Invasive Fungal Sinusitis in Immunocompromised Hosts

15

Andrew W. Chao and Dimitrios P. Kontoyiannis

Introduction

Acute invasive fungal sinus disease (IFS) is an uncommon disease that often has rapid and destructive clinical progression. Primarily, a disease of the immunocompromised, IFS is typically associated with patients undergoing chemotherapy, stem cell transplantation as well as in patients with uncontrolled diabetes mellitus and patients using corticosteroids or other immunosuppressive therapies (e.g., following organ transplantation) [1–3]. It is less commonly described in HIV-infected patients, in whom invasive aspergillosis rather than mucormycosis is usually described [4]. The estimated mortality of IFS varies markedly, with a range from 20% to 80% with an estimated aggregate mortality of approximately 50% [5–7]. Invasive fungal sinusitis can also have profound effects on malignancy-related survival by delaying or resulting in dose-reduction in chemotherapy regimens [8]. Limited available interventions as well as slow development of new anti-fungal agents have led to incremental improvements in outcomes.

Causative Organisms

The fungi responsible for IFS are ubiquitous in the environment, filling the niche of saprophytic microbes feeding on detritus. They can be found as colonizing and commensal organisms in humans as well, with invasive disease rarely developing, and typically in the setting of significant immunosuppression. Many fungi can potentially cause IFS; however, molds predominate as causative agents. The majority of causative molds belong to the *Aspergillus* genus and Zygomycetes phylum. *Aspergillus* species include *A. fumigatus*, *A. niger*, and *A. terreus* among others [1, 6]. Of the *Aspergillus* species, *A. fumigatus* is the most commonly identified cause of invasive infection [9]. Pathogenicity of these isolates is attributed to smaller conidial size facilitating inhalation and penetration [10] as well as blunting host defenses including opsonization and complement activation [11].

The most common Zygomycetes causing IFS are from the *Mucorales* order and include important genera such as *Mucor*, *Rhizopus*, and *Absidia* [1, 12]. These species are increasingly encountered in patients receiving Aspergillus-active antifungals such as voriconazole or echinocandins [13].

A. W. Chao
Division of Infectious Diseases, Medical College of Georgia at Augusta University, Augusta, GA, USA

D. P. Kontoyiannis (✉)
Division of Internal Medicine, Department of Infectious Diseases, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: dkontoyi@mdanderson.org

M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_15

Fusarium species are also implicated in IFS, though less commonly than *Aspergillus* and *Mucor* [14].

Acquisition of Infection

For an opportunistic pathogen to cause disease it must first reach the nasal sinus cavity, adhere to mucosal surfaces, and then bypass local and systemic host defenses to invade tissue. Although the underlying immunodeficiency of the host has received much attention, increasingly studies have highlighted the roles of anatomic abnormalities and environmental characteristics in facilitating disease pathogenesis [15].

The nasal mucosal membrane is the first physical and immunologic barrier in the infectious process [16]. Anatomic abnormalities such as a deviated nasal septum or nasal obstruction have been identified as predisposing host factors to developing IFS [15]. Specifically, it has been postulated that turbulent airflow as a consequence of these abnormalities, along with impaired ventilation, helps facilitate fungal spore deposition on the mucosa [17]. The nasal cavity flora has been demonstrated to interfere with bacterial upper respiratory infections and can resist spore deposition, but in turn can be disrupted by antimicrobial use [18]. Whether an altered composition of nasal microbiome is a permissive factor for invasive fungal infection remains to be shown. Nevertheless, studies have indicated that a preceding upper respiratory infection and prolonged antibacterial use are risk factors for IFS, likely due to the disturbance of the local microbiome [18]. With severe suppression in local and systemic innate host immunity, fungi can then invade in response to environmental cues, causing extensive necrosis and tissue infarction depending on the angioinvasive ability of the fungus.

Risk Factors and Pathogenesis

Several conditions are associated with diverse defects in the innate, more so than the adaptive immune system, which predispose to IFS. Thus, a heterogeneous population of patients is at risk including those with poorly controlled diabetes mellitus, chronic corticosteroid use, iron overload, HIV/AIDS, stem cell or organ transplant recipients, and patients with cancer [5]. Furthermore, practices such as inhaled cocaine abuse can cause erosion of nasal mucosa and structural abnormalities which then facilitate further fungal deposition and invasion [19]. Sporadic cases of IFS in apparently immunocompetent patients have been rarely reported [20, 21].

Hyperglycemia, secondary to diabetes mellitus or glucocorticoids use, results in a decrease in neutrophil and macrophage chemotaxis, impaired phagocytosis, and decreased oxidative and non-oxidative killing of fungi [22]. Furthermore, the acidemia of diabetic ketoacidosis (DKA) has been demonstrated to enhance the angioinvasion of *Mucorales* [23]. Ketoacidosis due to elevations of β-hydroxybutyrate in DKA facilitate *Mucorales* growth while further attenuating neutrophil-mediated responses. This is due to facilitation of fungal adherence to endothelium as well as disruption of host functions that lead to elevated free iron levels [24]. Iron overload and use of exogenous iron have been well described as an independent predisposing cause for mucormycosis [25, 26] and is part of the constellation of physiologic derangements seen in DKA.

Patients with hematological malignancies in particular have long been identified as being at risk for IFS due to primary dysfunction of the immune system as well as immunosuppression from cytotoxic chemotherapy. Cases of IFS have been described even during induction treatment shortly after the diagnosis of a primary hematological malignancy. This is further exacerbated by relapsed or recalcitrant disease, necessitating additional cycles of cyto-reductive chemotherapy. Hematopoietic stem cell transplant recipients can have a degree of neutropenia compounded by lymphocyte dysfunction and lymphopenia due to their immunosuppressive regimens used to prevent graft vs. host disease. Despite improvements in antifungal armamentarium, the incidence density of IFS has not decreased in this patient population.

Clinical Presentation

There is marked variation in the presenting symptoms, partially depending on the degree and perhaps the nature of the underlying immunosuppression. There may be few, if any, symptoms early in the clinical course which results in IFS misdiagnosed as a bacterial or viral upper respiratory tract infection. Symptoms can include, but are not limited to, fever, facial swelling, nasal congestion, facial pain, and headaches. A study from Thailand comparing 35 patients with IFS with 65 patients who had orbital complications of bacterial sinusitis found no significant differences between the two groups with regard to these nonspecific symptoms, although the IFS group had significantly higher incidence of diplopia and cranial nerve involvement [27]. Of note, fever was present in only one-third of patients with IFS, and the absence of fever or leukocytosis does not exclude IFS. Tissue with angioinvasion may be discolored and have a red, violaceous, or black appearance; the presence of discolored mucosa is suspicious for mucormycosis. Involvement can be seen in the nasal cavity and turbinates as well as facial lesions, including necrosis of the nasal bridge. However these findings, while typical for IFS, are not solely reliable for early diagnosis and their absence does not rule out disease. Necrotic eschars may be seen in only 50% of patients in the first 3 days of the onset of infection [22].

Patients with IFS often have invasion into contiguous structures [1] and present with additional complaints. There is a significantly higher rate of ocular symptoms associated with IFS, as noted above, indicative of invasion into the orbit and/or cavernous sinus [22, 27]. Fungal invasion into the orbit tends to be unilateral can result in decreased visual acuity, and dysfunction of extraocular movements. Such patients will often have proptosis and chemosis with periorbital and orbital edema with a cellulitis appearance (see Fig. 15.1). Sense of smell may be lost as well but may not necessarily reflect nerve dysfunction. Careful examination of the oral cavity, including the gingiva and hard palate, may demonstrate ulcerations and eschars as evidence of extending ischemia or necrosis. Erosion through bony and mucosal structures is occasionally seen, generally in late and progressive IFS. Patients with infraorbital nerve involvement can exhibit paresthesia in the malar/V2 distribution of the trigeminal nerve. Decreased sensation or paresthesias over the forehead and/or upper cheek suggest involvement of V1 or V2 and may occur from orbital apex or cavernous sinus invasion. Rarely, invasion into the central nervous system (CNS) can result in meningitis with associated symptoms of confusion, seizures, headache, and nuchal rigidity [5, 7]. Patients will need close monitoring and examination as the pace of disease progression can range from as short as hours (especially for Mucorales) to as long as days or weeks.

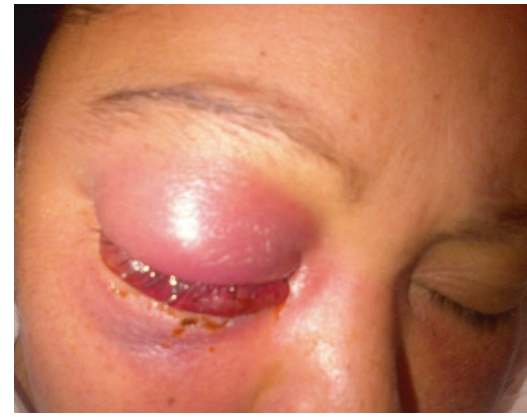

Fig. 15.1 A woman with relapsed acute myeloid leukemia and resultant 2 months of neutropenia presented complaining of 1 week of right-sided headaches with right eye photophobia and facial swelling. She was found to have sino-orbital mucormycosis due to *Rhizopus* species. Note the extensive orbital cellulitis and proptosis due to invasive fungal sinusitis with orbital invasion

Invasive mold infection beyond the sinuses is often concurrently found in immunocompromised patients who present with IFS; however, it is poorly described in the literature. In these instances, pulmonary involvement can be seen in addition to extension into the orbit or cranium [28] and is seen in over half of IFS cases [29]. Cutaneous involvement in IFS is usually a consequence of contiguous extension out of the sinuses into the skin but can also be rarely seen in remote sites [30].

Diagnostics

As symptoms can be nonspecific with significant overlap between viral or bacterial infections, clinicians must maintain a high index of suspicion for IFS in immunocompromised patients. Timely diagnosis is important for improved patient outcomes. Radiology studies, early ENT evaluation with procurement of material for microbiology and histopathological studies are all essential for diagnosis and to aid decision-making.

When IFS is suspected, a computed tomography (CT) scan of the sinuses is usually the first and easiest diagnostic imaging test to obtain. Plain film radiography may demonstrate air-fluid levels when sinusitis is suspected, but its role has been superseded by CT scan except in resource-limited settings. The most common early finding on CT is sinonasal mucosal thickening that is often unilateral [31]; however, this is a nonspecific finding that can be seen in all forms of rhinosinusitis. Characteristic invasion into soft tissue can be missed on CT, and bony destruction occurs late in the clinical course. Magnetic Resonance Imaging (MRI) is a more sensitive tool for determining early IFS changes in the soft tissue [32], evaluating for necrotic tissue that can be correlated with nasal endoscopy findings (see Fig. 15.2). Loss of contrast enhancement with gadolinium is strongly suggestive of tissue ischemia secondary to angioinvasion by fungal organisms [33] (see Fig. 15.3). An MRI can help establish the extent of disease by assessing for any intracranial or cavernous venous involvement, or invasion into other surrounding structures. This then helps determine appropriateness and extent of surgical excision. Persistent areas with loss of contrast enhancement on repeat imaging after debridement have been associated with worse outcomes [32].

Despite its usefulness, radiographic imaging will only indicate the extent of disease but cannot identify the causative etiology. Therefore, definitive diagnosis based on examination of tissue culture and pathology is required to guide the need and type of systemic antifungal therapy. Evaluation by an ENT specialist when IFS is suspected should be considered a surgical emergency, given the potential for rapid disease progression. Specifically, nasal endoscopy with biopsy is essential in the workup and management of these patients. Examination can be directed by radiographic findings toward the foci of greatest disease burden. Macroscopic findings of ischemic or necrotic tissue on nasal endoscopy are suggestive for IFS. The middle turbinate was

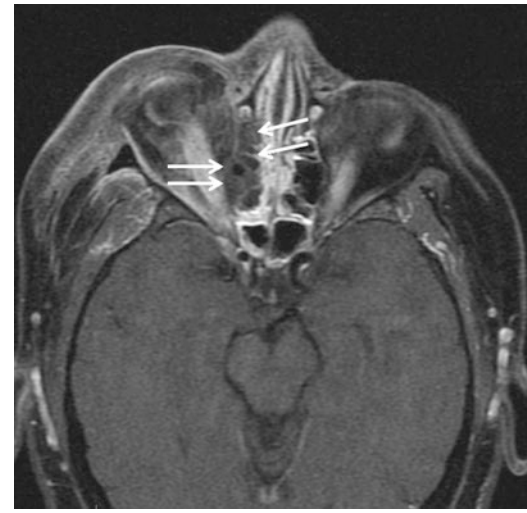

Fig. 15.2 MRI of the head of the patient in Fig. 15.1. There is hypodense material within the right nasal passage concerning for necrotic tissue. There is destruction of the medial wall of the right orbit

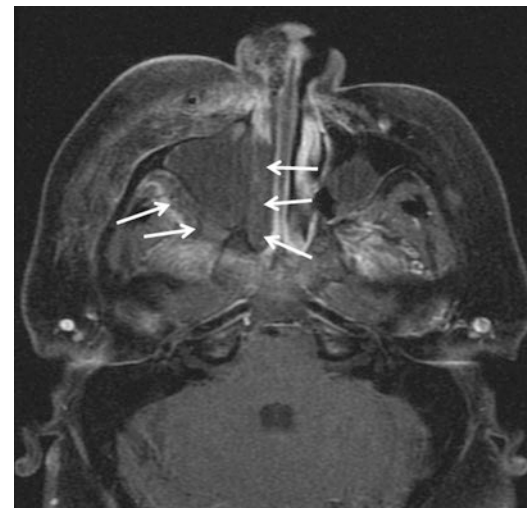

Fig. 15.3 MRI of the head with contrast of the patient in Fig. 15.1. There is a large hypodense mass within the right maxillary sinus. The loss of contrast enhancement in the posterior right maxillary sinus as well as nasal cavity is highly suggestive of tissue necrosis, suggesting an angioinvasive infection

the most common site of abnormality in over two-thirds of cases [34]. After samples are collected for further analysis, local debridement of necrotic tissue can be done.

Tissue obtained from biopsy of these areas should be sent for rapid pathology review by frozen section, and for culture. Samples should be of adequate amount to allow such evaluation and should be placed in saline for frozen section (also in saline or sterile cup for culture). Formalin-fixed samples should also be sent for permanent sections. Frozen section techniques for tissue can be done quicker than conventional methods [35] to help facilitate early diagnosis by identifying the presence of invading fungal hyphae in the sample. Small size case series indicate that this approach generally has a sensitivity of 60–80% and a specificity approaching 100% [34, 36]. Our own institutional experience with frozen section is excellent with 26 out of 27 cases showing evidence of IFS (>96% sensitivity) [1]. Beyond the fresh frozen section, histopathology techniques include fixation and processing with special staining such as Gomori methenamine silver (GMS), though they take longer than a day. Occasionally, characteristic fungal morphologies are distorted during the fixation process which may make identification of fungal more challenging. However important clues for organism identification can be found, specifically if there is evidence of perivascular or perineural invasion [37]. Samples sent for microbiology should not be swabs but should be tissue biopsies, placed in a sterile cup or saline and rapidly delivered to the microbiology laboratory. The microbiology laboratory should be alerted not to grind all the tissue prior to plating, as grinding can decrease the chance of growing molds. Traditional identification of fungal organisms comes from microscopic examination of growth from fungal cultures.

Laboratory Testing

Cultures remain the gold standard for confirming fungal growth and identification. However, the utility of cultures in early diagnosis remains limited as molds grow slowly or not at all [29], even when invasive tissue disease is seen on biopsy [38]. Given these limitations in pathological and microbial identification of fungi, there is an urgent need for non-culture-based diagnostics that can be done on a timely basis and can be used to supplement other clinical evidence to diagnose specific fungal infections.

A number of commercially available laboratory tests for fungal biomarkers could help as adjunct diagnostics in cases of possible IFS, though data on their performance remain limited. Many yeasts and molds have (1-3)-β-D-glucan as a component of their fungal cell wall which can be detected in serum. This test has shown utility in detecting invasive yeast and mold infections (although not mucormycosis) with an estimated sensitivity of 76.8% and specificity of 85.3% [39, 40]. There are limited data to suggest that trends in (1-3)-β-D-glucan can be used for evaluating response to therapy [41]. False positive (1-3)-β-D-glucan tests have been associated with factors that include blood transfusions, gauzes containing glucan, and some antibiotic suspensions.

Galactomannan is another fungal cell wall component found in hyalohyphomycetes, including *Aspergillus* species, also detected in serum. Like the (1-3)-β-D-glucan assay, a negative result does not rule out disease, especially in patients who are already receiving mold-active antifungals [42]. Galactomannan is a useful adjunct diagnostic for invasive aspergillosis but does not detect *Mucorales*. Choi et al. identified a sensitivity of 91.3% and specificity of 71.7% [43], though other studies note poorer results, ranging from 20% to 60% sensitivity and specificity [6, 44]. False positives can occur in the presence of other, usually non-pathologic, fungi such as *Penicillium* and *Paecilomyces* species.

Additional assays are available including quantitative, qualitative, and real-time PCR. PCR testing has been conducted on biopsied tissue as well as other sources including bronchoalveolar lavage fluid [45], serum [46], and even prior tissue samples that have been formalin-fixed and embedded in paraffin [47, 48]. Molecular testing in tissue via PCR, immunochemistry, and in situ hybridization has the advantage of assessing broadly for specific genera or could utilize specific primers or probes to detect individual

species [47]. Limitations to these methods include variable sensitivities, ranging from 60% to 90%, and a lack of standardization in primers, reagents, and overall methodology. Nevertheless, methods of molecular testing of fungi in tissue are promising and deserve further study.

Management

Not surprisingly, there are no randomized studies for the management of IFS in view of the rarity of the condition, the heterogeneity of afflicted hosts, site and degree of sinus involvement, offending fungi, comorbidities, and multiple concurrent surgical and medical interventions. The literature reflects single-institution retrospective experiences that encompass a limited number of patients that have significant variability in their presentation and prognostic factors. Therefore, such literature needs to be viewed with caution in light of significant publication and reporting biases. Nevertheless, surgical debridement continues to be regarded as an important part in the management of IFS as a part of the standard of care [49]. The scope of surgery can be variable, ranging from attempts at local resection all the way to radical resection. Endoscopic and open surgery have been compared, and given the complexity and sequelae of open surgery, the endoscopic approach is preferred in patients with early, limited disease or with significant medical comorbidities [34, 50].

Earlier studies suggested reserving open surgery for extensive disease, particularly with the involvement of the CNS or orbits [50, 51]. Surgeries in such cases have included maxillectomy, orbital exenteration, and/or craniofacial resection. However, more recent data suggest that "radical" surgeries did not result in any statistically significant improvement in survival, especially in patients with limited life expectancy [1, 5, 49]. Moreover, surgical resection of disease in such cases may be impractical when considering the morbidity and mortality of such extensive surgery, the underlying cytopenias that are often present, and the post-surgical complications that will arise. However, debridement of necrotic tissue may be important therapeutically in rapidly progressive IFS due to mucormycosis, particularly in diabetic patients where chance of survival is good. Surgical resection (beyond biopsy for diagnosis and minor debridement of necrotic tissue) is usually not necessary in invasive aspergillosis in diabetic or other minimally immunocompromised patients. The pace of aspergillosis is slower than in mucormycosis and these cases usually respond to antifungal therapy. As mortality from IFS in severely immunocompromised patients is still very high despite surgical intervention, a careful assessment of the risks and benefits of surgery should always be done.

Medical treatment of IFS focuses on addressing the active infectious process while simultaneously reversing the underlying immunosuppression, if possible. Selection of antifungals should be heavily influenced by local epidemiology with consideration for pharmacodynamics and adverse reactions [52]. For breakthrough cases on mold-active prophylaxis, changing class and initiation of broad-spectrum amphotericin B-based therapy, pending identification of the offending fungus seems prudent. Due to nephrotoxicity of amphotericin B-deoxycholate, liposomal amphotericin is preferred, at a dose of 5 mg/kg/day. Higher dosages of liposomal amphotericin have been studied prospectively at doses of 10 mg/kg/day [53] in patients with mucormycosis, including patients with IFS. No improvements in survival at 12 weeks were detected; on the other hand, high dose liposomal amphotericin was associated with increased frequency of adverse reactions especially renal injury and electrolyte derangements.

Triazole antifungals are a class of antifungal agents that deplete ergosterol from the fungal cell membrane. With their availability in both IV and PO formulations, they have an important role in bridging the initial management of IFS to long-term treatment. When dealing with invasive mold infections, the triazoles voriconazole, posaconazole, and isavuconazole/isavuconium sulfate offer good activity against many implicated organisms. Voriconazole has activity against both *Aspergillus* and *Fusarium* species but exhibits no activity against *Mucorales* [54]. The other new triazoles, posaconazole and isavuconazole, do have activity against both hyalohyphomycetes and *Mucorales* and are better empiric treatment options in IFS when no causative organism is

successfully identified [55]. Triazoles are known to have a significant number of drug-drug interactions due to their inhibition of the cytochrome P450 system, and in turn can have their pharmacokinetics altered by the presence of other drugs that induce the P450 system [56]. This can be particularly challenging in transplant recipients taking immunosuppressive agents and HIV patients on therapy with anti-retrovirals. It is important to develop a closely coordinated, multidisciplinary and individualized therapy tailored to patient circumstances [57].

Combination therapy, typically of liposomal amphotericin with another antifungal class, has been reported in the literature with varying success [1, 6]. While ineffective as monotherapy, an agent such as an echinocandin or terbinafine can improve outcomes when given as part of combination therapy [58–60]. Successful usage of local, retrobulbar injections of antifungals in selected cases of invasive sino-orbital infections in patients unable to tolerate intravenous amphotericin or as an adjunct to treatment of systemic amphotericin has been reported in small series [61–63].

It should be stressed that there are no clear definitions of antifungal breakpoints obtained in vitro for the fungi causing IFS. In vitro susceptibility breakpoints are not based on clinical data, but rather on pharmacokinetic and epidemiological concepts [64]. Care must be taken as results indicating in vitro susceptibility may not necessarily correlate with clinical success [65].

Adjunctive Therapies

Several strategies have been utilized to correct underlying the neutropenia found in many IFS patients. Granulocyte infusion has been used over several decades; however, results are drawn from experiences with small numbers of patients and have mixed outcomes [66]. In addition to having an unclear benefit, there are risks with therapy which include transfusion reactions, leuko-agglutination reaction, or even pulmonary edema. Therefore, no firm recommendations exist regarding use of granulocyte infusions but they may have a role in selected patients who fail to respond to initial surgical and anti-fungal interventions. Usage of granulocyte-stimulating factors to both resolve neutropenia and enhance neutrophil phagocytic activity against fungi has been shown to be successful in anecdotal reports [67, 68].

Use of hyperbaric oxygen therapy has been reported in small numbers with some degree of success. Hyperbaric oxygen therapy increases oxygen tension in tissues, leading to an increase in generation of oxygen-free radicals that can have fungicidal activity [69]. In vitro studies show inhibition of fungal growth in both aspergillosis and mucormycosis [70–72]. Limited data suggest that short-term survival is improved [71] though the effect on long-term outcomes is still unclear. No benefit has been found in cases of disseminated invasive fungal disease, suggesting that its use should be limited to only local infections. Aside from pneumothorax, there are few contraindications or complications from hyperbaric oxygen therapy and it offers a relatively low-risk adjunct to management with suggestion for improved outcomes. However, its use is limited to institutions with the facilities to administer it.

Reversal of Underlying Immunosuppression

As most IFS infections are associated with immunocompromised hosts, controlling the underlying condition to help restore normal immune function should be an important part of the treatment along with concomitant medical and surgical management. Patients with HIV/AIDS can be started on anti-retroviral therapy. Patients with immunosuppression from corticosteroids can be tapered off or transitioned to alternative non-steroidal therapy.

Patients with uncontrolled diabetes and/or diabetic ketoacidosis are a challenging population as there are a number of physiologic derangements at work that facilitate IFS. Aggressive glycemic control is an important part of treatment. Reversal of acidemia by the administration of sodium bicarbonate has been shown to partially block the ability of *Rhizopus oryzae* to invade endothelial cells, as well as to restore host iron chelation and neutrophil function. Sodium bicarbonate use is a treatment consideration even

in the absence of acidemia [24]. Treatment with iron chelators is a potential adjunctive therapy; however, caution is needed as some agents such as deferoxamine act as a siderophore for species of *Mucorales* and are historical causes of IFS [73–75]. New iron chelators such as deferasirox have no siderophore capability, but have not shown any benefit from their use as initial therapy for mucormycosis in hematological malignancy [76]. They still remain a potential therapy in other at-risk populations, especially in patients with uncontrolled diabetes and/or diabetic ketoacidosis.

Management of hematological malignancy patients with invasive fungal infections requires complex decision-making. It is common for the underlying malignancy to cause neutropenia and the production of non-functional phagocytic cells. Yet the treatment of leukemia and lymphoma by means of cytotoxic chemotherapy can have just as great a suppression on overall immune status. The challenge therein lies in determining the best time to re-initiate chemotherapy treatment. On one hand, some practitioners opt to delay or even postpone antineoplastic treatment to allow time for treating and controlling the infection, at the risk of having the malignancy becoming ultimately less amenable to chemotherapy. On the other hand, some proceed with early chemotherapy at the same time IFS is treated, in the hope of achieving cancer into remission sooner, allowing for earlier immune reconstitution and more effective clearance of infection. This carries the risk of having IFS worsen in the setting of heightened immunosuppression. In a case-control study, 57% of leukemia patients with probable or proven invasive fungal disease had a delay in chemotherapy with a median of 11 days [8]. Additionally, 28% of them had a change in their chemotherapy, either an earlier switch to maintenance, transition to palliative treatment or reduction in dose of chemotherapy. Decisions regarding timing of subsequent immune suppression in the setting of IFS should be made on a case-by-case basis.

Treatment Duration and Follow-Up

There is no fixed duration of treatment for IFS as therapy is dependent upon the severity and extent of IFS, the causative fungus, and the magnitude of clinical improvement on antifungal agents while reversing the underlying immunosuppression. In immunosuppressed patients with IFS due to *Mucorales*, clinicians should be conservative with a high threshold for discontinuing antifungal therapy as relapses of IFS off therapy often occur [77]. Similarly, there are no firm recommendations for frequency of follow-up or repeat studies. At a minimum, patients should have resolution of radiographic evidence of disease. Treatment is typically given for months, with initial intravenous therapy for many weeks followed by months of oral antifungal therapy.

We recommend routine outpatient follow-up on a monthly basis in patients undergoing treatment for IFS. An infectious disease specialist should be involved very early in the course of the disease and follow the patient closely, in conjunction with their other specialists. Close follow-up with otolaryngology initially is also helpful to monitor the endoscopic appearance of the nasal cavity and sinuses. Special attention is needed for monitoring changes in patient symptoms and tolerability of long-term antifungal therapy. If there are any concern signs or symptoms observed, repeat endoscopy should be performed by the otolaryngologist. Monitoring of drug serum levels in patients on chronic azole therapy, especially voriconazole, can help monitor compliance and adequacy of therapy. Although there are no data specifically for *Aspergillus* sinusitis, a baseline titer and monitoring of *Aspergillus* galactomannan trends can be useful to monitor therapeutic response [78]. If therapy is discontinued, patients should continue to have routine follow-up for monitoring for relapsed infection. Figure 15.4 depicts an algorithmic approach to management of IFS in immunocompromised hosts.

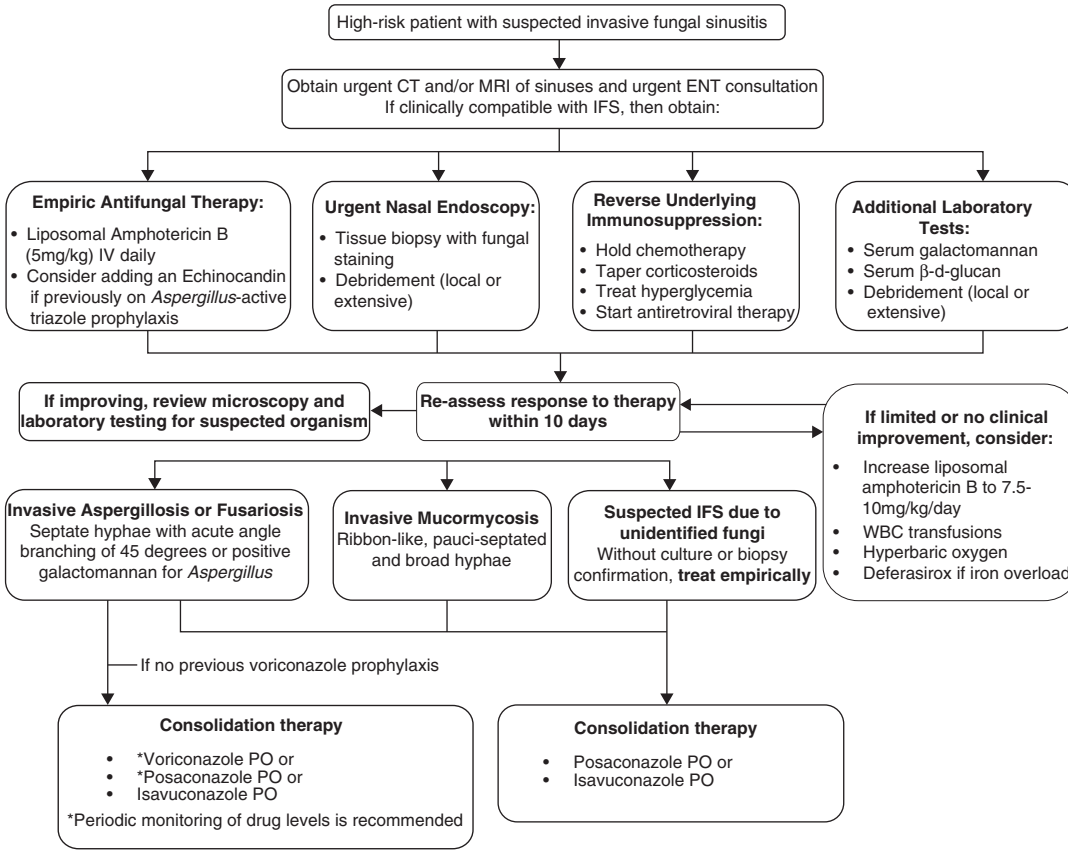

Fig. 15.4 Algorithm for evaluating and managing invasive fungal sinusitis

Outcomes

Despite the advances made in treatment options in antifungal agents and testing, long-term outcomes for patients with IFS still remain poor with 1-year mortality of approximately 50% [5]. This is particularly marked in patients with hematological malignancies as they often require further chemotherapy for refractory underlying disease [1]. Several studies have assessed negative prognostic factors in IFS patients. Factors associated with poor survival were leukemia, prolonged periods of neutropenia ≥10 days, advanced age, concomitant renal disease, as well as delays in treatment [1, 5]. Area and extent of IFS has also been demonstrated to have higher mortality [79]. For example, patients with IFS in only the lateral nasal wall had a mortality of 33%, but this figure climbed to 67% with involvement of the nasal septum and 100% when extending beyond the nasal cavity [80].

On the other hand, surgical or endoscopic debridement has been consistently shown to be a positive prognostic factor for patients with IFS [5, 49, 81] as it is associated with an earlier diagnosis and therefore earlier treatment for the disease [82]. It should be stressed that medical and surgical treatments are performed to manage the disease in the short term while attempting to reverse the underlying immunosuppression in patients who are immunocompromised.

Conclusion

Despite advances in medical and surgical therapy, IFS remains an opportunistic infection with a high morbidity and mortality. The disease most commonly occurs in patients with hematological

malignancies, receiving chronic corticosteroids or other immunosuppressive therapies, or uncontrolled diabetes mellitus. Presenting symptoms and clinical signs lack sensitivity and specificity for IFS. Early CT and endoscopic-based diagnosis along with combined surgical and medical treatment are important for improved survival. To this end, physicians should have a high index of suspicion for IFS and low threshold for consultation to ENT for additional evaluation. During this period, the plan for reversal of immunosuppression should be discussed. Treatment plans should be multidisciplinary and personalized. Patients should be given routine follow-up to monitor response to therapy and to re-evaluate for disease progression as needed.

References

1. Davoudi S, Kumar VA, Jiang Y, Kupferman M, Kontoyiannis DP. Invasive mould sinusitis in patients with haematological malignancies: a 10 year single-centre study. J Antimicrob Chemother. 2015;70(10):2899–905.
2. Chang C, Gershwin ME, Thompson GR. Fungal disease of the nose and sinuses: an updated overview. Curr Allergy Asthma Rep. 2013;13(2):152–61.
3. Thompson GR, Patterson TF. Fungal disease of the nose and paranasal sinuses. J Allergy Clin Immunol. 2012;129(2):321–6.
4. Humphrey JM, Walsh TJ, Gulick RM. Invasive Aspergillus sinusitis in human immunodeficiency virus infection: case report and review of the literature. Open Forum Infect Dis. 2016;3(3):ofw135.
5. Turner JH, Soudry E, Nayak JV, Hwang PH. Survival outcomes in acute invasive fungal sinusitis: a systematic review and quantitative synthesis of published evidence. Laryngoscope. 2013;123(5):1112–8.
6. Chen CY, Sheng WH, Cheng A, et al. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. BMC Infect Dis. 2011;11:250.
7. Parikh SL, Venkatraman G, JM DG. Invasive fungal sinusitis: a 15-year review from a single institution. Am J Rhinol. 2004;18(2):75–81.
8. Even C, Bastuji-Garin S, Hicheri Y, et al. Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived fungal disease: a case-control study. Haematologica. 2011;96(2):337–41.
9. Patterson TF. Aspergillus species. In: Bennett JE, Dolin R, Martin J, editors. Principles and practice of infectious diseases, vol. 2. 8th ed. Philadelphia, PA: Elsevier; 2015. p. 2895–908.
10. Stevens DA, Moss RB, Kurup VP, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis-state of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis. 2003;37(Suppl 3):S225–64.
11. Dagenais TR, Keller NP. Pathogenesis of Aspergillus fumigatus in invasive aspergillosis. Clin Microbiol Rev. 2009;22(3):447–65.
12. Michael RC, Michael JS, Ashbee RH, Mathews MS. Mycological profile of fungal sinusitis: an audit of specimens over a 7-year period in a tertiary care hospital in Tamil Nadu. Indian J Pathol Microbiol. 2008;51(4):493–6.
13. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis. 2005;191(8):1350–60.
14. Jain R, Singhal SK, Singla N, Punia RS, Chander J. Mycological profile and antifungal susceptibility of fungal isolates from clinically suspected cases of fungal rhinosinusitis in a tertiary care hospital in North India. Mycopathologia. 2015;180(1-2):51–9.
15. Fernandez IJ, Stanzani M, Tolomelli G, et al. Sinonasal risk factors for the development of invasive fungal sinusitis in hematological patients: are they important? Allergy Rhinol (Providence). 2011;2(1):6–11.
16. Botterel F, Gross K, Ibrahim-Granet O, et al. Phagocytosis of Aspergillus fumigatus conidia by primary nasal epithelial cells in vitro. BMC Microbiol. 2008;8:97.
17. Zhao K, Dalton P. The way the wind blows: implications of modeling nasal airflow. Curr Allergy Asthma Rep. 2007;7(2):117–25.
18. Brook I. The role of bacterial interference in otitis, sinusitis and tonsillitis. Otolaryngol Head Neck Surg. 2005;133(1):139–46.
19. Azulay-Abulafia L, Sousa MA, Pussanti A, Coimbra DD, Vega H, Bernardes Filho F. Invasive aspergillosis in a user of inhaled cocaine: rhinosinusitis with bone and cartilage destruction. Rev Soc Bras Med Trop. 2014;47(4):533–6.
20. Kaya S, Yavuz I, Cobanoğlu U, Ural A, Yılmaz G, Köksal I. Fatal sino-orbital aspergillosis in an immunocompetent case. Mikrobiyol Bul. 2011;45(3):546–52.
21. Pushker N, Meel R, Kashyap S, Bajaj MS, Sen S. Invasive aspergillosis of orbit in immunocompetent patients: treatment and outcome. Ophthalmology. 2011;118(9):1886–91.
22. Kontoyiannis DP, Lewis RE. Agents of mucormycosis and entomophthoramycosis. In: Bennett JE, Dolin R, Blaser MJ, editors. Principles and practice of infectious diseases, vol. 2. 8th ed. Philadelphia, PA: Elsevier; 2014. p. 2909–19.
23. Liu M, Spellberg B, Phan QT, et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest. 2010;120(6):1914–24.
24. Gebremariam T, Lin L, Liu M, et al. Bicarbonate correction of ketoacidosis alters host-pathogen interactions and alleviates mucormycosis. J Clin Invest. 2016;126(6):2280–94.

25. Howard DH. Acquisition, transport, and storage of iron by pathogenic fungi. Clin Microbiol Rev. 1999;12(3):394–404.
26. Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability. Diabetes. 1982;31(12):1109–14.
27. Piromchai P, Thanaviratananich S. Invasive fungal rhinosinusitis versus bacterial rhinosinusitis with orbital complications: a case-control study. ScientificWorldJournal. 2013;2013:453297.
28. Iwen PC, Rupp ME, Hinrichs SH. Invasive mold sinusitis: 17 cases in immunocompromised patients and review of the literature. Clin Infect Dis. 1997;24(6):1178–84.
29. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41(5):634–53.
30. del Giudice P, Moulonguet L, Ranchin B, Abraham B, Sellier P. Cutaneous aspergillus invasion from sinusitis. Clin Infect Dis. 1999;29(3):690–1.
31. DelGaudio JM, Swain RE, Kingdom TT, Muller S, Hudgins PA. Computed tomographic findings in patients with invasive fungal sinusitis. Arch Otolaryngol Head Neck Surg. 2003;129(2):236–40.
32. Kim JH, Kang BC, Lee JH, Jang YJ, Lee BJ, Chung YS. The prognostic value of gadolinium-enhanced magnetic resonance imaging in acute invasive fungal rhinosinusitis. J Infect. 2015;70(1):88–95.
33. Monteagudo M, Palazón-García E, Lozano-Setién E, García-García J. The 'black turbinate sign' in a case of rhinocerebral mucormycosis. Rev Neurol. 2014;58(5):234–5.
34. Gillespie MB, O'Malley BW, Francis HW. An approach to fulminant invasive fungal rhinosinusitis in the immunocompromised host. Arch Otolaryngol Head Neck Surg. 1998;124(5):520–6.
35. Taxy JB, El-Zayaty S, Langerman A. Acute fungal sinusitis: natural history and the role of frozen section. Am J Clin Pathol. 2009;132(1):86–93.
36. Zimmermann N, Hagen MC, Schrager JJ, Hebbeler-Clark RS, Masineni S. Utility of frozen section analysis for fungal organisms in soft tissue wound debridement margin determination. Diagn Pathol. 2015;10:188.
37. Safdar A, Dommers MP, Talwani R, Thompson CR. Intracranial perineural extension of invasive mycosis: a novel mechanism of disease propagation by Aspergillus fumigatus. Clin Infect Dis. 2002;35(5):e50–3.
38. Tarrand JJ, Lichterfeld M, Warraich I, et al. Diagnosis of invasive septate mold infections. A correlation of microbiological culture and histologic or cytologic examination. Am J Clin Pathol. 2003;119(6):854–8.
39. Obayashi T, Yoshida M, Mori T, et al. Plasma (1-->3)-beta-D-glucan measurement in diagnosis of invasive deep mycosis and fungal febrile episodes. Lancet. 1995;345(8941):17–20.
40. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. β-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis. 2011;52(6):750–70.
41. Nakanishi W, Fujishiro Y, Nishimura S, Fukaya T. Clinical significance of (1-->3)-beta-d-glucan in a patient with invasive sino-orbital aspergillosis. Auris Nasus Larynx. 2009;36(2):224–7.
42. Marr KA, Laverdiere M, Gugel A, Leisenring W. Antifungal therapy decreases sensitivity of the Aspergillus galactomannan enzyme immunoassay. Clin Infect Dis. 2005;40(12):1762–9.
43. Choi SH, Kang ES, Eo H, et al. Aspergillus galactomannan antigen assay and invasive aspergillosis in pediatric cancer patients and hematopoietic stem cell transplant recipients. Pediatr Blood Cancer. 2013;60(2):316–22.
44. Kostamo K, Richardson M, Eerola E, et al. Negative impact of Aspergillus galactomannan and DNA detection in the diagnosis of fungal rhinosinusitis. J Med Microbiol. 2007;56(Pt 10):1322–7.
45. Torelli R, Sanguinetti M, Moody A, et al. Diagnosis of invasive aspergillosis by a commercial real-time PCR assay for Aspergillus DNA in bronchoalveolar lavage fluid samples from high-risk patients compared to a galactomannan enzyme immunoassay. J Clin Microbiol. 2011;49(12):4273–8.
46. Millon L, Herbrecht R, Grenouillet F, et al. Early diagnosis and monitoring of mucormycosis by detection of circulating DNA in serum: retrospective analysis of 44 cases collected through the French Surveillance Network of Invasive Fungal Infections (RESSIF). Clin Microbiol Infect. 2016;22(9):810.e1–8.
47. Salehi E, Hedayati MT, Zoll J, et al. Discrimination of aspergillosis, mucormycosis, fusariosis, and scedosporiosis in formalin-fixed paraffin-embedded tissue specimens by use of multiple real-time quantitative PCR assays. J Clin Microbiol. 2016;54(11):2798–803.
48. Bialek R, Konrad F, Kern J, et al. PCR based identification and discrimination of agents of mucormycosis and aspergillosis in paraffin wax embedded tissue. J Clin Pathol. 2005;58(11):1180–4.
49. Zuniga MG, Turner JH. Treatment outcomes in acute invasive fungal rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2014;22(3):242–8.
50. Kasapoglu F, Coskun H, Ozmen OA, Akalin H, Ener B. Acute invasive fungal rhinosinusitis: evaluation of 26 patients treated with endonasal or open surgical procedures. Otolaryngol Head Neck Surg. 2010;143(5):614–20.
51. Ferry AP, Abedi S. Diagnosis and management of rhino-orbitocerebral mucormycosis (phycomycosis). A report of 16 personally observed cases. Ophthalmology. 1983;90(9):1096–104.
52. Kontoyiannis DP, Lewis RE. Treatment principles for the management of mold infections. Cold Spring Harb Perspect Med. 2014;5(4)
53. Lanternier F, Poiree S, Elie C, et al. Prospective pilot study of high-dose (10 mg/kg/day) liposomal

amphotericin B (L-AMB) for the initial treatment of mucormycosis. J Antimicrob Chemother. 2015;70(11):3116–23.
54. Dannaoui E, Meletiadis J, Mouton JW, Meis JF, Verweij PE, Network E. In vitro susceptibilities of zygomycetes to conventional and new antifungals. J Antimicrob Chemother. 2003;51(1):45–52.
55. Almyroudis NG, Sutton DA, Fothergill AW, Rinaldi MG, Kusne S. In vitro susceptibilities of 217 clinical isolates of zygomycetes to conventional and new antifungal agents. Antimicrob Agents Chemother. 2007;51(7):2587–90.
56. Nagappan V, Deresinski S. Reviews of anti-infective agents: posaconazole: a broad-spectrum triazole antifungal agent. Clin Infect Dis. 2007;45(12):1610–7.
57. Leventakos K, Lewis RE, Kontoyiannis DP. Fungal infections in leukemia patients: how do we prevent and treat them? Clin Infect Dis. 2010;50(3):405–15.
58. Lewis RE, Lortholary O, Spellberg B, Roilides E, Kontoyiannis DP, Walsh TJ. How does antifungal pharmacology differ for mucormycosis versus aspergillosis? Clin Infect Dis. 2012;54(Suppl 1):S67–72.
59. Ibrahim AS, Gebremariam T, Luo G, et al. Combination therapy of murine mucormycosis or aspergillosis with iron chelation, polyenes, and echinocandins. Antimicrob Agents Chemother. 2011;55(4):1768–70.
60. Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008;47(3):364–71.
61. Colon-Acevedo B, Kumar J, Richard MJ, Woodward JA. The role of adjunctive therapies in the management of invasive sino-orbital infection. Ophthal Plast Reconstr Surg. 2015;31(5):401–5.
62. Mainville N, Jordan DR. Orbital apergillosis treated with retrobulbar amphotericin B. Orbit. 2012;31(1):15–7.
63. Wakabayashi T, Oda H, Kinoshita N, Ogasawara A, Fujishiro Y, Kawanabe W. Retrobulbar amphotericin B injections for treatment of invasive sino-orbital aspergillosis. Jpn J Ophthalmol. 2007;51(4):309–11.
64. Elefanti A, Mouton JW, Verweij PE, Zerva L, Meletiadis J. Susceptibility breakpoints for amphotericin B and Aspergillus species in an in vitro pharmacokinetic-pharmacodynamic model simulating free-drug concentrations in human serum. Antimicrob Agents Chemother. 2014;58(4):2356–62.
65. Heo ST, Tatara AM, Jiménez-Ortigosa C, et al. Changes in in vitro susceptibility patterns of Aspergillus to triazoles and correlation with aspergillosis outcome in a tertiary care cancer center (1999-2015). Clin Infect Dis. 2017;65:216.
66. Carter KB, Loehrl TA, Poetker DM. Granulocyte transfusions in fulminant invasive fungal sinusitis. Am J Otolaryngol. 2012;33(6):663–6.
67. Casadevall A, Pirofski LA. Adjunctive immune therapy for fungal infections. Clin Infect Dis. 2001;33(7):1048–56.
68. Liles WC, Huang JE, van Burik JA, Bowden RA, Dale DC. Granulocyte colony-stimulating factor administered in vivo augments neutrophil-mediated activity against opportunistic fungal pathogens. J Infect Dis. 1997;175(4):1012–5.
69. Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. QJM. 2004;97(7):385–95.
70. John BV, Chamilos G, Kontoyiannis DP. Hyperbaric oxygen as an adjunctive treatment for zygomycosis. Clin Microbiol Infect. 2005;11(7):515–7.
71. García-Covarrubias L, Barratt DM, Bartlett R, Metzinger S, Van Meter K. Invasive aspergillosis treated with adjunctive hyperbaric oxygenation: a retrospective clinical series at a single institution. South Med J. 2002;95(4):450–6.
72. Segal E, Menhusen MJ, Shawn S. Hyperbaric oxygen in the treatment of invasive fungal infections: a single-center experience. Isr Med Assoc J. 2007;9(5):355–7.
73. Ibrahim AS, Spellberg B, Edwards J. Iron acquisition: a novel perspective on mucormycosis pathogenesis and treatment. Curr Opin Infect Dis. 2008;21(6):620–5.
74. Boelaert JR, de Locht M, Van Cutsem J, et al. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection. In vitro and in vivo animal studies. J Clin Invest. 1993;91(5):1979–86.
75. Windus DW, Stokes TJ, Julian BA, Fenves AZ. Fatal Rhizopus infections in hemodialysis patients receiving deferoxamine. Ann Intern Med. 1987;107(5):678–80.
76. Spellberg B, Ibrahim AS, Chin-Hong PV, et al. The Deferasirox-AmBisome therapy for mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial. J Antimicrob Chemother. 2012;67(3):715–22.
77. Kontoyiannis DP, Lewis RE. How I treat mucormycosis. Blood. 2011;118(5):1216–24.
78. Kovanda LL, Kolamunnage-Dona R, Neely M, Maertens J, Lee M, Hope WW. Pharmacodynamics of isavuconazole for invasive mold disease: role of galactomannan for real-time monitoring of therapeutic response. Clin Infect Dis. 2017;64(11):1557–63.
79. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis. 2001;32(3):358–66.
80. Valera FC, do Lago T, Tamashiro E, Yassuda CC, Silveira F, Anselmo-Lima WT. Prognosis of acute invasive fungal rhinosinusitis related to underlying disease. Int J Infect Dis. 2011;15(12):e841–4.
81. Hachem RY, Boktour MR, Hanna HA, et al. Sinus surgery combined with antifungal therapy is effective in the treatment of invasive Aspergillus sinusitis in neutropenic patients with cancer. Infection. 2008;36(6):539–42.
82. DelGaudio JM, Clemson LA. An early detection protocol for invasive fungal sinusitis in neutropenic patients successfully reduces extent of disease at presentation and long term morbidity. Laryngoscope. 2009;119(1):180–3.