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FUNGAL INFECTIONS IN NEUTROPENIC PATIENTS. A 8-YEAR PROSPECTIVE STUDY

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SUMMARY

In this paper we report a eight-year prospective study designed to further characterize incidence, epidemiology, specific syndromes, treatment and prognosis associated with fungal infections in neutropenic patients. During the study period 30 fungal infections were diagnosed in 30 patients among 313 episodes of fever and neutropenia (10%). There were 15 cases of candidiasis, 5 pulmonary aspergillosis, 3 sinusitis by *Aspergillus fumigatus*, 5 infections by *Fusarium* sp., one infection by *Trichosporon* sp., and one infection due to *Rhodotorula rubra*. Blood cultures were positive in 18 cases (60%). The predisposing factors for fungal infection in multivariate analysis were the presence of central venous catheter ($p<0.001$), longer duration of profound ($<100/mm^3$) neutropenia ($p<0.001$), the use of corticosteroids ($p<0.001$), gram-positive bacteremia ($p=0.002$) and younger age ($p=0.03$). In multivariate analysis only recovery of the neutropenia ($p<0.001$) was associated with good prognosis whereas the diagnosis of infection by *Fusarium* sp. ($p=0.006$) was strongly associated with a poor outcome. The death rate was 43%. There was no statistically significant difference in the death rate between patients who did receive (52%) or did not receive (50%) antifungal treatment. Identifying patients at risk, specific syndromes and prognostic factors may help to reduce the high mortality associated with disseminated fungal infections in neutropenic patients.

KEYWORDS: Aspergillosis; *Fusarium* sp. infections; Candidiasis; *Trichosporon* sp. infections; Opportunistic fungal infections.

INTRODUCTION

Systemic fungal infections have been increasingly recognized as an important cause of morbidity and mortality in neutropenic cancer patients.[4] Previous studies have shown that the most important risk factors for fungal infections are the duration of neutropenia and the use of corticosteroids[1,11]. In addition, different fungi may lead to diverse clinical syndromes and prognosis.

There are a number of difficulties in the diagnosis and treatment of fungal infections. The clinical manifestations of fungal infections are often non-specific and the number of available antifungal agents is limited. Attempts to identify patients at risk, recognize specific syndromes and to treat as early as possible are major goals in the management of fungal infections in neutropenic patients.

In this paper we report a eight-year prospective study designed to further characterize incidence, epidemiology, specific syndromes, treatment and progno-

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sis associated with fungal infections in neutropenic patients.

PATIENTS AND METHODS

Since 1987 we have studied prospectively all neutropenic patients at the Hematology Services of two University Hospitals in Rio de Janeiro, Brazil (Federal University of Rio de Janeiro and State University of Rio de Janeiro). The clinical course of all episodes of neutropenia was recorded in a data base file. We then reviewed the records of all neutropenic patients who developed a fungal infection between July 1987 and December 1994.

Fever was defined as two or more axillary temperature readings above 38ºC in a 24 hour period, or as a single reading of 38.5ºC or higher. Patients were considered neutropenic if they had fewer than 500 neutrophils per mm^3, or if the granulocyte count was greater than 500 per mm^3 but falling progressively and expected to be less than 500 per mm^3 within 24-48 hours.

Criteria for the diagnosis of disseminated fungal infections were: (1) histopathological demonstration of fungal tissue invasion; (2) fungal growth from blood or biopsied tissue cultures; (3) on a clinical basis, in patients with persistent fever and neutropenia, the presence of cough, chest pain, and radiological evidence of pulmonary aspergillosis, defined as a cavitary lesion showing the air crescent sign.[12] Catheter-related fungemia was defined as the isolation of fungi from blood cultures taken from a central venous catheter or as the growth of fungal colonies from a catheter-tip culture, in the absence of positive blood cultures taken from peripheral veins.

Blood cultures were performed using bottles containing brain heart infusion agar, examined daily for at least 4 weeks, and subcultured blindly after 6 to 24 hour of incubation at 37ºC, or whenever examination of the bottles suggested growth of microorganisms. Specimens for mycological evaluation were plated onto Sabouraud's dextrose agar and brain heart infusion agar. Biopsy specimens were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with hematoxillin and eosin, Giemsa stain, periodic acid-Schiff stain, and methenamine silver.

Clinical evaluation and management of fever were accomplished according to routine of the hematology services of both hospitals and were detailed elsewhere[20].

RESULTS

Patient Population. During the study period 30 fungal infections were diagnosed in 30 patients among 313 episodes of fever and neutropenia (10%). There were 14 males and 16 females. The age of the patients ranged from 2 to 64 years (mean, 21 years). The underlying diseases were as follows: acute myeloid leukemia in 15 (5 relapses), acute lymphoblastic leukemia in 13 (10 relapses), and aplastic anemia and Hodgkin's disease (autologous bone marrow transplantation) in one patient each. The incidence of fungal infections has been steady: 8 fungal infections in 71 episodes of fever and neutropenia (11%) in the period from 1987 to 1990 and 22 fungal infections in 242 episodes of fever and neutropenia (9%) in the period from 1991 to 1994. Figure 1 shows the yearly incidence of infections by yeasts and molds.

Fungal infections. There were 15 cases of candidiasis, 5 cases of acute necrotizing pulmonary aspergillosis (one infection by *Aspergillus fumigatus*, with mycological and histopathological documentation and 4 cases with clinical documentation), 3 sinusitis by *Aspergillus fumigatus*, 5 infections by *Fusarium* sp., one infection by *Trichosporon* sp. and one infection due to *Rhodotorula rubra*. Blood cultures were positive in 18 cases (60%): 13/15 (87%) cases of candidiasis, 3/5 (60%) cases of infection by *Fusarium* sp. and in the single cases of infection by *Trichosporon* sp. and *Rhodotorula rubra*.

Clinical characteristics

Candida infections. Table 1 shows the characteristics and clinical manifestations of the patients with *Candida* infection. We divided the cases in three categories: catheter-related candidemias, disseminated candidiasis and candidemias with possible disseminated candidiasis. Five cases were classified as catheter-related candidemias. All patients had fever with no other clinical manifestation of fungal infection. Only one patient received amphotericin B (530 mg), which had been started empirically because of persistent fever and neutropenia despite antibiotic therapy. All patients recovered from the neutropenia and fever disappeared after catheter removal.

Five patients had disseminated candidiasis. The clinical manifestations of two of these cases have been previously reported.[18] Cutaneous lesions were present in four cases. Biopsies of the nodules were performed in all patients, and demonstrated fungal invasion of blood vessels in the dermis in 3 cases. Cultures of the skin were positive for *Candida* sp. in all cases. Five patients with candidiasis had candidemia and died with clinical complaints that could be attributed to disseminated candidiasis: persistent fever in all patients, pulmonary infiltrates in 3, and jaundice and hepatomegaly in 3 (no ra-

diological findings consistent with chronic disseminated candidiasis). All patients died while neutropenic, and autopsy was not performed.

Infections by Fusarium sp.. Table 2 shows the characteristics and clinical manifestations of the 5 patients with infection by *Fusarium* sp. Three cases were reported previously.[19] Four patients had a clinical picture very characteristic of the disseminated infection : fever, violaceous skin nodules that rapidly presented central necrosis and myalgias. One patient had pulmonary infection by *Fusarium* sp.. The patient had fever, pleuritic chest pain, cough, and developed a pulmonary abscess. Culture of a bronchoalveolar lavage grew *Fusarium* sp.. The late course of the infection was complicated by diffuse lung infiltrates and respiratory failure. Lung biopsy was diagnostic of cytomegalovirus infection. No fungal elements were demonstrated.

Acute necrotizing pulmonary aspergillosis. Table 3 shows the characteristics and clinical manifestations of the five patients with pulmonary aspergillosis. All patients had fever, pleuritic chest pain and cough. During neutropenia the radiological picture consisted of pulmonary infiltrates predominantly in the subpleural area. Computerized tomography was performed during neutropenia in two patients and showed nodules and other infiltrates not demonstrated in the radiographs. The recovery from neutropenia was accompanied by the development of nodules with cavitation (the air crescent sign) in the thorax radiographs. One patient had dissemination to the central venous system.

Sinusitis. Table 4 shows the characteristics and clinical manifestations of the patients with sinusitis. All patients complained of fever, unilateral epistaxis, nasal discharge and headache. Two patients developed necrotic lesions in the hard palatus and the other had necrosis of the nostril. The diagnosis in all cases included radiological documentation and culture of material taken from surgical drainage (two cases) or by nasal swab (one).

Infection by *Trichosporon* sp. and *Rhodotorula rubra* infection. The patient with infection by *Trichosporon* sp. complained of fever, the appearance of two skin nodules, pulmonary infiltrates and respiratory failure. The diagnosis was based on the growth of *Trichosporon* sp. in a skin biopsy as well as in the blood. The patient with *Rhodotorula rubra* fungemia had fever as the only manifestation of infection.

Predisposing factors. The predisposing factors for fungal infection in multivariate analysis were the presence of a central venous catheter ($p<0.001$), the duration of profound ($<100/mm^3$) neutropenia ($p<0.001$), the use of corticosteroids ($p<0.001$), gram-positive bacteremia ($p=0.002$) and younger age ($p=0.03$). Candidiasis was most frequently associated with the presence of a central venous catheter compared with other fungal infections (80% vs. 40%, $p=0.02$).

Prognostic factors. Table 5 shows the prognostic factors for death in univariate analysis. The factors that positively influenced prognosis were recovery from neutropenia (100% death in patients who did not recover from the neutropenia and 7% death in the patients who recovered, $p<0.001$), longer duration of antifungal treatment and the diagnosis of pulmonary aspergillosis or sinusitis. On the other hand, severe neutropenia (less than 100 neutrophils/mm^3) and a diagnosis of infection by *Fusarium* sp. were associated with a higher death rate. There was no statistically significant difference in the death rate between patients who did receive (52 %) or did not receive (50 %) antifungal treatment. Likewise, neither the mean dosage of amphotericin B or the interval between the first manifestation of fungal infection and the start of antifungal treatment influenced the prognosis. In multivariate analysis only recovery of the neutropenia ($p<0.001$) was associated with good prognosis whereas the diagnosis of infection by *Fusarium* sp. ($p=0.006$) was strongly associated with a poor outcome.

Therapy. Table 6 shows the therapy and outcome of the patients with fungal infections. Four patients did not receive antifungal therapy: one patient with disseminated candidiasis who died the day amphotericin B would be started and three patients with catheter-related candidemia. The patients with catheter-related candidemia did not receive treatment because at the time the blood cultures became positive they had already recovered from neutropenia and were asymptomatic. The central venous catheter was then removed, and the outcome was good.

Amphotericin B was the drug of choice for all treated patients, and was administered at an initial dose of 1 mg/kg daily. Some patients received a higher dose (1.5 mg/kg daily) because of no response. The mean cumulative dosage of amphotericin B for the responding patients was 950 mg (range 60 - 2400).

Itraconazole was administered concurrently with amphotericin B in one patient with infection by *Fusarium* sp.. In six patients amphotericin B was administered until the number of neutrophils reached 500/mm^3, and then itraconazole was substituted. Five patients had a complete response: three with pulmonary aspergillosis and two with sinusitis. The mean dose of amphotericin B before itraconazole was started was 540 mg (range 60-1360). One patient with disseminated candidiasis received fluconazole after bone marrow re-

TABLE 1

Characteristics and clinical manifestations of 15 patients with candidiasis

Case, year of diagnosis	Age, sex	Underlying disease	Venous access	Clinical findings	Diagnosis
Catheter-related					
1, 1992	5/M	ALL	CVC totally implantable	fever	blood
2, 1992	5/M	ALL	CVC totally implantable	fever	blood
3, 1993	19/F	AML	CVC semi-implantable	fever	blood
4, 1993	7/M	ALL	CVC totally implantable	fever	blood
5, 1994	4/M	AML	CVC totally implantable	fever	blood
Disseminated					
1, 1989	11/F	AML	peripheral vein	fever, skin nodules, myalgias	blood, skin biopsy and culture
2, 1990	11/F	AML	peripheral vein	fever, skin nodules	skin biopsy and culture
3, 1991	33/M	ALL	peripheral vein	fever, skin nodules	skin biopsy and culture
4, 1993	40/M	AML	CVC totally implantable	fever, skin nodules, myalgias	blood,skin culture
5, 1994	22/F	HD.ABMT	CVC semi-implantable	fever, lung infiltrates, jaundice	blood, brain, lungs, kidneys
Possibly disseminated					
1, 1988	22/M	ALL	peripheral vein	fever, lung infiltrates	blood
2, 1994	18/M	ALL	peripheral vein	fever, lung infiltrates	blood
3, 1994	50/M	ALL	peripheral vein	fever, lung infiltrates, jaundice	blood
4, 1994	64/F	AML	CVC semi-implantable	fever, jaundice	blood
5, 1994	2/F	AML	peripheral vein	fever, jaundice	blood

ALL= acute lymphoblastic leukemia; AML= acute myeloid leukemia; CVC = central venous catheter; HD= Hodgkin's disease; ABMT= autologous bone marrow transplant

TABLE 2

Characteristics and clinical manifestations of 5 patients with infection by *Fusarium* sp.

Case, year of diagnosis	Age, sex	Underlying disease	Venous access	Clinical findings	Diagnosis
1, 1989	15/M	ALL	CVC totally implantable	fever, skin nodules, myalgias	blood, skin biopsy
2, 1989	15/F	Aplastic anemia	peripheral vein	fever, skin nodules, myalgias, sinusitis blindness	blood, skin biopsy and culture, culture of nasal discharge
3, 1991	25/F	AML	CVC semi-implantable	fever, skin nodules, lung infiltrates	skin biopsy
4, 1991	9/F	AML	peripheral vein	fever, skin nodules, myalgias	blood
5, 1992	24/F	ALL	peripheral vein	fever, lung abscess	culture of a bronchoalveolar lavage

ALL=acute lymphoblastic leukemia, AML = acute myeloid leukemia; CVC = central venous catheter

TABLE 3

Characteristics and clinical manifestations of 5 patients with pulmonary aspergillosis

Case, year of diagnosis	Age, sex	Underlying disease	Clinical findings	Diagnosis
1, 1988	18/F	AML	fever, thoracic pain, cough, hemoptysis, lung nodules, hemyparesis	Chest X-ray, cranial CT scan
2, 1989	25/M	AML	fever, thoracic pain, cough, hemoptysis, lung nodules	Chest X-ray, biopsy and culture of lung
3, 1991	36/M	ALL	fever, thoracic pain, dry cough, lung infiltrates	Chest X-ray
4, 1991	20/F	AML	fever, thoracic pain, dry cough, lung infiltrates	Chest X-ray
5, 1991	36/F	AML	fever, thoracic pain, cough, lung nodules	Chest X-ray and CT scan

ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CT = computerized tomography

TABLE 4

Characteristics and clinical manifestations of 3 patients with sinusitis

Case, year of diagnosis	Age, sex	Underlying disease	Clinical findings	Diagnosis
1, 1991	9/F	ALL	fever, epistaxis, nasal discharge, headache, necrosis of the nostril	Sinus X-ray, culture of surgical material
2, 1991	6/M	AML	fever, epistaxis, nasal discharge, headache, necrotic lesion in the hard palatus, edema of the nose	Sinus X-ray, culture of surgical material
3, 1994	35/F	AML	fever, epistaxis, nasal discharge, headache, necrotic lesion in the hard palatus, edema of the nose, periorbital cellulitis	Sinus X-ray, culture of nasal discharge

ALL=acute lymphoblastic leukemia; AML = acute myeloid leukemia

TABLE 5

Prognostic factors for death in patients with fungal infections (univariate analysis)

Characteristic	p value
No influence	
Shock	1.00
Candidiasis	0.85
Catheter-related fungemia	0.10
Antifungal treatment	0.65
Mean dosage of amphotericin B (mg)	0.46
Interval (days) between first manifestation of fungal infection and antifungal treatment, mean	0.15
Factors associated with good prognosis	
Pulmonary aspergillosis, sinusitis	0.007
Higher duration (days) of antifungal treatment	0.01
Recovery from neutropenia	0.000002
Factors associated with death	
Infection by *Fusarium* sp.	0.04
Severe neutropenia (days with neutrophils < 100/mm^3)	0.02

covery. The overall death rate was 53%, and the case-fatality rate was 43%.

DISCUSSION

This eight-year prospective study confirms the observations from other centers that fungi represent an important etiology of infections in neutropenic patients. The 10% cumulative incidence in our series is relatively low in comparison with the incidence rates published in the literature.[9] Accurate figures of the true frequency of fungal infections are difficult to obtain, and the best estimates come from autopsy surveys. BODEY et al.[8] re-

TABLE 6

Therapy and outcome of the fungal infections

Case	Therapy	BM recovery	Outcome
Candidiasis, catheter-related			
1	catheter removal	Yes	cure
2	catheter removal	Yes	cure
3	catheter removal + AMB 530 mg	Yes	cure
4	catheter removal	Yes	cure
Candidiasis, disseminated			
1	AMB 1150 mg	Yes	cure
2	AMB 260 mg—> fluconazole (60 days)	Yes	improved
3	AMB 400 mg —> itraconazole (30 days)	No	death
4	AMB 1400 mg	No	death
5	AMB 300 mg	No	death
Candidiasis, possibly disseminated			
1	AMB 150 mg	No	death
2	AMB 80 mg	No	death
3	AMB 335 mg	No	death
4	No treatment	No	death
5	AMB 75 mg	No	death
Infection by Fusarium sp.			
1	AMB 180 mg	No	death
2	AMB 320 mg	No	death
3	AMB 280 mg	No	death
4	AMB 180 mg	No	death
5	AMB 900 mg + itraconazole (15 days)	Yes	death
Pulmonary Aspergillosis			
1	AMB 2400 mg	Yes	cure
2	AMB 2320 mg	Yes	cure
3	AMB 325 mg—>itraconazole (52 days)	Yes	cure
4	AMB 650 mg—>itraconazole (69 days)	Yes	cure
5	AMB 60 mg—>itraconazole (68 days)	Yes	cure
Sinusitis			
1	AMB 450 mg—>itraconazole (80 days)	Yes	cure
2	AMB 300 mg	No	death
3	AMB 1360 mg—>itraconazole (35 days)	Yes	improved
Rhodotorula rubra	AMB 400 mg	No	death
Trichosporon sp.	AMB 250 mg	No	death

AMB = amphotericin B

ported a 25 % frequency of disseminated fungal infections in leukemic patients and 12% in lymphoma patients in an autopsy survey was performed in 12 hospitals from Europe, Canada and Japan. In our series, autopsy was performed in only one patient who died with fungal infection. Although it demonstrated candidiasis in the brain, lungs and kidney, the diagnosis had been previously established by a positive blood culture. However, considering that the autopsy rate in our hospitals is lower than 10%, we can speculate that more cases could have been diagnosed if more autopsies had been performed.

As shown in Figure 1, except from a higher incidence of infection by molds in 1991, the frequency of fungal infections seems to be stable. There are many reports of outbreaks of aspergillosis in neutropenic patients, related to construction sites in or around the hospital.[25] Among the 6 infections by molds in 1991, 3 were acute necrotizing pulmonary aspergillosis and 2 were sinusitis by *Aspergillus fumigatus*. In both hospitals in this study building repairs occur almost constantly. Therefore we could not attribute this outbreak to a specific environmental factor.

There are many difficulties in the diagnosis of disseminated fungal infections in neutropenic patients.[16] There are few characteristic clinical findings that can help in the diagnosis, and the blood culture is positive in less than fifty-percent of the cases. In sixty-percent of our cases the blood culture was positive. Both hospitals have a mycology laboratory, with experience in processing fungal blood cultures. We did not use lysis centrifugation, which is reported to increase the yield of fungal blood cultures.[3]

We identified three clinical patterns that have a high correlation with the diagnosis of disseminated fungal infection: fever plus skin nodules, fever plus thoracic pain and cough, and fever plus nasal complaints. Skin nodules were present in 8 cases (27%): 3 disseminated candidiasis, 4 infections by *Fusarium* sp. and 1 by *Trichosporon* sp.. When present, skin nodules may be the only clue to the diagnosis.[18] Patients with skin nodules frequently complain of myalgias. The nodules in the infection by *Fusarium* sp. differ from those of candidiasis. They are usually larger and develop a central necrosis very early. This is because filamentous fungi invade the blood vessels of the profound dermis to produce a necrotizing vasculitis. Therefore, the skin biopsy must be as deep as possible.[18]

The second clinical pattern identified was fever plus thoracic pain and cough. This picture was present in 6 patients (20%) : all cases of pulmonary aspergillosis and one pulmonary infection by *Fusarium* sp.. While neutropenic, the patients developed fever, thoracic pain, and dry cough. The chest radiographs were normal. When the granulocytes begun to rise, the cough became more intense, and some patients developed hemoptisis. At that time, the chest radiographs disclosed subpleural densities, some of them triangular. Subsequently nodules appeared, with cavitation, with the "air crescent sign".[10] This sequence is very typical of pulmonary infection by molds. As in the skin, the fungus invades the pulmonary blood vessels and produces a pulmonary infarction (chest pain, subpleural densities), followed by the formation of nodules with cavitation. The computerized chest scan may disclose the lesions earlier than the radiography.[15]

The third clinical pattern was fever plus nasal complaints, such as epistaxis, nasal discharge, necro-

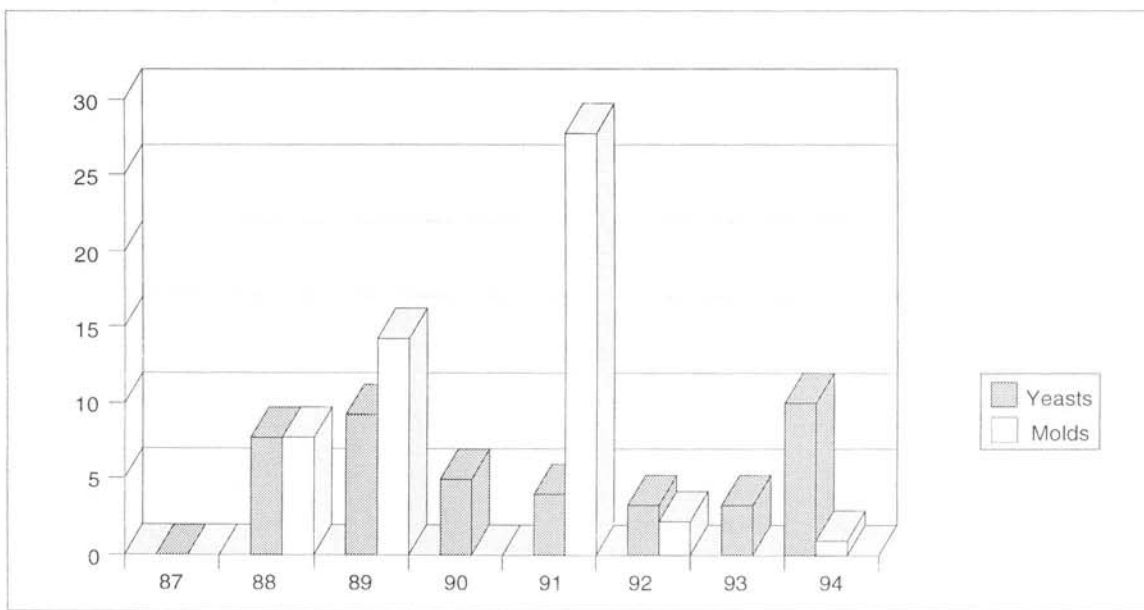

Fig. 1: Yearly incidence of infections by yeasts and molds

sis of the nostril or the hard palatus, and cellulitis. These findings are compatible with the diagnosis of fungal sinusitis.[23] The most frequent etiologic agents are *Aspergillus* sp. and Mucor.

We did not see any case of chronic disseminated candidiasis (formerly hepatosplenic candidiasis).[24] Three patients presented with fever, jaundice and rising alkaline phosphatase. Repeated abdominal ultrasonographies (2 patients) or computerized tomography (one patient) were normal. Liver biopsy was performed in one case, but was normal. In the diagnosis of chronic disseminated candidiasis the CT scan is better than ultrasonography.[2]

The risk factors for disseminated fungal infections in neutropenic patients have been assessed.[5] The most important are duration and intensity of neutropenia and the use of steroids. In a previous study, analyzing 79 episodes of fever and neutropenia, we identified duration of profound neutropenia, female sex, younger age and the antibiotic regimen as risk factors.[20] In the present study the risk factors identified were the use of central venous catheters, steroids, duration of profound neutropenia, younger age and gram-positive bacteremias. Bacteremia was a risk factor for candidemia in one study.[14]

Infection by *Fusarium* sp. was a risk factor for death in this study. Indeed, this infection is fatal in the majority of the cases.[17] This study also showed that antifungal treatment had no impact on the prognosis if bone marrow recovery did not occur. Likewise, the delay in beginning treatment was not a prognostic factor. The strongest prognostic factor was recovery from neutropenia (100% death for the patients who did not recover). In this setting, the use of colony-stimulating factors might be imperative. Colony-stimulating factors, in addition to accelerate bone marrow recovery, enhance the killing capacity of the immune system, and may be used as adjuvant therapy against fungal infections.[7,13]

Amphotericin B was the drug of choice for the treatment of fungal infections. The overall response rate to amphotericin B was 39%. Catheter-related fungemia was managed with catheter removal alone in 3 patients and catheter removal plus amphotericin B in one. The management of catheter-related fungemia is a matter of controversy. There are no data to recommend immediate removal of the catheter. However, the majority of the authors agree that the patient must receive antifungal treatment.[22]

Another matter of discussion is the role of the newer azole antifungal agents in the treatment of disseminated infections in neutropenic patients.[6] In this setting, we have used amphotericin B during neutropenia followed by itraconazole after bone marrow recovery with success.[21]

The 43% case-fatality rate confirms the negative impact of disseminated fungal infections in neutropenic patients. In our experience fungal infections represent the main infectious cause of death, much higher than gram-negative bacteremia, which was our main problem ten years ago.[20] In this series the case-fatality rate for gram-negative bacteremias was 34% (13 deaths in 41 cases, data not shown).

In summary, disseminated fungal infections are increasingly frequent in neutropenic patients, with a high case-fatality rate. In our patients we have seen infections by *Candida* sp. and *Aspergillus* sp., as well as by the emerging fungal pathogens. Although the diagnosis is difficult, some clinical clues are very helpful. The same is true for a good mycology laboratory, with experience in processing blood cultures. Bone marrow recovery was the most important prognostic factor.

RESUMO

Infecções fúngicas em pacientes neutropênicos. Estudo prospectivo de 8 anos.

Com o objetivo de melhor caracterizar incidência, epidemiologia, síndromes específicas, tratamento e prognóstico associado com infecções fúngicas sistêmicas em pacientes neutropênicos foi feito um estudo prospectivo de 8 anos. Durante este período foram diagnosticadas 30 infecções fúngicas em 30 pacientes neutropênicos febris (10%). Houve 15 casos de candidíase, 5 aspergiloses pulmonares, 3 sinusites por *Aspergillus fumigatus*, 5 infecções por *Fusarium* sp., uma infecção por *Trichosporon* sp., e uma infecção por *Rhodotorula rubra*. As hemoculturas foram positivas em 18 casos (60%). Os fatores de risco para infecção fúngica em análise multivariada foram: presença de cateter venoso central ($p<0,001$), duração maior de neutropenia $<100/mm^3$ ($p<0,001$), uso de corticosteróides ($p<0,001$), bacteremia por germes gram-positivos ($p=0,002$) e idade menor ($p=0,03$). Em análise multivariada apenas recuperação da neutropenia ($p<0,001$) esteve associada com bom prognóstico, enquanto que o diagnóstico de infecção por *Fusarium* sp. ($p=0,006$) se correlacionou com um mau prognóstico. A taxa de óbito foi de 43%. Não houve diferença estatisticamente significante nas taxas de óbito em pacientes que receberam (52%) ou não (50%) terapia anti-fúngica. A identificação de grupos de risco, síndromes específicas e

fatores prognósticos pode contribuir para a redução na elevada letalidade das infecções fúngicas em pacientes neutropênicos.

REFERENCES

1. ANAISSIE, E.J. - Opportunistic mycosis in the immunocompromised host: experience at a cancer center and review. **Clin. infect. Dis., 14** (suppl. 1):S43-S53, 1992.

2. ANTTILA, V.; RUUTU, P.; BONDESTAM, S. et al.-Hepatosplenic yeast infection in patients with acute leukemia: a diagnostic problem. **Clin. infect. Dis., 18**:979-981, 1994.

3. BILLE, J.; STOCKMAN, L.; ROBERTS, G.D.; HORSTMEIER, C.D. & ILSTRUP, D.M. - Evaluation of a lysis-centrifugation system for recovery of yeasts and filamentous fungi from blood. **J. clin. Microbiol., 18**:469-471, 1983.

4. BODEY, G.P. - Fungal infection and fever of unknown origin in neutropenic patients. **Amer. J. Med., 80** (suppl. 5C):112-119, 1986.

5. BODEY, G.P. - Fungal infections in cancer patients. **Ann. N. Y. Acad. Sci., 544**: 431-442, 1988.

6. BODEY, G.P. - Azole antifungal agents. **Clin. infect. Dis., 14**(suppl.1):S161-S169, 1992.

7. BODEY, G.P.; ANAISSIE, E.; GUTTERMAN, J. & VADHAN-RAJ, S. - Role of granulocyte-macrophage colony-stimulating factor as adjuvant therapy for fungal infection in patients with cancer. **Clin. infect. Dis., 17**:705-707, 1993.

8. BODEY, G.P.; BUELTMANN, B.; DUGUID, W. et al. - Fungal infections in cancer patients: an international autopsy survey. **Europ. J. clin. Microbiol. infect. Dis., 11**:99-109, 1992.

9. DEGREGORIO, M.W.; LEE, W.M.F.; LINKER, C.A.; JACOBS, R.A. & RIES, C.A. - Fungal infections in patients with acute leukemia. **Amer. J. Med., 73**:543-548, 1982.

10. GEFTER, W.B.; ALBELDA, S.M.; TALBOT, G.H. et al. - Invasive pulmonary aspergillosis and acute leukemia. Limitations in the diagnostic utility of the air crescent sign. **Radiology, 157**:605-610, 1985.

11. GERSON, S.L.; TALBOT, G.H.; HURWITZ, S. et al. - Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. **Ann. intern. Med., 100**:345-351,1984.

12. GERSON S.L.; TALBOT,G.H.; LUSK, E. et al. - Invasive pulmonary aspergillosis in adult acute leukemia; clinical clues to its diagnosis. **J. clin. Oncol., 3**:1109-1116, 1985.

13. GROOPMAN, J.E.; MOLINA,J.M. & SCADDEN, D.T. - Hematopoietic growth factors. **New Engl. J. Med.,321**:1449-1459,1989.

14. GUIOT, H.F.L.; FIBBE, W.E. & van't WOUT, J.W. - Risk factors for fungal infection in patients with malignant hematologic disorders: implications for empirical therapy and prophylaxis. **Clin. infect. Dis., 18**: 525-532, 1994.

15. KUHLMAN, J.E.; FISHMAN, E.K.; BURCH, P.A. et al. - Invasive pulmonary aspergillosis in acute leukemia. The contribution of CT to early diagnosis and aggressive management. **Chest, 92**:95-99, 1987.

16. MAARTENS, G. & WOOD, M.J. - The clinical presentation and diagnosis of invasive fungal infections. **J. Antimicrob. Chemother., 28**(suppl.A):13-22,1991.

17. MARTINO, P.; GASTALDI, R.; RACCAH, R. & GIRMENIA, C.- Clinical patterns of *Fusarium* infections in immunocompromised patients. **J. Infect., 28** (suppl.1):7-15,1994.

18. NUCCI, M.; PULCHERI, W.; SPECTOR, N. et al. - Cutaneous involvement of systemic fungal infections in neutropenic patients. **Haematologica, 77**:522-523,1992.

19. NUCCI,M.; SPECTOR,N.; LUCENA, S.et al. - Three cases of *Fusarium* species in neutropenic patients. **Europ. J. clin. Microbiol. infect. Dis., 11**:1160-1162,1992.

20. NUCCI, M.; SCHECHTER, M.; SPECTOR, N. et. al. - Antibiotic regimen as an independent risk factor for disseminated fungal infections in neutropenic patients in Brazil. **Trans. roy. Soc. trop. Med. Hyg, 89**:107-110,1995.

21. NUCCI, M.; PULCHERI, W.; BACHA, P.C. et al. - Amphotericin B followed by itraconazole in the treatment of disseminated fungal infections in neutropenic patients. **Mycoses, 37**:433-437,1994.

22. RAAD, I.I. & BODEY, G.P. - Infectious complications of indwelling vascular catheters. **Clin. infect. Dis., 15**:197-210,1992.

23. TALBOT, G.H.; HUANG, A. & PROVENCHER, M. - Invasive aspergillosis rhinosinusitis in patients with acute leukemia. **Rev. infect. Dis., 13**:219-232,1991.

24. THALER, M.; PASTAKIA, B.; SHAWKER, T.H.; O'LEARY, T. & PIZZO, P.A. - Hepatic candidiasis in cancer patients: the evolving picture of a syndrome. **Ann. intern. Med., 108**:88-100,1988.

25. WALSH, T.J. & DIXON, D.M. - Nosocomial aspergillosis: environmental microbiology, hospital epidemiology, diagnosis and treatment. **Europ. J. Epidem., 5**:131-142,1989.

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