Changing trends in the survival of immunosuppressed children with invasive fungal rhinosinusitis: a retrospective observational cohort study

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Abstract

Objectives: Acute invasive fungal rhinosinusitis has been associated with high mortality rates. We aimed to explore the contribution of novel detection and treatment methods on the outcome of immunosuppressed children with acute invasive fungal rhinosinusitis. Design: Retrospective observational cohort study. Setting: A tertiary children's hospital. Participants: The records of all children with a hematologic or oncologic disease who developed AIFR between 2005-2020 were reviewed. Results: Thirty-four patients were included. Aspergillosis and mucormycosis were diagnosed in 20 patients (59%) and 12 patients (35%), respectively. Panfungal polymerase chain reaction (PCR) was associated with a change of treatment in 36% of patients. Aggressive surgical approach was adopted and 71% of the patients underwent multiple surgical procedures. Overall, 26% of patients died of disease, however no disease-specific death occurred since 2012. Diagnosis using panfungal PCR (p=.04) and treatment with novel antifungal medications (p=.017) were significantly associated with disease-specific survival. Conclusions: Enhanced fungal detection using panfungal PCR and treatment with novel antifungal agents, combined with rapid diagnosis and treatment, aggressive surgical approach and better control over the underlying oncological disease, may significantly improve the outcome of immunosuppressed children with acute invasive fungal rhinosinusitis.

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Results: Thirty-four patients were included. Aspergillosis and mucormycosis were diagnosed in 20 patients (59%) and 12 patients (35%), respectively. Panfungal polymerase chain reaction (PCR) was associated with a change of treatment in 36% of patients. A more aggressive surgical approach as well as treatment with liposomal amphotericin B and novel antifungals were adopted in recent years. Overall, 26% of patients died of disease, however no disease-specific death occurred since 2012. Diagnosis using panfungal PCR (*p=.04*)

and treatment with novel antifungal medications ($p=.017$) were significantly associated with disease-specific survival.

Conclusions: Enhanced fungal detection using panfungal PCR and treatment with novel antifungal agents, combined with rapid diagnosis and treatment, aggressive surgical approach and better control over the underlying oncological disease, may significantly improve the outcome of immunosuppressed children with acute invasive fungal rhinosinusitis.

Key words: Infectious/inflammatory, Pediatric sinus/nose, Pediatric rhinology.

KEY POINTS

- The survival of immunosuppressed children with acute invasive fungal rhinosinusitis (AIFR) has improved dramatically over the past decade.
- No patient has died of AIFR since 2012.
- Utilization of PCR for fungal detection was associated with significantly improved fungal detection rate.
- Panfungal PCR along with treatment with novel antifungal medications were associated with improved survival.
- Low threshold for investigation, rapid and aggressive surgical treatment, and better control over the underlying oncological disease are also crucial for improved AIFR-specific survival.

INTRODUCTION

The expanding use of bone marrow transplantation (BMT) and intensive chemotherapy in the treatment of children with hematologic and oncologic disease has placed them at an increased risk for opportunistic infections such as acute invasive fungal rhinosinusitis (AIFR), a life threatening infection[1,2].

The diagnosis of AIFR is challenging owing to the often-nonspecific presenting symptoms[3]. The disease has a rapidly progressive course, and timely diagnosis and detection of the fungal pathogens is crucial for successful management and clinical outcome of patients[4]. Direct microscopy and histopathology are the gold standard for diagnosis[5]. Cultures are used to identify the culprit agents and their antimicrobial susceptibility. Since the late 1990s more rapid and sensitive detection methods, such as in-situ hybridization and polymerase chain reaction (PCR), have been applied. Nevertheless, the detection spectrum of real-time PCR has been mostly restricted to a variety of *Candida* or *Aspergillus*species[6].

In recent years, new panfungal PCR assays have been developed in order to detect a wider range of fungal pathogens[7,8]. The use of panfungal PCR assay in addition to histopathology and cultures seems to contribute to higher detection rates in cases of AIFR[4]. Additionally, the introduction of novel antifungal drugs such as posaconazole and isavuconazole may improve patients survival rates[9,10]. Finally, timely surgical debridement, a cornerstone of the management of AIFR, has been shown to be an independent prognostic factor in the survival of patients[11,12]. Improved endoscopic surgical skills using advanced instrumentation, high-definition cameras and intraoperative stereotactic navigation may lead to better survival outcomes in the management of children with AIFR[13].

Objective

The aim of the present study was to investigate whether novel rapid detection methods, advanced antifungal agents, and application of prompt and aggressive surgical interventions are associated with improved outcome of immunosuppressed children with AIFR.

MATERIALS AND METHODS

Study Design and Subjects

The study protocol was approved by the Institutional Review Board. The electronic medical records of a tertiary children's hospital were reviewed for all children (age <18 years) who underwent endoscopic sinus surgery (ESS) between 2005-2020. Only children with pathology proven AIFR were included.

Diagnostic Methods

Direct microscopy and histopathology demonstrating invasive fungal pathogens in the sinonasal mucosa served as the gold standard for diagnosis of AIFR. Cultures were used for identification of the fungal pathogen. Panfungal PCR, which was first introduced to our institution in 2011, was used for rapid detection of the fungal species in addition to the standard detection methods.

All patients underwent computed tomography (CT) scans of the head and sinuses, while magnetic resonance imaging (MRI) was used in cases where intracranial complications were suspected.

Endoscopic Sinus Surgery

Necrotic tissues were endoscopically debrided until macroscopically healthy bleeding margins were reached. Patients were taken back to the operating room for further debridement whenever suspicion for continued infection remained. Of note, a more aggressive surgical approach was adopted in the latter years of the study, including endoscopic resection of the anterior skull base, clivus, pterygopalatine fossa and infratemporal fossa whenever these sites were involved.

Systemic Antifungal Therapy

Prior to the diagnosis of AIFR, all patients were stratified into categories of risk to develop invasive fungal disease according to accepted guidelines[14]. High-risk criteria included acute myelogenous leukemia (AML), high-risk acute lymphoblastic leukemia (ALL), relapsing leukemia, and post-BMT. High-risk patients received prophylactic antifungal therapy with itraconazole or fluconazole, as part of the institutional policy. In addition, all other children with hematologic malignancies were prophylactically treated with nystatin or clotrimazole.

Empirical systemic antifungal therapy was administered as soon as AIFR was suspected. Indications for empirical antifungal treatment included persistence of fever and neutropenia despite broad spectrum antibiotic therapy, signs of locally advanced rhinosinusitis, nasal biopsy positive for calcofluor-white stain or evidence of invasive fungus in frozen section. Therapy was adjusted after definitive diagnosis and identification of the pathogen, in accordance with accepted guidelines[15].

Data Collection

The following data were collected from patients' files: demographics, type of the underlying disease, remission status, laboratory results, clinical and imaging characteristics, microbiology and pathology, medical treatment, surgical data, complications, and outcomes.

The follow-up period was defined as the time from diagnosis to data collection for the study or patient death. Death was considered due to AIFR when a patient with persistent signs of disease died from systemic fungal infection, sepsis and/or intracranial complications.

Statistical Analysis

All statistical analyses were performed with SPSS v.23.0 (IBM Corp., Armonk, NY, USA). Associations between nominal variables were examined using χ^2 test and Fisher's exact test. Associations between continuous and quantitative variables were examined using Mann-Whitney U-Test. Potential confounding variables were assessed by Cox proportional hazards regression model. A two-sided p-value of $<.05$ was considered statistically significant for all analyses.

RESULTS

Demographic and Clinical Characteristics

The study included 34 pediatric patients with a median age of 10 years (range, 3-17 years), and a female to male ratio of 1:1. The demographic and clinical characteristics of the study cohort are shown in**Table 1.**

ALL and AML accounted for the majority of all underlying diseases (56% and 24%, respectively). Twenty-two patients (65%) met high-risk criteria for fungal infection and were given prophylactic itraconazole or fluconazole prior to the diagnosis of AIFR.

Most of the patients developed AIFR during disease remission (23 patients, 68%). In patients post-BMT AIFR was first diagnosed within a median of 112 days post transplantation (range, 6-1203 days). Ten patients (29%) developed AIFR within 6 months of BMT. Thirty-one patients (91%) were severely neutropenic (absolute neutrophil count $<500/mm^3$) at the time of diagnosis of acute infection; the mean duration of neutropenia was 17 ± 14 days (median, 13 days; range, 1-68 days). Fever was the most common presenting symptom of AIFR, in 29 children (85%), followed by facial swelling in eleven (32%). Orbital complications included proptosis (n=4, 12%), periorbital edema (n=3, 9%) and oculomotor nerve palsy (n=3, 9%).

Imaging Findings

Sinus opacification was apparent on preoperative CT in 25 patients (74%), with the maxillary (65%) and ethmoid sinuses (53%) primarily involved. Eight patients (24%) had radiological signs of extrasinus involvement. These included bony erosion of the maxillary sinus walls, hard palate, and orbital walls in five patients (15%), and involvement of the infratemporal fossa and medial pterygoid muscle in two cases (6%). Periorbital or orbital involvement was apparent on CT in 5 patients (15%). Nine children (26%) also underwent MRI to assess for neural invasion or infratemporal or intracranial extension. In two of these cases MRI revealed skull base involvement with dural enhancement, and in one case an extension to the pterygopalatine and infratemporal fossa with thickening and enhancement of the maxillary nerve.

Surgical Data

The median time from onset of fever (29 patients, 85%) to first surgical intervention was 4 days (range, 1-10 days). The average number of ESS per-patient was 3.2 (range, 1-11 surgeries per-patient). Twenty-four children (71%) required multiple procedures to control the disease. The nasal structures that were most involved in AIFR included the middle turbinates (n=16, 47%), nasal septum (n=13, 38%) and inferior turbinates (n=10, 29%). Eleven patients (33%) were diagnosed with extrasinus involvement, including the palate (n=5, 15%), the orbit (n=4, 12%) and the skull base (n=3, 9%). Involvement of the pterygopalatine fossa, nasopharynx or clivus was documented in 4 cases (12%). Major surgical complications included one case of significant intraoperative bleeding which was successfully treated surgically, along with blood transfusions, anterior and posterior packing and 24-hour observation in the intensive care unit.

Fungal Detection Methods

Overall, in 17 children (50%) multiple fungal species were detected. In twelve cases (35%) identification of fungal pathogens relied solely on histopathology and fungal cultures. Panfungal PCR, which was first introduced in our institution in 2011, was utilized in the remaining 22 patients (65%). PCR detected fungal pathogens in four patients with negative cultures, and additional fungal species in four patients with positive cultures (18% of patients tested by PCR). Overall, the use of panfungal PCR resulted in a change in antifungal therapy in 8 patients (36% of patients tested by PCR).

The most common fungus identified was *Aspergillus* in 20 patients (59%). Fifteen fungal pathogens of the order Mucorales were detected in 12 patients (35%), including *Mucor* (n=6), *Rhizopus* (n=7) and *Absidia* (n=2). Other pathogens included *Alternaria*(n=6), *Exserohilum* (n=6), *Curvularia* (n=3),*Fusarium* (n=3) and *Candida* (n=2).

Systemic Antifungal Therapy

Amphotericin B (AmB) (n=8, 24%) was the empirical antifungal treatment of choice until 2010, when it was replaced mainly by liposomal amphotericin B (ambisome) (n=13, 38%). Novel antifungals, posaconazole and isavuconazole, have been employed as additional treatment options in our institution since 2008 and 2017, respectively. Antifungal treatment was adjusted following the identification of infectious agent.

Disease Outcomes

Patients were followed with an average duration of 30.5 ± 44.5 months (median, 12 months; range, 9 days to 167.5 months). Thirteen patients (38%) died by the end of follow-up. Systemic fungal infection, sepsis, and intracranial complications of AIFR were the causes of death in 9 patients (26%); other complications of the underlying disease, including non-remission and secondary infections, accounted for the remaining four deaths (12%).

The mean survival time of patients who died of AIFR was 98 ± 144 days (median, 36 days; range, 14-462 days). In a univariate analysis, diagnosis using panfungal PCR (*p=.04*) and treatment with novel antifungal agents (*p=.017*) were associated with increased rates of AIFR-specific survival. Remission status was associated with overall survival (*p=.008*). However, a regression analysis using the Cox-proportional hazard model to control for confounding effects did not identify any significant variable associated with survival (**Table 2**).

The overall and disease-specific survival rates increased throughout the study period. The last patient to die of AIFR was diagnosed in February 2012. Since then, no other patient has died of the disease. Moreover, since April 2013 only one patient has died of his underlying malignant disease (**Figure 1**). Increased survival was evident specifically among patients with mucormycosis. Seven of these patients were diagnosed before 2012 and the remaining five between 2013-2020. Four patients (33%) died from complications related to mucormycosis, all diagnosed before 2012. Of note are two patients with mucormycosis who survived despite an aggressive disease involving, in one patient, the orbit, skull base and dura, and in the second the hard palate and skull base. Both patients received rapid empirical treatment with ambisome as soon as AIFR was suspected, and underwent multiple aggressive surgical procedures, including resection of the skull base, the hard palate and orbit.

DISCUSSION

In this study we analyzed the diagnostic and management patterns of children with AIFR over the past 15 years and their implications on outcomes. While still considered an extremely aggressive disease with dismal prognosis, the results of this study showed a significant increase in patients' survival in the past decade compared to earlier years. AIFR had historically been associated with high mortality rates of 50%–90%[16]. Recently published data indicated better prognosis with mortality rates of 30-50% which was attributed mainly to early detection of AIFR[17] and aggressive surgical management[18]. In the present study, the overall mortality rate was 38%, and the disease-specific mortality rate was 26%. Nonetheless, no patient has died of AIFR since 2012.

The status of the underlying disease was previously shown to be among the leading prognostic factors[4,19]. Hematologic malignancies, most notably ALL and AML, were reported to be the leading causes of immunosuppression[3,4]. The decrease in overall mortality rate in our study may reflect better control of the underlying disease, which may have contributed to the change in AIFR-specific survival. The majority of patients (68%) developed AIFR during disease remission, and as expected, had better overall survival outcomes compared to patients with non-complete remission. These data highlight the importance of better control of the immunosuppressive state to improve the prognosis of patients with AIFR.

Early diagnosis and aggressive surgical treatment of AIFR have been proven to be critical in improving patients' outcomes[20]. In the present study a low threshold for diagnosis led to early investigation and surgical intervention within a median of 4 days from the onset of fever. In 71% of our patients, multiple surgical procedures were performed, and debridement was repeated until no further disease progression was observed. Moreover, along with the improvement in technology and experience, a more aggressive surgical approach was adopted in our institution in the latter years of the study including pterygopalatine fossa, infratemporal fossa and skull base debridement as needed, which may have been associated with the improved survival, observed in recent years.

Novel detection methods and newer systemic antifungal therapies may also have contributed to improved patient survival. Culture studies had long been considered the gold standard for identification of the culprit subspecies in AIFR, but their reported sensitivity was low (30-54%), and their diagnostic value was further

limited by the slow growth rate of fungal pathogens, leading to delays in appropriate antifungal therapy[20,21]. Since PCR first came into use in our practice in 2011, it has become a leading detection method, and was used in >90% of cases. Although recognized as an augmenting tool to improve diagnosis of AIFR, PCR was not included in the revised definitions of invasive fungal disease published in 2008, because the technique had not yet been clinically validated[22]. More recent data, however, have shown that with the advantage of rapid detection of mixed infection in a single specimen, panfungal PCR is more sensitive and specific than cultures and direct sequencing in patients with fungal rhinosinusitis[8]. In our practice, we found panfungal PCR to be superior to fungal cultures in the detection of pathogens and to be associated with a change of treatment in nearly one-fifth of cases.

Historically, AmB has been considered the drug of choice for treatment of invasive fungal infections, and it remains the agent with the broadest antifungal spectrum[23]. However, its use has become limited due to high incidence of adverse effects and substantial risk of nephrotoxicity which led to adaptations of therapy[23,24]. With improved safety profile and greater efficacy, novel agents such as liposomal AmB, triazoles and echinocandins have gradually become the drugs of choice for invasive fungal infections[10,22,24,25]. In the current study, since 2011 AmB, which was associated with decreased survival, has been replaced as the treatment of choice by liposomal AmB, and novel triazoles and echinocandins. We believe that this may have contributed to the improved survival in recent years.

The main limitations of this study include its retrospective design and small cohort size. Nonetheless, the study's duration period enabled us to view with perspective the trends in management and survival of children with AIFR.

CONCLUSION

In this study we present encouraging data on improved survival in immunosuppressed children with AIFR. While still considered one of the deadliest infectious diseases in this population, we observed that low threshold for investigation, utilization of PCR for fungal detection, treatment with novel antifungal agents combined with rapid and aggressive surgical treatment and better control over the underlying oncological disease, dramatically reduced AIFR mortality rates. We suggest that panfungal PCR should have an increasing role in the detection of fungal pathogens and that novel antifungal drugs should become an essential part of the treatment regimen.

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Table 1. Baseline characteristics of the study population

Characteristic	All patients (no. of patients = 34)
Male gender	17 (50%)
Median age at study entry, year (range)	10 (3-17%)
Underlying disease*	
ALL	19 (56%)
AML	8 (24%)
Other+	9 (26%)
Stem-cell transplantation	
Overall	13 (38%)
Allogeneic	13 (38%)
Autologous	0
BMT <6 months before infection	10 (29%)
Disease status	
Remission	23 (68%)
Non-complete remission	11 (32%)
Severe neutropenia (ANC<500/mm^3)	31 (91)
Mean duration of neutropenia, days ± SD	17 ± 14
Risk classification for fungal infection++	
Standard risk	12 (35%)
High risk	22 (65%)
Post-BMT	13 (38%)
Relapsing leukemia	11 (32%)
AML	8 (24%)
High-risk ALL	6 (18%)
Surgical treatment	
No. of ESS, mean (range)	3.2 (1-11)
Multiple procedures	24 (71%)
Extrasinus extension	11 (33%)
PCR detection	22 (65%)
Fungal pathogen	
Aspergillus	20 (59%)
Mucormycosis	12 (35%)
Other	20 (59%)
Systemic antifungal therapy	
Amphotericin B	9 (26%)
Ambisome	13 (38%)
Voriconazole	11 (32%)
Mortality	
Overall	13 (38%)
Dead of infection	9 (26%)

Abbreviations: *ALL* , acute lymphoblastic leukemia; *AML* , acute myeloid leukemia; *ANC* , absolute neutrophil count; *BMT* , bone marrow transplantation;*ESS* , endoscopic sinus surgery; *PCR* , polymerase chain reaction; *SD,* standard deviation

* Two patients were diagnosed with more than one underlying disease

+ Other diagnoses included aplastic anemia, lymphomas, severe combined immunodeficiency, hemophagocytic lymphohistiocytosis and Wilm's tumor.

++ Risk to develop invasive fungal disease according to the European Conference on Infections in Leukemia (reference 14).

Covariates	Coefficient	Standard error	P value	HR	95% CI	95% CI
					Lower	Upper
Age	.179	.114	.116	1.197	.957	1.496
Remission	-.433	.970	.655	.648	.097	4.343
BMT	-2.652	1.418	.061	.071	.004	1.135
Mucormycosis	.554	.775	.475	1.740	.381	7.939
Panfungal PCR	-.039	1.406	.978	.961	.061	15.120
Amphotericin B	-2.667	1.682	.113	.069	.003	1.879

Table 2. Results of multivariate Cox regression model

Abbreviations: *BMT*, bone marrow transplantation; *CI* , confidence interval; *HR*, hazard ratio; *PCR* , polymerase chain reaction.

FIGURES LEGEND

Figure 1

The proportion of patients who died of acute invasive fungal rhinosinusitis and other complications of the underlying disease throughout the study period.

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