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A RETROSPECTIVE ANALYSIS OF 12 INVASIVE ASPERGILLOSIS PEDIATRIC CASES TREATED AT A SINGLE TERTIARY MEDICAL CENTER IN CROATIA (1997-2017)

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Background: Invasive aspergillosis is a major cause of morbidity and mortality in immunocompromised children. The aim of our study was to evaluate the in-hospital mortality over a period of 21 years (January 1st, 1997, to December 31st, 2017) and identify factors affecting the outcomes.

Methods: We retrospectively examined hospital records of all patients younger than 18 years of age with proven, probable or possible invasive aspergillosis defined by the European Organization for Research and Treatment of Cancer-Mycoses Study Group criteria.

Results: We identified 12 patients with invasive aspergillosis; 4 had proven, 6 probable and 2 had a possible disease. The majority of the children had a hematologic malignancy. All patients had invasive pulmonary aspergillosis. Aspergillus fumigatus was the species most frequently identified (75.0%). Galactomannan antigen was analyzed in 83.3% of our patients and found positive in 60.0%. The most frequent radiologic pulmonary finding was bilateral opacity and infiltrations (66.6%). After the diagnosis, all but one child were treated with voriconazole; however, 75.0% received concomitant antifungal agents. Outcome was poor; overall mortality was 83.3%.

Conclusion: Hematologic malignancy and chronic granulomatous disease are risk factors for development of invasive aspergillosis. In children, the disease most commonly involves the lungs. Frequently, children do not manifest specific radiologic signs which can significantly postpone diagnosis. Galactomannan assay and BALF culture may facilitate the diagnosis as shown in our case series. The high in-hospital mortality is affected by the diagnostic delay possibly leading to a disseminated infection with worse prognosis, side effects of chemotherapy and other comorbidities, as well as therapeutic delay in administrating voriconazole as the drug of choice.

Descriptors: ASPERGILLOSIS, CHILDREN, GALACTOMANNAN, VORICONAZOLE

BACKGROUND

Invasive aspergillosis (IA) is a major cause of morbidity and mortality in severely immunocompromised children - those with new onset or a relapse of hematological malignancy, allogeneic hematopoietic stem cell transplants (HSCT) or solid organ transplants, congenital or acquired immunodeficiency, as well as those on corticosteroids and other immunosuppressive drugs (1-3). While prematurity is the predominant underlying condition among infants, leukemia is the most frequent underlying disease in children (1).

Incubation period is unknown (2). IA most frequently occurs in the sinuses (5-10%) or lungs (80%) after inhalation of conidia, although, less commonly, disease can spread from the gastrointestinal tract or result from the direct inoculation into the skin (3). Aspergillus fumigatus is the most common cause of IA with Aspergillus flavus being the next most common (2, 6, 7). Predominant clinical features of invasive pulmonary aspergillosis (IPA) are lack of symptoms, fever, cough, nondescript chest discomfort, trivial hemoptysis, and shortness of breath (3). Dissemination of Aspergillus species is relatively common in children, with the central nervous system (CNS) being one of the most frequent sites of IA after the lungs (1, 3, 4).

CNS aspergillosis in children may result either from contiguous spread of the infection from the paranasal sinuses or via the hematogenous route due to its angioinvasive nature (5). Predominant presentation is brain abscess(es). CNS symptoms eventually develop in one-half of patients and are the presenting feature in one-third (1).

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The diagnosis of IA is difficult and early diagnosis and initiation of antifungal therapy is important to achieve the best outcome. Serum biomarkers, galactomannan (GM) and beta-D-glucan assays, with bronchoalveolar lavage fluid (BALF) for fungal staining, culture and GM all helps to establish the diagnosis of IA. Aspergillus spp (except for Aspergillus terreus) are seldom cultured from blood (even in patients with disseminated aspergillosis), but can be cultured from lungs, sinuses, and skin biopsy specimens (2, 3, 6).

The utility of blood-based polymerase chain reaction (PCR) in diagnosing IA is still debatable. As for radiologic diagnosis of IA, according to the most recent Infectious Diseases Society of America (IDSA) guidelines, chest computed tomography (CT) scan is recommended whenever there is a clinical suspicion for IPA regardless of chest radiograph results (8). When osseous, paranasal sinus or CNS aspergillosis is suspected, magnetic resonance imaging (MRI) is indicated (3, 8). Broenen et al. recommend MRI of the CNS upon diagnosis of IPA even if neurological signs and symptoms are absent, due to the fact that they appear late in the course of disease (4).

Empirical antifungal therapy has been regarded as the standard practice for neutropenic or immunosupressed patients with persistent or recrudescent fever despite receiving broad-spectrum antibiotics (9). The IDSA guidelines recommend voriconazole as initial therapy of IA and considering combination therapy for refractory or progressive aspergillosis (2, 3, 8). In IPA surgery is indicated only when a mass is impinging on a great vessel (2).

IA in infants and children exhibits differences from cases in adults, such as less specific findings and even greater difficulties in early diagnosis and antifungal treatment. The aim of our study was to evaluate the in-hospital mortality over a period of 21 years (January 1st, 1997, to December 31st, 2017) and identify factors affecting the outcomes of pediatric patients with IA.

METHODS

We retrospectively examined hospital records including patient history, clinical presentations, diagnostic tools, management and outcome of all patients younger than 18 years of age with proven, probable or possible IA defined by the European Organization for Research and Treatment of Cancer-Mycoses Study Group (EORTC/MSG) criteria. This study included all the pediatric patients (0-18 years old) treated at the Pediatric Infectious Diseases Department of University Hospital for Infectious Diseases "Dr. Fran Mihaljević" in Zagreb, Croatia.

Detection of Aspergillus GM in serum or BALF was performed using the Platelia Aspergillus enzyme immunoassay (EIA), according to the manufacturer's protocol. GM assay index >1.2 was considered positive in tracheal aspirate and >0.5 in other specimens. Beta-D-glucan serum assay was not performed in any patient. Fungal DNA was extracted using the "SeptiFast" PCR, a multipathogen probe-based real-time PCR system targeting DNA sequences of bacteria and fungi present in blood samples. Radiologic studies such as chest X ray and CT of each body site were performed in patients according to clinical signs and symptoms. MRI of the CNS was performed in patients with neurological symptoms.

Classification of patients was performed according to the EORTC/MSG protocols (10). The category of proven IA can apply to any patient, whereas probable and possible categories are proposed for immunocompromised patients only. Proven IA requires microscopic analysis of a specimen obtained by needle aspiration or biopsy in which hyphae are seen, or recovery of mold by culture of a specimen obtained by a sterile procedure. Probable IA requires host factor (malignant disease, recipients of allogeneic HSCT and solid-organ transplants, patients who receive corticosteroid therapy and other T cell suppressants as well as patients with primary/hereditary immunodeficiency's or connective tissue disorders), clinical features and mycological evidence to be present. Mycological evidence includes direct and indirect tests. Direct tests consist of cytology, direct microscopy or culture of mold in sputum, BALF, bronchial brush or sinus aspirate samples. Indirect tests consist of GM antigen detected in plasma, serum, BALF or cerebrospinal fluid and beta-D-glucan detected in serum. Possible IA requires host factor and clinical features, but no mycological proof is needed. Molecular methods of detecting fungi in clinical specimens, such as PCR, were not included in the definitions because there is as yet no standard, and none of the techniques has been clinically validated (10).

Decisions about the institution of antifungal therapy were made by the residing physicians according to the actual guidelines.

RESULTS

We identified 12 patients with invasive aspergillosis - 4 had proven, 6 probable and 2 had a possible disease. Female patients represented 66.6% of the patients and the mean age was 8.67 years. The majority of the children had a hematologic malignancy. As an underlying condition, acute lymphoblastic leukemia (ALL) was the most represented (58%), while other conditions included chronic granulomatous disease (CDG), one patient with acute myeloid leukemia (AML) and one with metastatic intracranial germinoma. Although, any critically ill patient in the intensive care unit may also be at increased risk for IA, even in the absence of hematologic malignancy (6).

All patients had pulmonary aspergillosis with disseminated infection being present in 3 patients (25.0%). Disseminated forms included one patient with osteomyelitis and cutaneous aspergillosis, one with CNS aspergillosis and one with hepatic aspergillosis. Aspergillosis in patients with CGD rarely displays angioinvasion (2). However, one of our patients with CGD and proven IPA presented with subcutaneus back abscess and osteolytic lesions in several ribs, cervical and thoracic vertebrae. A. fumigatus was cultured from the back abscess. Characteristics of the patients with proven and probable Aspergillus infection are presented in Table 1. As for the two possible

Table 1.
Characteristics of patients with proven and probable IA

Patient	Sex/age	Background	GM	Method of diagnosis	Culture	Site Infection	Specimen	IA group
1	M/6	CGD	NA	Needle aspiration/Radiology	A. fumigatus	Lung/Skin/Bone	Skin abscess	Proven
2	M/4	CGD	-	Needle aspiration/Radiology	A. fumigatus	Lung	Pleural fluid/BALF	Proven
3	M/12	ALL	-	Clinical/Radiology	A. terreus, A. niger	Lung	Tracheal aspirate	Probable
4	F/12	Aplastic anemia	+	Biopsy/Radiology	A. fumigatus	Lung	Lung tissue/BALF	Proven
5	M/16	ALL	+	Clinical/Radiology	A. fumigatus	Lung/Brain	BALF/ CSF	Probable
6	F/15	ALL	-	Clinical/Radiology	A. fumigatus, A. flavus	Lung	BALF	Probable
7	F/9	ALL	-	Clinical/Radiology	A. fumigatus	Lung	BALF	Probable
8	F/4	ALL	+	Clinical/Radiology	A. fumigatus	Lung	Tracheal aspirate	Probable
9	F/3	ALL	+	Biopsy/Radiology	A. fumigatus	Lung/Liver	Liver tissue/ Tracheal aspirate	Proven
10	F/1	AML	+	Clinical/Radiology	A. fumigatus	Lung	BALF/Tracheal aspirate	Probable

NA – Not applicable

cases of IA, one patient had host factor, clinical features and PCR positive for A. fumigatus from blood, and the other one had host factor along with radiologic pulmonary diagnosis, without sufficient mycological evidence.

A. fumigatus was the species most frequently identified in our patients (75.0%). Bronchoscopy was performed in 66.6% of patients with A. fumigatus cultured from BALF in 62.5% and A. flavus in 12.5%. In other cases A. fumigatus has been cultured from skin abscess aspirate, pleural fluid aspirate and tracheal aspirate. A. terreus and Aspergillus niger were cultured from tracheal aspirate in one patient. Isolation of Aspergillus spp from respiratory tract samples is still often assumed to be colonization, but in the right clinical surrounding there should be no doubt about the diagnosis (11). None of the patients with IA had Aspergillus spp cultured from blood.

Serum and BALF GM is recommended as an accurate marker for the diagnosis of IA in pediatric patients when used in certain patient subpopulations (hematologic malignancy, HSCT). However, GM is not recommended for blood screening in patients receiving mold-active antifungal therapy or prophylaxis, but can be applied to bronchoscopy specimens from those patients. A limitation of the GM test reported in many studies is the observation of false-positive results in patients with IA treated with antibiotics such as amoxicillin-clavulanate, piperacilin-tazobactam, and other beta-lactams, even up to five days after the cessation of treatment (12). False-negative GM test results consistently occur in patients with CGD, so the test is not reliable in these patients (2). GM antigen was analyzed in 83.3% of our patients and found positive in 60.0%. It was positive in 50% of patients with proven or probable IA; specimens included serum, blood, cerebrospinal fluid (CSF), BALF and tracheal aspirate. One patient previously treated with piperacilin-tazobactam and voriconazole had negative blood GM, but positive BALF GM. PCR for Aspergillus DNA from blood was found negative in three patients with probable and one with proven diagnosis.

A chest CT is commonly used in the early diagnosis of IPA, but the results are often inconclusive and further diagnostic testing is required. In addition, there may be differences between CT scans from pediatric and adult patients with IPA that require consideration (6). Follow-up chest CT scan is suggested after a minimum of 2 weeks of treatment, sooner if the patient clinically deteriorates (8). All of our patients had serial chest X-rays, most of them had chest CT. The most frequent radiologic pulmonary finding was bilateral opacity and infiltrations (66.6%) with segmental consolidation seen in 33.3% and nodular formities in 25.0% of our patients. No air crescent sign, halo sign or cavitation was noted. Chest CT scan was not performed in 16.6% of our patients and radiologic diagnosis was in those cases supported by chest X-ray only. Brain MRI was performed in two patients with neurological symptoms where multiple brain lesions have been observed bilaterally in both. In one patient, MRI revealed asymmetric solid lesions with surrounding edema involving right basal ganglia, parietal lobe, pons and cerebellum as well as T1 hypointensity and T2 hyperintensity consistent with aspergillosis. In the other patient, changes were suggestive of inflammatory response or global transitory ischemia rather than aspergillosis.

Voriconazole is the drug of choice for IA in children and adults, except in neonates for whom amphotericin B deoxycholate in high doses is recommended (2). Voriconazole is extensively metabolized by the cytochrome

P450 system with CYP2C19 being the major route for elimination. Individuals who are CYP2C19 ultrarapid metabolizers have decreased voriconazole trough concentrations, delaying achievement of target blood concentrations; whereas poor metabolizers have increased trough concentrations and are at increased risk of adverse drug events (14, 15). This makes CYP2C19 genotype-guided voriconazole dosing a promising strategy. Accumulation of the metabolites occurs in patients with renal insufficiency when administered intravenously. This does not apply to orally administered voriconazole which also has a good bioavailability. However, the mode of administration in the context of IA and renal failure should be determined on an individual patient basis. Fundamental pharmacokinetics of voriconazole are different in children (linear) than in adults (nonlinear). In pediatric patients weighing <50 kg, higher voriconazole doses are needed and measurement of serum levels is useful, both to evaluate for potential toxicity or to document adequate drug exposure (8). In children, voriconazole should be given as intravenous 9 mg/kg loading dose twice daily to be comparable to a 6 mg/kg dose in adults, with maintenance intravenous dosing at 8 mg/kg (4 mg/kg in adults) or oral 9 mg/kg (200 mg in adults) twice daily. Younger adolescents (ages 12-14) should be dosed as children if their weight is <50 kg and as adults if their weight is >50 kg (9). Therapy should be continued for at least 6-12 weeks (2, 3). CNS toxicity (visual side effects or photopsia) is more common with higher drug levels, but is self-limiting and reversible. Other adverse reactions to voriconazole include: hepatotoxicity (dose limiting), skin rash and eryhroderma, photosensitivity and perioral excorations, nausea, vomiting and diarrhea, cardiovascular events (tachyarrhytmias and QT interval prolongations) (8). Caspofungin is the drug of choice for salvage therapy of IA in pediatric patients older than 3 months of age (2). Suggested combination therapy, as initial therapy or salvage therapy in patients who have not responded to their initial regimen, is voriconazole with anidulafungin (13). Serial monitoring of serum GM can be used in the appropriate patient subpopulations (hematologic malignancy, HSCT) who have an elevated GM at baseline to monitor disease progression, therapeutic response and predict outcome (8). Examples of extrapulmonary aspergillosis showcased in this study - CNS aspergillosis, osteomyelitis with cutaneous aspergillosis and hepatic aspergillosis - all require voriconazole as primary therapy with surgical consultation needed in the last two. Unfortunately, none of those patients was stable enough to undergo any surgical intervention at the given moment. Strongly recommended secondary prophylaxis of IA includes posaconazole, voriconazole and itraconazole throughout the duration of immunosuppression (8). Our surviving patients have been receiving voriconazole or itraconazole.

Before IA was diagnosed, half of our patients received lipid formulations of amphotericin B, and 33.3% received voriconazole. After the diagnosis, all but one (voriconazole was not available at that time) were treated with voriconazole; 75.0% received concomitant antifungal agents; out of which lipid formulations of amphotericin B were the most preferred option (44%). Diagnostic delay (time from symptom onset to the correct diagnosis), antifungal therapy and outcome of patients with proven and probable IA are presented in Table 2. Late administration of voriconazole in our patients is in close correlation with their diagno-

Table 2.
Antifungal therapy and outcome of patients with proven and probable IA

Patient	Sex/age	Background	Diagnostic delay (weeks)	Therapy before the diagnosis	Therapy after the diagnosis	Total antifungal therapy duration (weeks)	Outcome
1	M/6	CGD	8.0	AmBd	LBAmB	12.0	Died
2	M/4	CGD	3.5	AmBd	AmBd + voriconazole	5.4	Survived
3	M/12	ALL	3.0	AmBd ≥ LBAmB	AmBd + voriconazole	2.5	Died
4	F/12	Aplastic anemia	2.5	LBAmB + voriconazole	12.0	Died	
5	M/16	ALL	1.3	LBAmB	voriconazole	4.4	Died
6	F/15	ALL	3.0	AmBd	voriconazole	1.5	Died
7	F/9	ALL	1.3	voriconazole	2.4	Survived	
8	F/4	ALL	1.3	LBAmB	LBAmB + voriconazole	1.3	Died
9	F/3	ALL	4.3	LBAmB	LBAmB + voriconazole	2.6	Died
10	F/1	AML	2.0	LBAmB	voriconazole + anidulafungin	3.6	Died

AmBd - amphotericin B deoxycholate; LBAmB - lipid-based amphotericin B

stic delay with a mean time of 2.6 weeks. Some patients with leukemia (37.5%) were receiving chemotherapy when IA was diagnosed and treated. One of our patients with IPA underwent surgical procedure (lobectomy) due to radiological verification of a mass causing impingement of the bronchus.

IA is a major cause of death in immunosuppressed children with a high mortality rate (generally >50%) (6). Outcome was poor in our patients; overall mortality was 83.3%. The 21-day mortality was 66.6%. CNS aspergillosis in children has even higher mortality than IPA only, ranging from 65-95% depending on the time of diagnosis and the start of treatment (1, 4, 16). Disseminated infection is associated with worse prognosis than IPA alone. That contributes to the high mortality rate in our case series as none of the patients with disseminated disease survived. Nevertheless, the mortality of 77.7% for patients with IPA alone is still higher then noted in other studies. Side effects of chemotherapy and comorbidities play a crucial role in the high mortality rate, especially underlying viral or bacterial pneumonia and sepsis. Also, late administration of voriconazole (only after the diagnosis of IA in most patients) contributes to the high mortality rate.

CONCLUSION

In the period of twenty-one years we had twelve cases of IA in immunocompromised children, out of which only two survived. Our study confirmed hematologic malignancy, relapsed hematologic malignancy and CGD as risk factors for the development of IA. In children, the disease most commonly involves the lungs. One fourth of our patients had disseminated infection at the time of presentation. A. fumigatus was the predominant causative agent.

Frequently, symptoms of IA are subtle and children do not manifest specific radiologic signs which can significantly postpone the diagnosis. However, galactomannan assay and BALF culture may facilitate the diagnosis in suspected cases as shown in our case series. Some of our patients did not have GM tested and two patients did not have chest CT scan taken, both of which delayed diagnosis.

Voriconazole is the preferred treatment for IA in children and should be started when IA is suspected. Nevertheless, only a few patients received voriconazole before the diagnosis of IA was established. This delay in administration of the most efficient drug could have also been a reason for a higher mortality rate in our case series. Higher dosages of particular antifungal agents are required in pediatric patients to achieve similar exposures as in adults receiving a lower dosage.

In conclusion, the high in-hospital mortality is affected by the lack of screening methods in high-risk patients, diagnostic delay possibly leading to a disseminated infection with worse prognosis, side effects of chemotherapy and other comorbidities, as well as therapeutic delay in administrating voriconazole as the drug of choice.

Abbreviations:

ia - invasive aspergillosis
hsct - hematopoietic stem cell transplants
ipa - invasive pulmonary aspergillosis
cns - central nervous system
gm - galactomannan
balf - bronchoalveolar lavage fluid
pcr - polymerase chain reaction
ct - computed tomography
mri - magnetic resonance imaging
idsa - Infectious Diseases Society of America
eortc/msg - European Organization for Research and Treatment of Cancer-Mycoses Study Group
EIA - enzyme immunoassay
all - acute lymphoblastic leukemia
cgd - chronic granulomatous disease
aml - acute myeloid leukemia
csf - cerebropinal fluid

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Sažetak

RETROSPEKTIVNI PREGLED 12 PEDIJATRIJSKIH SLUČAJEVA INVAZIVNE ASPERGILOZE LIJEČENIH U USTANOVI TERCIJARNE RAZINE ZDRAVSTVENE ZAŠTITE U HRVATSKOJ (1997.-2017.)

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Cilj: Invazivna aspergiloza je značajan uzrok morbiditeta i mortaliteta u imunokompromitirane djece. Cilj našeg rada bio je identificirati i procijeniti čimbenike koji su utjecali na unutarbolnički mortalitet pedijatrijskih pacijenata s invazivnom aspergilozom u razdoblju od 21 godine (01.01.1997.-31.12.2017.).

Izvori i ekstrakcija podataka: Retrospektivno smo pregledali bolničke podatke pacijenata mlađih od 18 godina s dokazanom, vjerojatnom ili mogućom dijagnozom invazivne aspergiloze definirano prema revidiranim kriterijima "European Organization for Research and Treatment of Cancer-Mycoses Study Group".

Rezultati: Prikazali smo 12 pacijenata s invazivnom aspergilozom; od kojih je 4 imalo dokazanu, 6 vjerojatnu i 2 moguću. Većina je u podlozi imala hematološku malignu bolest. Svi su imali invazivnu aspergilozu pluća. Aspergillus fumigatus bio je najčešće izolirani patogen (75,0%). Galaktomanan je određivan u 83,3% slučajeva od kojih je u 60,0% bio pozitivan. Najčešći radiološki nalaz pluća bio je bilateralno zasjenjenje i infiltrati (66,6%). Nakon postavljene dijagnoze, sva djeca osim jednoga liječena su vorikonazolom; 75% primalo je konkomitantnu antigljivičnu terapiju. Ishod je generalno bio loš, mortalitet prikazanih bolesnika iznosi 83,3%.

Zaključci: Hematološka maligna bolest ili njen relaps, te kronična granulomatozna bolest rizični su čimbenici za razvoj invazivne aspergiloze. Bolest u djece najčešće zahvaća pluća. Često se ne prikazuju specifični radiološki znakovi što odgađa postavljanje dijagnoze. Međutim, analiza galaktomanana i kultiviranje bronhoalveolarnog lavata mogli bi ubrzati dijagnostički postupak. Na visoki unutarbolnički mortalitet utječe nedostatak metoda probira u visoko rizičnih pacijenata, kasno postavljanje dijagnoze što omogućuje razvoj diseminirane infekcije s lošijom prognozom, zatim nuspojave kemoterapije i ostali komorbiditeti, kao i kašnjenje u primjeni vorikonazola kao terapije prvog izbora.

Deskriptori: ASPERGILOZA, DJECA, GALAKTOMANAN, VORIKONAZOL

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