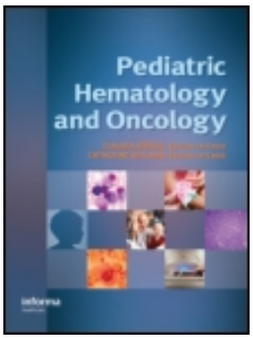

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INVASIVE RESPIRATORY ASPERGILLOSIS IS A TREATABLE DISEASE WITH EARLY DIAGNOSIS AND AGGRESSIVE THERAPY

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□ *This study aimed to document outcome of invasive respiratory aspergillosis (IRA) in pediatric malignancy patients. Patients with febrile neutropenia episodes followed between January 2003 and May 2007 were enrolled. Antifungal therapy was added to those who were still febrile on the 5th day of febrile neutropenia treatment. Patients were screened with computerized tomographies. IRA was identified in 22 of 98 patients. There were 13 males and the mean age was 97 months. Proven infection was established in 3, probable in 7, and possible in 12 patients. Liposomal amphotericin B was administered to all patients and was successful in 10 patients. Modifications with caspofungin or voriconazole were done in liposomal amphotericin B failures. The median duration of antifungal therapy was 5.5 months. The median follow-up time was 29 months. There was no evidence of IRA in 12 patients after completion of cancer chemotherapy. Six patients died due to underlying disease, whereas IRA was either in remission or stable disease. Four patients were lost due to IRA. The remission rate for IRA was 82%. Survival at 37 months was 55% (95% confidence interval 25–47 months). The amount of time that absolute neutrophil count after initiation of treatment*

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for IRA remained at zero was found to be an independent prognostic factor on survival ($P = .01$). These results suggest that early diagnosis and aggressive treatment may increase the successful outcome of IRA.

Keywords aspergillosis, malignancy, pediatric

Invasive respiratory aspergillosis (IRA) is an increasingly common fungal infection that primarily affects immunocompromised patients, particularly those with prolonged neutropenia receiving cancer chemotherapy. Despite improvements in early diagnosis and effective treatment, IRA remains a devastating opportunistic infection. Data from the Centers for Disease Control and Prevention reveal that the mortality associated with invasive aspergillosis has increased by 357% since 1980 [1]. The mortality of untreated IRA is nearly 100%; however, the survival among patients treated with amphotericin B is nearly 34% [1–3]. Definitive diagnosis is difficult and many patients are recognized to have IRA at relatively late stages of infection. In this study, we aimed to document the outcome of early IRA diagnosis and aggressive treatment on prognosis.

MATERIALS AND METHODS

Pediatric malignancy patients with febrile neutropenia (FNP) episodes followed between January 2003 and May 2007 were enrolled to the study retrospectively. Fever is defined as a single axillary temperature of $\geq$38.3°C or $\geq$38.0°C for more than 1 hour. Neutropenia is defined as an absolute neutrophil count (ANC) $<$500 cells/mm^3 or a count of $<$1000 cells/mm^3 with a predicted decrease to $<$500 cells/mm^3 [4]. After obtaining cultures from throat, urine, blood, and if present the catheter; cefepime and amikacin were initiated as empirical therapy. Conventional amphotericin B (AmB) was added to those who were still febrile on the 5th day of FNP treatment. However, liposomal amphotericin B (L-AmB) was replaced after 1 or 2 doses of AmB due to infusion-related reactions and nephrotoxicity in all patients. Patients were screened for fungal infections with computerized tomographies (CTs) of thorax, sinus, and other relevant sites. Lung biopsy, sinus aspiration, and flexible fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) were performed when infiltrations were detected in thorax CT in clinically stable patients. All tissue samples underwent histological examination, microbiological isolation, and culture studies. Serum galactomannan (GM) test was performed twice weekly by using the GM enzyme immunoassay (Platelia Aspergillus; Bio-Rad Laboratories) when available. Results were interpreted as positive when an optical density index of $>$0.5 was reached at 2 consecutive measurements [5]. Sequential CT scans were obtained for each IRA case in 2- to 3-week intervals.

IRA patients were classified as proven, probable, or possible according to the European Organisation for Research and Treatment of Cancer and

the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases (EORTC/MSG) consensus report [6]. Briefly, proven IRA case was demonstration of infection by either culture or histological examination of tissue biopsy. Probable IRA was considered when each of the criteria among host factors, clinical features, and mycological evidence were present. Possible IRA was contemplated in a patient who has at least 1 criterion among host factors category and 1 microbiological or 1 major clinical criterion (Table 1). According to response to L-AmB therapy, modification with caspofungin or voriconazole was done for each IRA case. Voriconazole or itraconazole was administered as the maintenance therapy in patients with clinical and radiological resolution and in patients with less intensive chemotherapy. We administered monotherapy or dual therapy until partial responses that last for at least 1 month were achieved. Maintenance therapies continued until all lesions disappeared even after cessation of chemotherapy. The treatment efficacy was evaluated according to report published by Denning [7]. Complete response (CR) was accepted as resolution of all clinical signs and symptoms attributable to mycosis with complete or very nearly complete radiographic resolution. Partial response (PR) was defined as major improvement or resolution of the attributable clinical signs and symptoms with at least a 50% improvement in radiological signs. Stable disease (SD) was consistent with some improvement but less than 50% radiologic improvement. Failure (F) was progression of the disease or death as a result of mycosis. Survival was defined as the follow-up time for each patient from the initial diagnosis of IRA to death due to either failure of IRA treatment or their primary disease.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows 17.0 program. Numerical parameters were described with mean and median values, whereas distributions of the categorical measurements were investigated by frequency and percentages. Estimates of survival were calculated with Kaplan-Meier method. Univariate analysis was performed with Kaplan-Meier, log rank (Mantel-Cox) method for each probable prognostic factor (age, gender, the amount of time that ANC remained at zero till the initial diagnosis of IRA, the amount of time that ANC remained at zero after initiation of treatment for IRA, antifungal treatment modality) effective for survival. The amount of time that ANC remained at zero till the initial diagnosis of IRA and the amount of time that ANC remained at zero after initiation of treatment for IRA were categorized according to their mean values. Then multivariate analysis was performed with limited Cox regression for all of the probable prognostic factors included in univariate analysis.

RESULTS

A total of 226 FNP episodes occured in 98 pediatric malignancy patients between January 2003 and May 2007. IRA was identified in 22 of 226 (9.7%) FNP episodes. There were 13 (59%) males and the mean age was 97 ± 65

TABLE 1 Properties and Outcome of the Patients

Patient	Primarydisease	Clinical involved Site	Evidence	Classification	Therapy	Maintenance therapy	Outcome
1	Biphenotypic leukemia	Lung, sinus, liver	*Aspergillus* hyphae from lung biopsy through fine-needle aspiration, cavitation and pleural effusion in chest x-ray	Proven	L-AmB → L-Amb + C	I	PR/E
2	AML M7	Sinus	*Aspergillus* isolation from hard palate biopsy culture, mucosal thickening in sinus CT	Proven	L-AmB		F
3	LL	Lung	*Aspergillus* hyphae from lung biopsy, halo sign with ground-glass appearance, multiple nodule formation, and air crescent in thorax CT	Proven	L-AmB → C + V	V	CR
4	ALL	Lung	Fungal plaques in bronchoscopy, *Aspergillus* isolation from BAL culture, air crescent in thorax CT	Probable	L-AmB		F
5	MDS	Lung	*Aspergillus* isolation from BAL culture, multiple nodules, halo sign with ground-glass appearance, and pleural effusion in thorax CT	Probable	L-AmB		PR/E
6	PNET	Lung	*Aspegillus* isolation from hemoculture and port catheter culture, multiple nodules in thorax CT	Probable	L-AmB →V → V + C	V	CR/E
7	LL	Lung, sinus	*Aspergillus* isolation from sputum culture, multiple nodules and air crescent in thorax CT	Probable	L-AmB → L-AmB + C	V	CR
8	HLH	Lung, cranium	*Aspergillus* isolation from endotracheal aspirate culture, cavity formation in thorax CT	Probable	L-AmB → L-AmB + V		SD/E
9	ALL	Lung	Halo sign with ground-glass appearance, multiple nodules, and cavitary lesion in thorax CT, two positive GM from blood sample	Probable	L-AmB → L-AmB + C	I	CR
10	Neuroblastoma	Lung	Halo sign with ground-glass appearance and multiple nodules in thorax CT, two positive GM from blood sample	Probable	L-AmB → V → C + V	V	CR/E
11	AML M2	Lung	Halo sign with ground-glass appearance, multiple nodules, and cavitary lesion in thorax CT	Possible	L-AmB → L-AmB + C	V	CR
12	NF-1 AML M2	Lung	Halo sign with ground-glass appearance and multiple nodules in thorax CT	Possible	L-AmB → V	V	CR

(Continued on next page)

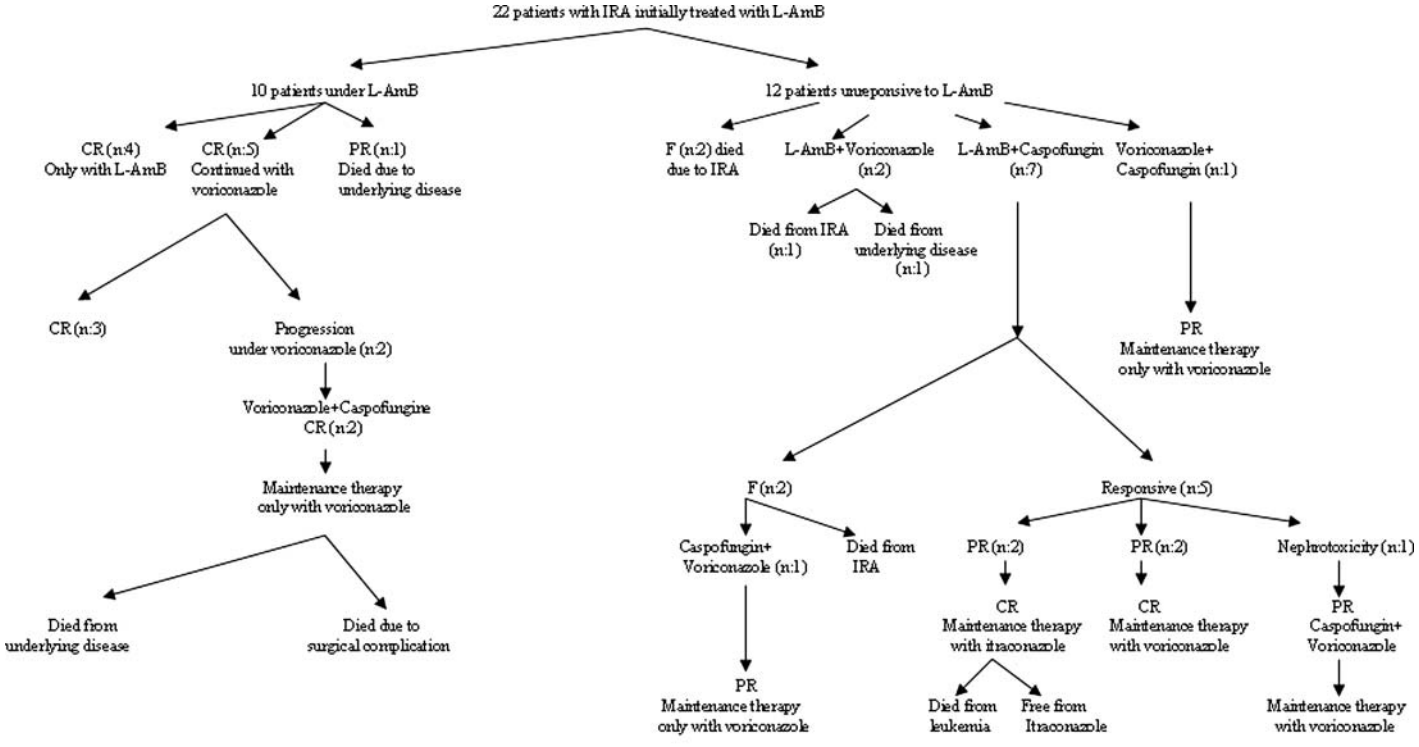
TABLE 1 Properties and Outcome of the Patients *(Continued)*

Patient	Primarydisease	Clinical involved Site	Evidence	Classification	Therapy	Maintenance therapy	Outcome
13	AML M2	Lung,sinus	Halo sign with ground-glass appearance and multiple nodules formation in thorax CT	Possible	L-AmB → L-AmB + C → C + V	V	CR
14	ALL	Lung, cranium	Halo sign with ground-glass appearance and multiple nodules formation in thorax CT, multiple parenchymal lesions in contrast enhanced MRI	Possible	L-AmB → V	V	CR
15	ALL	Lung	Multiple nodules in thorax CT	Possible	L-AmB → V	V	CR
16	DS-AML M2	Lung, liver, spleen	Halo sign with ground-glass appearance in thorax CT, multiple microabscess formation in liver and spleen in abdominal CT	Possible	L-AmB → L-AmB + C → C + V	V	CR
17	ALL	Lung	Halo sign with ground-glass appearance and multiple nodules formation in thorax CT	Possible	L-AmB		CR
18	ALL	Lung	Air crescent and cavitary lesion in thorax CT	Possible	L-AmB		CR
19	RMS	Lung	Multiple nodules in thorax CT	Possible	L-AmB		CR
20	Medulloblastoma	Lung	Bilateral patchy consolidation and multiple nodules in thorax CT	Possible	L-AmB		CR/E
21	AML M4	Lung	Multiple air crescent and cavitation in thorax CT	Possible	L-AmB → L-AmB + C		F
22	AML M5	Lung	Peribronchial membraneous formation in CT	Possible	L-AmB → L-AmB + V		F

Note. L-AmB: liposomal amphotericin B; C: caspofungin; I: itraconazole; PR: partial response; E: exitus from primary disease; AML: acute myeloid leukemia; CT: computerized tomography; F: failure; LL: lymphoblastic lymphoma; V: voriconazole; CR: complete response; ALL: acute lymphoblastic leukemia; BAL: bronchoalveolar lavage; MDS: myelodysplastic syndrome; PNET: primitive neuroectodermal tumor; HLH: hemophagocytic lymphohistiocytosis; SD: stable disease; GM: galactomannan; NF: neurofibromatosis; MRI: magnetic resonance imaging; DS: Down syndrome; RMS: rhabdomyosarcoma.

months (range 7–204 months). There were 18 hematological malignancies. The mean amount of time that ANC remained at zero was 14 ± 8.8 days (range 5–30 days). Symptoms associated with IRA included fever in all patients, cough in 18 (82%) patients, facial swelling in 2 (9%), and hemoptysis in 1 (5%) patient. All patients had CT scanning performed on the 5th day of FNP treatment, except one who was entubated and had to be followed with chest x-rays. Eighteen (82%) patients had typical major findings on initial and sequential CT scannings as described by EORTC (Table 1). We were able to obtain lung biopsies in 4 patients, 2 with fine-needle biopsies, and 2 with open lung surgery. Sinus aspiration was performed in only 1 of 3 patients who had both sinusitis and pulmonary involvement in CT and another patient was biopsied from his hard palate. FOB and BAL were performed in 18 (82%) patients, of whom only 2 (9%) revealed positive cultures for *Aspergillus*. One of these patients had plaques on tracheobronchial mucosa seen during bronchoscopy. GM test could be performed only in 7 patients and it was positive in 2 patients. Proven infection was established in 3 children by histopathological evidence from lung biopsy ($n = 2$) and biopsy of hard palate ($n = 1$). Probable infection was defined in seven patients with positive cultures from bronchoalveolar lavage ($n = 2$), sputum ($n = 1$), endotracheal aspirate ($n = 1$), blood and catheter concurrently ($n = 1$), and serology ($n = 2$). Possible infection was identified in 12 patients (Table 1). Extrapulmonary aspergillosis concurrently with the evidence of pulmonary disease was present in 6 (27%) patients. One patient had maxillary sinusitis with erosion of the sinus wall and hard palate as the only manifestation of disease (Table 1). Although L-AmB was successful in 10 of 22 patients, the rest of them required combination therapies due to clinical and radiological deterioration (Figure 1). The most common side effect of L-AmB was severe electrolyte imbalance observed in all patients, which was reversible when the drug was stopped. Transient visual hallucinations possibly related to voriconazole therapy occured in 1 patient. The median duration of antifungal therapy was 5.5 months (interquartile range 1–14 months). The median follow-up time was 29 months (interquartile range 3–43 months). Six (27%) patients died due to underlying disease while IRA was either in remission or stable disease. Four patients (18%) were lost due to IRA. The remission rate was 82%. Survival for IRA at 37 months was 55% (95% confidence ınterval 25–49 months) (Figure 2). None of the nonhematological malignancy patients were lost due to IRA. They have all scummbed to their primary diseases. When the patients lost due to their primary diseases were excluded from the analysis ($n = 16$), survival at 38 months was found to be 75%.

Univariate analysis of probable prognostic factors effective on survival is shown in Table 2. The amount of time that ANC remained at zero after initiation of treatment for IRA was found to be poor prognostic factor on survival both in univariate ($P = .01$) and multivariate analysis ($P = .01$) (Figure 3).



CR: Complete Response, PR: Partial Response, F: Failure L-Amb: Liposomal Amphotericin B, IRA: Invasive respiratory aspergillosis

FIGURE 1 Outcome 22 IRA patients.

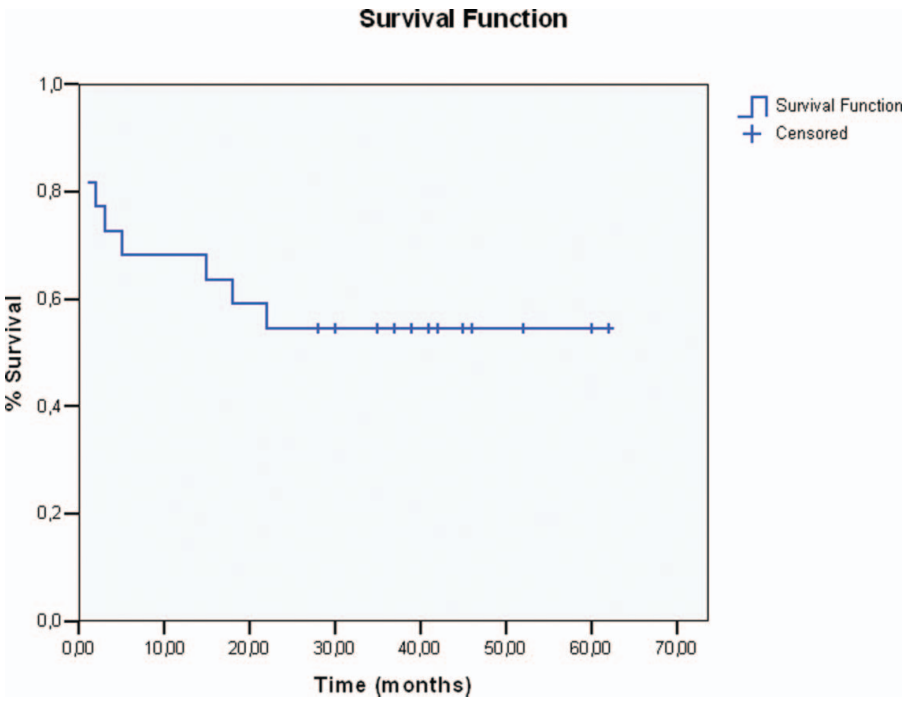


FIGURE 2 Kaplan-Meier estimate of 37 months survival for invasive respiratory aspergillosis.

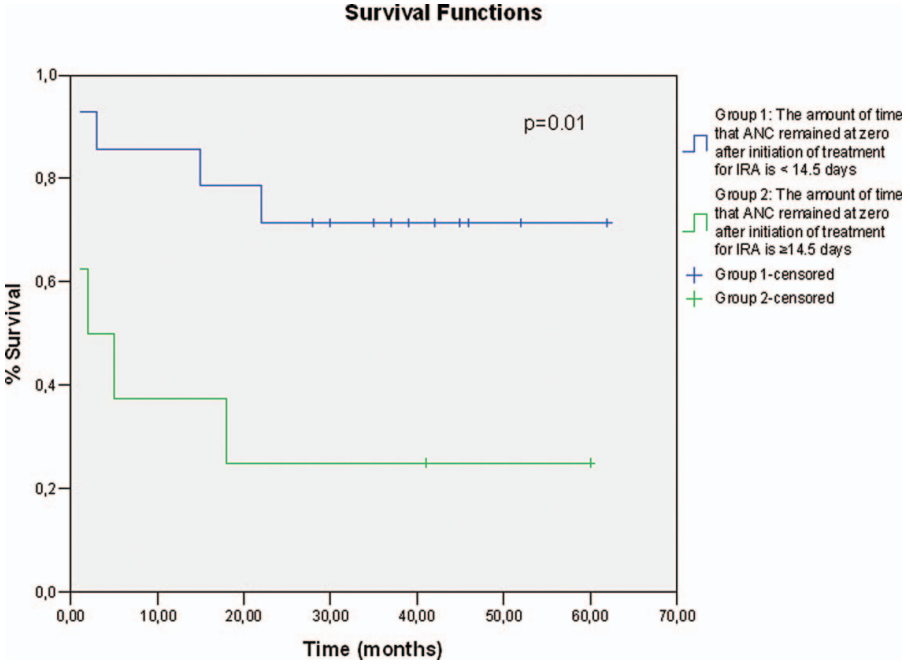


FIGURE 3 The amount of time that absolute neutrophil count remained at zero after initiation of treatment for invasive respiratory aspergillosis was found to be poor prognostic factor on survival.

TABLE 2 The Effect of Probable Prognostic Factors in Invasive Respiratory Aspergillosis Patients

Prognostic factors		*n*	5-Years survival (%)	*P**
Age	<97 months	11	46 ± 15	.39
	>97 months	11	64 ± 14	
Gender	Male	13	54 ± 14	.82
	Female	9	56 ± 17	
The amount of time that ANC remained at zero till the initial diagnosis of IRA	<14 days	14	57 ± 13	.95
	≥14 days	8	50 ± 18	
The amount of time that ANC remained at zero after initiation of treatment for IRA	<14.5 days	14	71 ± 12	**.01**
	≥14.5 days	8	25 ± 15	
Antifungal treatment modality	Single	10	60 ± 16	.76
	Combination	12	50 ± 14	

*Kaplan-Meier, log rank (Mantel-Cox) test.
ANC: absolute neutrophil count; IRA: invasive respiratory aspergillosis.

DISCUSSION

Although IRA is an increasing life-threatening problem in immunocompromised hosts, there are few specific data in the pediatric literature. Although IRA has been reported with an incidence ranging from 0% to more than 20% among immunosuppressed pediatric patients, the true incidence of IRA in children remains unknown [8–11]. One of the largest pediatric malignancy population revealing the incidence of fungal infections was from St. Jude's Children's Hospital, with 57 (0.06%) proven IRA patients in 9500 children treated during 34 years [8]. Eleven-year incidence of fungal infection was reported as 4.9% (74/1052) from another pediatric institution in United States [11]. Rosen et al pointed out the linear increase in the incidence of fungal infections from 2.9% to 7.8% between 1996 and 2001. A pediatric center from Germany identified an incidence of 6.8% of IRA, including 7 proven, 1 probable, and 5 possible in 189 acute leukemia and lymphoma pediatric patients [10]. In our series, there were 3 proven, 7 probable, and 12 possible IRA patients in 98 patients with 226 FNP episodes, an incidence of 9.7%. In the last 10 years, more intensive chemotherapy regimens predisposed patients to more fungal infections. Nevertheless, the fact that observed increase in fungal infections may be secondary to improved diagnostic methods should not be ignored. Screening patients with FNP episodes unresponsive to broad-spectrum antibiotics has become a routine in our center since 2003. EORTC/MSG also advises early screening with CT in order to identify IRA. Therefore early and sequential CT imaging is absolute for diagnosis and follow-up.

The gold standard for diagnosis is demonstration of *Aspergillus* hypae or isolation from culture obtained by tissue biopsy [6]. Because most of these patients are critically ill requiring some degree of respiratory support, biopsy was performed to 5 clinically stable patients. Biopsy findings were compatible with fungal infection for 3 patients and they were classified as proven IRA.

Pathology was nonconclusive for the other 2 patients. Unless tissue biopsy was obtained, the second step in diagnosis might be isolation of aspergillus through microbiological sampling from various body fluids or serology. In our series, according to these measures, 7 patients (31.8%) were classified as probable IRA. The radiological findings have an essential role both in the diagnosis and in follow-up of IRA [12–18]. However, radiological data from pediatric population are limited. Kuhlman et al described the value of halo sign as an indicator of pulmonary aspergillosis initially in adult population [12]. Caillot et al reported the systematic use of CT scanning reducing time of diagnosis from 7 days to 1.9 days [15]. Numerous authors acknowledged the value of halo sign and nodule formation in CT as a highly predictive early sign of IRA [14, 15, 17]. Nevertheless, IRA has a dynamic course related to inflammatory response of the patient depending on bone marrow recovery. Cavitation and air-crescent sign are delayed findings of IRA and appear on CT nearly 2 weeks after the initial diagnosis correlating with marrow recovery. In a 10-year review of 27 pediatric patients, there was cavity formation in 25% of children and no halo sign was observed on CT [16]. This reflected late stage of disease in which the patients were scanned and the author pointed out the limited use of CT scanning in the early years of 10-year cohort. In two other pediatric series, there were 22% cavitating lesions on chest radiography and 43% cavity formation on CT, respectively [13, 18]. These figures also coincided probably with the recovery phase of neutropenia, thereby a late finding of disease. In our series, 14 of 22 (66.6%) patients had typical halo sign and nodule formation in the 1st week, air-crescent sign was seen in 5 (23.8%) patients and cavity formation in 6 (28.5%) patients as the late manifestations of IRA. Because we obtained early CT in our clinic, we were able to detect more patients and much earlier compared to the literature. Therefore, as a consequence, the diagnosis of IRA depends upon clinical, microbiological, and radiological findings of the patients and remains a challenge.

Novel guidelines recommend voriconazole as the primary treatment and L-AmB as the alternative therapy for patients who are refractory or intolerant to voriconazole [19, 20]. However, until recently the first-line therapy had to be amphotericin B preparations. Liposomal formulations in comparison to conventional forms offer superior safety and lower toxicity [21–23]. Response rates in L-AmB monotherapy vary from 39% to 65% in large pediatric series [22, 23]. L-AmB is generally well tolerated in pediatric patients. In our series, response rate to L-AmB was 45.4% (10/22). We administered voriconazole both as maintenance monotherapy following L-AmB and as salvage therapy with other antifungals. There are few pediatric case reports about voriconazole maintenance therapy in the literature [24, 25]. Cesaro et al obtained fair response in 7/8 children with voriconazole as maintenance therapy [24]. In our study, voriconazole was the maintenance monotherapy in 5 patients and response rate was 60% (3/5). Refractory

IRA patients are still challenging and the efficacy of voriconazole as salvage therapy in combination with L-AmB is controversial. Previous data have suggested a negative effect when an azole was combined with L-AmB [26, 27], but more recent data have shown no negative impact with such combination [28]. Voriconazole was combined with L-AmB in 2 refractory patients, resulting in 1 stable disease and 1 failure in our study. Voriconazole might also be combined with caspofungin in refractory IRA patients. Data for this combination are limited to case reports [29–31]. Our series is one of the largest pediatric series reported to date for this combination. We utilized this combination in 5 patients and achieved successful responses in all of them. We also administered L-AmB with caspofungin as salvage therapy in our study. A few series about efficacy and safety of this combination in children with IRA were reported [24, 31, 32]. Cesaro et al obtained favorable response with this combination in 18 children with invasive aspergillosis [31]. In our series, the response rate was 42.8% (4/7). Successful responses were obtained with itraconazole as maintenance therapy in pediatric aspergillosis [9, 33]. It was also successful as the maintenance therapy in 2 of our patients.

The response rates of the pediatric case series with combination therapies vary between 40% and 80% [9, 24, 25, 30]. Comparisons of response rates between different therapy modalities are difficult and also inappropriate. We achieved a response rate of 82% in this study. The high response rate seen in our study may be explained by early diagnosis and appropriate modifications in treatment. Previous pediatric studies report survival ranging from 15% to 45% [8–10, 24, 29, 31]. However, duration of survival of IRA patients was variable in each study and not reported in all pediatric series, making comparisons between studies difficult. Also, survival was not mentioned in some series and different treatment schedules were applied in each study. Our survival for IRA at 37 months was 55% (95% confidence ınterval 25–49 months). The survival in our study is one of the highest rates in terms of follow-up time. The amount of time that ANC remained at zero after initiation of treatment for IRA was found to be an independent prognostic factor on survival. This finding is also expressed as a strong prognostic factor in the literature [17, 34]. Our study also established that IRA patients with nonhematological malignancies were lost due to their primary diseases rather than IRA. It is very well known that the chemotherapies used in nonhematological malignancies do not lead to as much immunosupression as the hematological malignancies. Thus this result adds up to our finding on of the effect low ANC on survival of IRA. Hence we believe that our high survival rate is due to early diagnosis and aggressive treatment.

In conclusion, the use of CT scan for early detection and follow-up is absolute for diagnosis of IRA. Any approach aimed at reducing the incidence of fatal IRA must first address the problem of diagnosis, and it is seen, from our own experience and that of many other centers, that the information obtained from CT imaging is the cornerstone of early diagnosis. We

established the effect of early diagnosis and aggressive treatment on prognosis of pediatric IRA patients. However, the roles of novel antifungal drugs need to be defined by large, well-designed clinical trials.

Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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