosis was classified as *probable* in 155 episodes (60%) and *proven* in the remaining 104 (40%). Only 22 of the proven diagnoses relied on autopsy findings.

Mortality rates ranged from about 2.6% in AML patients to 0.2% in those with multiple myeloma or Hodgkin's lymphoma. The AMR were 42% for aspergillosis, 64% for zygomycosis, and 53% for fusariosis (Table 3). Two of the three *Scedosporium* infections were fatal, as was one of the two infections caused by *Acremonium* and the single case due to *Cladosporium*. The patient suffering from a *Penicillium spp.* infection survived. The AMR for aspergillosis ranged from 38% in AML patients to 80% in those with CLL. An analysis of the relationship between the AMR for aspergillosis and the phase of the underlying malignancy (based on data for 259 assessable patients) revealed that 31 of the 112 deaths due to aspergillosis (28%) occurred during the induction cycle at the beginning of the treament of the hematologic malignancy. Over half of the patients who developed aspergillosis during a disease relapse (45/72; 63%) died, as opposed to only 25% (14/55) of those who were receiving salvage treatment and 20% (4/20) of patients whose infections occurred during complete remission.

Comparison of data for 1987 and 2003 on acute leukemia patients (available for six centers only) revealed increases in the absolute numbers of infections due to *Aspergillus spp.* and those caused by other molds although incidence rates remained stable for both types of infection (aspergillosis: RR 0.81, 95%CI

0.50-1.30, *p*=0.38; other molds: RR 0.60, 95%CI 0.17-2.10). The AMR for aspergillosis dropped significantly (RR 1.90, 95%CI 1.17-3.09, *p*=0.019) from 60% (12 of 20 cases) in 1987 to 32% (24 of 76 cases) in 2003 (Figure 2), but there was no change in the rates for infections caused by other molds.

Yeasts infections

Most of the yeast infections were caused by *Candida spp.* (175 episodes, 33% of all IFI). The diagnosis was based on blood cultures in all cases. *Candida* non–albicans species were responsible for over half the episodes of candidemia (100/175; 57%) (Table 4). The remaining 17 yeast infections were caused by *Cryptococcus spp*. (8 cases), *Trichosporon spp.* (7 cases), and *Hansenula* and *Rhodotorula* (1 case each) (Table 2). Twelve of the 175 cases of candidemia (7%) were followed by chronic disseminated candidiasis. Eighty-three percent of the cases of candidiemia occurred in patients with acute leukemia (71% in AML, 12% in ALL). Overall, 3.5% (146/4185) of all patients with acute leukemia developed candidemia (Table 4). The incidence of *C. albicans* infections increased from 8% in 2001 to 19% in 2003 (RR 0.52; 95%CI 0.26-1.04; *p*=0.049).

The mortality rate was highest among AML patients (1.4%). There were no deaths due to candidemia among patients with CML, CLL, or HL. The AMR of patients with yeast infections was 33% for candidemia (57/175), 50% for cryptococcosis (4/8), and 29% for trichosporonosis (2/7). The patient who developed a *Hansenula* infection died while the one infected by *Rhodotorula* recovered from the infection. The AMR for candidemia ranged from 19% in NHL to 36% in ALL (Table 4). Species-specific AMR ranged from 6% for infections caused by *C. parapsilosis* to 54% for those due to *C. tropicalis.*

Discussion

In recent years numerous studies have been conducted to identify risk factors or prognostic factors for IFI, but only a few attempts have been made to assess the real incidence of these infections in patients with hematologic malignancies.[3-8] Data on the incidence of IFI in transplanted patients (one of the highest risk groups) are widely available, but they tell us very little about the situation in other patients being treated for hematologic malignancies.[7,8,24-26] The present study was not designed to establish an inventory of risk or prognostic factors or to evaluate the safety and efficacy of certain antifungal regimens. On the contrary, we terminated the investigation in 2003 to avoid a biased assessment of outcome related to the recent introduction of new and possibly more effective antifungal agents, such as voriconazole and caspofungin. Instead, our objectives were to determine the true incidence of IFI among patients with hematologic malignancies and to identity the predominant and emerging causes of these infections.

The reported incidence of proven or probable aspergillosis in patients with acute leukemias ranges from 6% to 12% in series that included both adults and children.[2-4,27,28] Our data confirm that molds were responsible for the majority of the IFI, and that aspergillosis is the most frequent complication in patients with hematologic malignancies. *A. fumigatus* is still the most frequently isolated species, while we did not observe the increase in infections due to *A. terreus* reported by other authors.[29]

Several studies have evaluated the incidence of candidemia, particularly in critical care settings.[30] Conversely there are far fewer reports on the frequency of candidemia among patients with hematologic malignancies.[21,30-34] Our data confirm that yeast infections are less common than mold infections in this population. *Candida spp.* were still the predominant yeast pathogens, but eight infections were caused by *Cryptococcus spp.*, which confirms our previous report on the possible occurrence in patients with hematologic malignancies of an infection typically associated with patients infected by human immunodeficiency virus.[19]

The influence of previous antifungal prophylaxis with fluconazole on the distribution of different *Candida spp.* has already been ascertained.[34,35] Patients who received fluconazole appeared more likely to acquire C. *non-albicans* infections than those who were not treated with it. As a result, *C. non-albicans spp.* became the leading cause of candidemia that developed during the administration of fluconazole prophylaxis. In our study, *C. non-albicans spp.* were responsible for 57% of all IFI episodes although the switch from fluconazole to itraconazole for prophylaxis seemed to be associated with a progressive increase in the percentage of bloodstream infections caused by *C. albicans.*

A previous study by the GIMEMA-Infection revealed that *Zygomycetes* were the second most frequent cause of mold infections in patients with hematologic malignancies.[14] During recent years, various studies have revealed apparent increases in the frequency of zygomycosis, particularly among patients who had received voriconazole for antifungal prophylaxis or treatment.[15,36] In our population, however, the incidence of *Zygomycetes* and *Fusarium* infections remained low; this finding might reflect our participating centers' limited use of voriconazole during the study period. On the other hand, in institutions where

these infections are on the rise,[8,15] the increase might be due to other factors, such as more aggressive chemotherapy resulting in more severe immunosuppression that renders patients vulnerable to infections by these intrinsically less virulent fungi. As noted, there were no significant changes in the chemotherapy regimens used by the participating centers during the study period, which suggests that immunosuppression might be a major factor in the etiology of these rare fungal infections. It is rather difficult to establish the AMR for aspergillosis or other mold infections since the underlying hematologic malignancies represent an important determinant of outcome. A meta-analysis of 50 studies on aspergillosis revealed mortality rates of approximately 60% in acute leukemia and lymphoma patients and up to 90% in allogeneic stem cell recipients.[37]

About 2% of the patients with hematologic malignancies in our survey died as a result of their IFI, and 39% of the infections had fatal outcomes. The lowest AMR was observed in patients with trichosporonosis. Zygomycosis was associated with the highest mortality, i.e. 64%, which is consistent with the figure reported by Gleissner *et al*.[38] Interestingly, invasive aspergillosis caused by *A. fumigatus* carried a higher AMR than those recorded for *A. niger* and *A. terreus* infections. In the six participating centers with data collected 17 years ago, the incidence of aspergillosis among patients with acute leukemia appeared unchanged, but there was a significant reduction in the aspergillosis-AMR.[3] The AMR for infections caused by *Candida spp.* was 33%, which is consistent with figures published between 1993 and 1998 (34-39%).[21,30,31] Unfortunately, the mortality rate has not improved in spite of the availability of improved diagnostic tools and therapeutic alternatives that are safer than conventional amphotericin B.

Despite the limitations related to its retrospective nature, our study provides important information. The fact that we were able to collect relevant information on all patients admitted to the participating hematology departments during the study period is a very strong point of this survey. Our data confirm that, among non-transplanted patients, those with AML are at highest risk of developing an IFI. About 8% of our AML patients developed mold infections (mainly aspergillosis) whereas 4% had yeast infections. The reduction in aspergillosis-related mortality is a striking finding, which can probably be attributed to improved diagnostics combined with more appropriate treatment strategies since the reduction apparently predated the widespread use of new-generation antifungals. Indeed, the recent introduction into clinical practice of drugs such us voriconazole and caspofungin, which are effective against both *Aspergillus spp.* and *Candida spp.*,[38-40] and posaconazole, which also displays promising activity against *Zygomycetes*,[41] could conceivably lead to additional improvements in the prognosis of patients with hematologic malignancies.

We did not observe any increase in the frequency of infections caused by rarer fungal pathogens, so there appears to be no reason to include routine coverage for these obscure agents in standard antifungal regimens. Thus far, experience has justified decisions to initiate specific treatment only when serious suspicion of a particular infection has arisen. This may, however, change in the near future when the use of new forms of treatment for hematologic malignancies becomes more widespread, since new categories of patients will emerge who can be classified as *high risk*. Purine analogs, for example, which produce profound and prolonged immunosuppression, will extend the risk of IFI to other patients (e.g. those CLL) even in the absence of neutropenia or steroid therapy. The rate of fungal complications in NHL can also be expected to increase with the growing use of monoclonal antibodies, rituximab or alemtuzumab. Likewise, the continuous intensification of chemotherapeutic regimens with increasingly shorter intervals between treatment cycles could significantly increase the incidence of IFI in NHL patients.[4] When this occurs, it will be time for a new epidemiological survey, and the present data can be used for historical comparison.

All authors contributed equally to the manuscript.

The authors wish to thank Prof. B. de Pauw for his useful and enlightening suggestions and comments. The authors also declare that they have no potential conflicts of interest. This work was supported by a grant from the Italian Ministry of University and Scientific and Technological Research (MURST) of Italy.

Manuscript received March 22, 2005. Accepted June 7, 2006.

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