Current Infectious Disease Reports (2019) 21: 53
https://doi.org/10.1007/s11908-019-0707-4

TRANSPLANT AND ONCOLOGY (M ISON, N THEODOROPOULOS AND S PERGAM, SECTION EDITORS)

Diagnosis and Treatment of Acute Invasive Fungal Sinusitis in Cancer and Transplant Patients

Monica Fung[1] · Jennifer Babik[1] · Ian M. Humphreys[2] · Greg E. Davis[2]

Published online: 26 November 2019

Abstract

Purpose of Review Modern advances in oncologic and end-organ therapies have led to an increase in immunocompromised patients and a corresponding rise in acute invasive fungal sinusitis (AIFS). Here, we present a comprehensive medical and surgical approach to the diagnosis and management of immunocompromised cancer and transplant patients with AIFS.

Recent Findings *Aspergillus* and *Mucorales* are the most common fungi to cause AIFS, though atypical fungal pathogens have been implicated particularly among patients on azole prophylaxis. Symptoms present in the majority of AIFS cases include fever, nasal congestion, and facial swelling. Nasal endoscopy and radiology are adjuncts to clinical exam with the gold standard diagnostic test still being histopathology, though molecular testing such as panfungal PCR is playing a larger role. The treatment of AIFS requires surgery, antifungal therapy, and reversal of immunosuppression. We recommend initiation of liposomal amphotericin B as an empiric therapy for AIFS, transitioned to targeted therapy when/if a fungal pathogen is identified. Goals of surgery include diagnostic sampling and debridement of necrotic tissue. Equally, if not more important, is reversal of underlying immune suppression. Immune-stimulating therapies hold promise for reducing mortality, but require additional study.

Summary Despite improvements in medical and surgical management of AIFS, mortality continues to approach 50%. Early diagnosis of this disease entity followed by aggressive surgical and medical management are important, including reversal of the underlying immunosuppression.

Keywords Acute invasive fungal sinusitis · Transplant · Immunocompromise

Introduction

With advances in oncologic and end-organ disease treatment, there has been a corresponding rise in the number of immunocompromised patients [1, 2]. This has led to an increase in invasive fungal infections, of which acute invasive fungal sinusitis (AIFS) is a particularly severe form [3]. Optimal management requires a multidisciplinary approach including both medical and surgical therapies. Despite high morbidity and mortality associated with AIFS [4, 5], there remains no standardized protocol for managing this disorder. Here, we present a comprehensive medical and surgical approach to the diagnosis and management of AIFS in immunocompromised patients focusing on cancer and transplant patients.

This article is part of the Topical Collection on *Transplant and Oncology*

✉ Monica Fung
Monica.Fung@ucsf.edu

Jennifer Babik
jennifer.babik@ucsf.edu

Ian M. Humphreys
ihumphre@uw.edu

Greg E. Davis
gedavis@uw.edu

[1] Division of Infectious Diseases, University of California San Francisco, San Francisco, CA 94143, USA

[2] Department of Otolaryngology, University of Washington, Seattle, WA, USA

Definition of AIFS

Fungal sinusitis is categorized into non-invasive and invasive forms depending on the presence of fungal invasion into the submucosa and adjacent vasculature [3, 6]. Non-invasive forms include allergic fungal sinusitis and sinus mycetoma (fungal ball). Invasive fungal sinusitis is further subcategorized into chronic and acute forms, both of which occur predominantly in patients with some degree of immunocompromise.

Chronic invasive fungal sinusitis occurs over the course of months to decades, most often in diabetics or patients on chronic low-dose corticosteroid therapy. These patients often present with low-grade, non-acute symptoms such as facial pain, epistaxis, or nasal congestion with findings of nasal mucosal ulceration and necrosis on examination.

In contrast, AIFS progresses rapidly with a typical time course of less than 1 month and occurs in patients with more severe immunosuppression including hematologic malignancies, recent chemotherapy, hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), and those with poorly controlled diabetes. Presenting symptoms may include fever and often localize to the paranasal sinuses with nasal congestion, facial swelling, rhinorrhea, and facial pain. With more extensive disease, visual changes and cranial neuropathies can be present. Pathology demonstrates fungal submucosal invasion with associated necrosis of nasal mucosa and underlying bone. The mortality rate of AIFS is reported as high as 50–80% [4, 7, 8]. From here on out, we will focus our discussion on AIFS.

Epidemiology and Risk Factors

Patients with severe immunosuppression such as those with hematologic malignancies, HSCT, SOT, and poorly controlled diabetes account for the majority of cases of AIFS. In a meta-analysis of 52 publications including 802 patients with AIFS, diabetes was the most common predisposing condition, occurring in nearly half (47.8%) of patients. Others risk factors included hematologic malignancy (39.0%), corticosteroid use (27.6%), renal or liver failure (6.6%), SOT (6.3%), HIV/AIDS (2.3%), and autoimmune disease (1.2%) [4].

Among patients with hematologic malignancy, those at particular increased risk of AIFS are patients with active disease, either at onset or relapse, neutropenia, and HSCT [9]. While neutropenia with an absolute neutrophil count (ANC) < 500 is common among hematology malignancy patients with AIFS, a recent multi-institutional retrospective review of 114 AIFS patients found that 52% had an an ANC > 1000 at the time of AIFS diagnosis. Among SOT recipients with invasive mold infection, sinus involvement occurred most among renal (11%) and liver (3%) transplant recipients compared with thoracic transplant recipients (0%) [10].

Microbiology

The most commonly implicated fungal pathogens in AIFS are *Aspergillus* and *Mucorales* [5, 8, 9, 11]. Among hematologic malignancy patients, *Aspergillus* species tend to predominate with a prevalence up to 72%, whereas among patients with poorly controlled diabetes, the prevalence of mucormycosis has been reported up to 75% [5, 12]. Atypical fungal pathogens that are less commonly involved include *Fusarium*, *Scedosporium*, *Alternaria*, *Paecilomyces*, and *Scopulariopsis* species. It is important to note that prevalence of fungal pathogens varies by healthcare setting and geographic region depending on local epidemiology and antifungal prophylaxis use. Specifically, breakthrough AIFS among patients on azole prophylaxis is more concerning for infection due to *Mucorales* spp. and atypical fungal organisms [13, 14].

In a study comparing patients with *Aspergillus* versus mucormycosis AIFS, patients with mucormycosis had higher mortality (71%) compared with those with *Aspergillus* (29%) though this was notably not statistically significant [15]. In contrast, another recent study found that patients with AIFS caused by atypical fungi (e.g., non-*Aspergillus* or *Mucorales*) had significantly poorer survival at 1 month (HR 3.1, $p = 0.04$) [5].

Clinical Manifestations

As AIFS can present in a variety of patterns, it is important to have a high degree of clinical suspicion in patients from high-risk populations including those with neutropenic fever. Symptoms worrisome for AIFS are similar to those of commonly occurring conditions such as viral or bacterial sinusitis. However, the clinical context (e.g., immunocompromised host) raises the index of suspicion and thus consideration for AIFS.

Several studies have shown that patients with AIFS can present with a range of symptoms. Turner et al. found facial swelling, fever, nasal congestion, and eye pain occur in greater than 50% of patients [4]. Similarly, Wandell et al. reported facial pain, facial swelling, nasal congestion and fever to be the most common presenting signs and symptoms. Visual changes, proptosis, and extraocular muscle weakness are less common signs, but in these authors' experience, tend to manifest in more advanced disease [5].

The most common anatomic locations for AIFS to occur are the nasal cavity turbinates and paranasal sinuses. Overall, most cases occur in either the nasal cavity (e.g., septum and turbinates) or maxillary sinus. When disease extends beyond the sinuses, it can involve the orbit, cavernous sinus, pterygopalatine fossa, or intracranial space, each with its own anticipated sequelae. Most studies report the orbit as the most frequent site of disease extension beyond the sinuses. Therefore, special attention should be given to any

ophthalmologic symptoms, especially ophthalmoplegia that tends to be a harbinger of AIFS. Spread to the cavernous sinus and orbit can quickly progress to complications including orbital apex syndrome, superior orbital fissure syndrome, or cavernous sinus syndrome/thrombosis. Intracranial extension will present with altered mental status or cranial neuropathy based on the anatomic location of invasion.

Diagnosis

Physical Exam

Evaluation of a patient with suspected AIFS should first begin with a comprehensive head and neck exam with particular attention to the nasal, oral cavity (including teeth and palate), soft tissue, ophthalmologic, and cranial nerve assessments. The nasal and oral mucosa should be examined for signs of pallor or necrosis, the dentition should be assessed for mobility or hypesthesia, and the ophthalmologic exam should detail visual acuity, pupil symmetry, reactivity, gaze mobility, and health of the sclera and conjunctiva. A comprehensive cranial nerve exam should be carried out and any deficits or asymmetry noted. If there are abnormalities on any of these exam findings, or if suspicion of AIFS is high, immediate otolaryngology consultation is advised.

Nasal Endoscopy

Nasal endoscopy is a valuable tool in the assessment of AIFS. A detailed endoscopic exam without local anesthesia is critical and provides immediate information regarding the health of the mucosal surfaces within the nasal cavity. Signs of pallor or decreased sensation can be subtle clues that indicate early signs of AIFS, whereas frank necrosis is a late but typical finding. Importantly, when AIFS presents in the paranasal sinuses (without nasal cavity involvement), the nasal endoscopy may show normal healthy mucosa as the sinus proper may not be visualized; therefore, a negative nasal endoscopy does not preclude the diagnosis of AIFS. Given this limitation of nasal endoscopy, radiographic imaging is a complimentary and equally important diagnostic tool.

Radiology

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most frequently used forms of imaging for AIFS. Overall, CT is the most common and provides helpful, quick, non-invasive information regarding bone integrity around the sinuses, orbits, and skull base. If CT demonstrates bony erosion or evidence of soft tissue extension of paranasal sinus disease (Fig. 1), suspicion for AIFS must remain high. Additionally, fat stranding, loss of fat planes, and inflammatory changes extending beyond the bony boarders of the sinuses could indicated extension of AIFS beyond the sinuses (Fig. 2) [16].

Some authors have proposed MRI as an initial diagnostic tool for AIFS. However, access to MRI, length of image acquisition time, and cost can be limiting [17]. A recent study reported approximately 50% of AIFS patients had loss of contrast enhancement on MRI, which may be an early radiographic finding that further supports the need for surgical exploration. Additional data has demonstrated that patients have increased mortality after surgical debridement if they develop new lesions with loss of contrast enhancement (Fig. 3) [18]. If there is suspicion of intracranial or intraorbital involvement, CT and MRI are complementary and both studies should be considered.

Beyond dedicated imaging of the sinuses and brain, CT chest should be considered to assess for concurrent pulmonary infection, which may offer an additional site for diagnostic sampling. Pulmonary involvement occurs in the minority of patients with AIFS, but portends increased mortality [7, 19, 20].

Histopathology

The current gold standard for diagnosing AIFS is evidence of angioinvasion by hyphal elements on hematoxylin and eosin (H&E)–stained anatomic pathology specimens. In a review of 271 biopsies evaluated for AIFS [21], 41 were positive on permanent H&E staining. Of those 41 positive specimens, 34 were found positive on frozen H&E pathology, whereas 39 were positive on frozen periodic acid-Schiff stain frozen pathology (PASF-Fs). Thus, the addition of PASF improved sensitivity from 85 to 95%. Additional findings of tissue necrosis and branching patterns of the fungal organism are often commented on by pathologists familiar with the diagnosis. Intraoperatively, frozen section can support operative decision-making as well as confirm the presence of tissue invasion by fungal organisms, especially when frank necrosis is not present endoscopically. Gomori methenamine silver (GMS) stain is a useful tool in the histologic visualization of fungi as well, and can confirm the presence of fungal organisms seen within tissue on H&E stains.

Fungal Markers

The use of the serum *Aspergillus* galactomannan assay (GM) can be a helpful component in the diagnosis of invasive *Aspergillus* infections, although with imperfect sensitivity and specificity [22]. There are only a few small studies evaluating the use of serum GM in AIFS, where it was found to be < 50% sensitive for the diagnosis of *Aspergillus* AIFS; in addition, false-positives were common due to cross-reactivity with other fungal causes of AIFS [11, 23, 24]. Another serum fungal marker, beta-D-glucan, is a component of most fungal cell walls, although mucormycosis is a notable

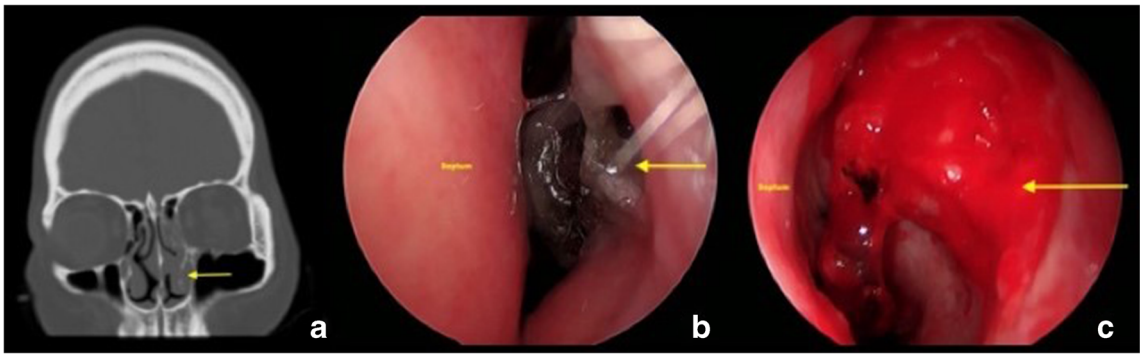

Fig. 1 **a** Coronal non-contrast CT demonstrating left inferior turbinate demineralization (arrow) and soft tissue thickening. **b** Intraoperative endoscopic view of necrotic left inferior turbinate (arrow). **c** Intraoperative view after turbinate resection (arrow); note that residual areas of black tissue are from cautery effect and not necrosis

exception. While this test is sometimes used in the diagnosis of invasive *Aspergillosis* with modest sensitivity and specificity [25], there is a paucity of data on its use in AIFS. Taken together, serum fungal markers may be a helpful adjunct in diagnosis, especially for *Aspergillus* AIFS, but it is critical to recognize that their sensitivity is poor and negative testing does not exclude a diagnosis of AIFS.

Microbiology

As opposed to histopathology stains, fungal stains performed on tissue specimens in the microbiology laboratory are positive in the minority (~ 30%) of cases [11]. Cultures have higher yield and are positive in anywhere from 50 to 95% of cases [11, 26–28].

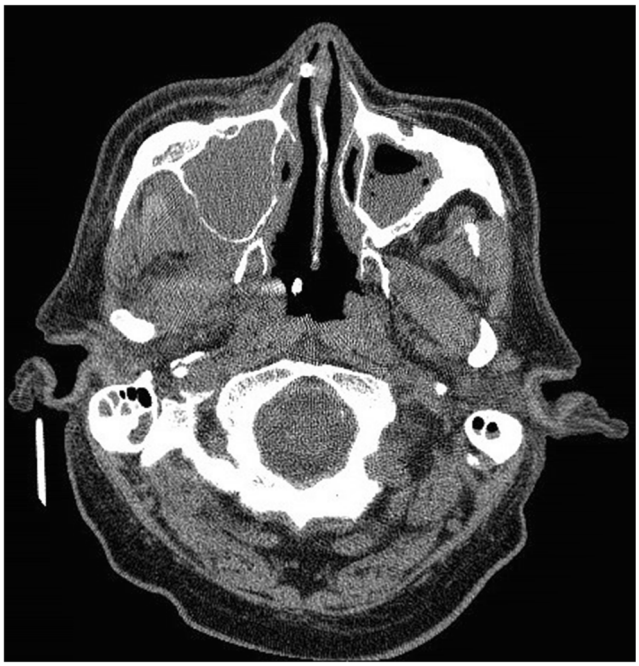

Fig. 2 Non-contrast axial CT demonstrating total opacification of the right maxillary sinus with demineralization and defects in the posterior-lateral maxillary sinus wall in a patient with AIFS. Note the loss of the fat plane posterior to the maxillary sinus indicating an infectious/inflammatory process

Molecular diagnostics are a promising new tool for diagnosis of invasive fungal infections, including AIFS. Recent data indicate that species-specific PCR (for *Aspergillus* or *Mucorales*) and broad-range panfungal PCR can increase the diagnostic sensitivity to > 70–80% and potentially even decrease time to diagnosis [27–29]. Unfortunately, these techniques are often only available at tertiary research medical centers and generally do not have FDA approval. One additional downside to making a diagnosis solely by PCR is the lack of antifungal susceptibility information, although identification to the species level can help guide antifungal stepdown therapy based on published minimum inhibitory concentration (MIC) data. Regardless of technique used for fungal identification, specimens should be sent for antifungal resistance testing to appropriately target systemic therapy.

Definition

As with other invasive fungal infections, it is important to appropriately categorize AIFS cases as proven versus probable invasive mold infection based on the 2008 European Organization for Research and Treatment of Cancer criteria [30].

Medical Management

There are three pillars in the treatment of invasive AIFS: (1) urgent surgical debridement, (2) antifungal therapy, and (3) reversal of immunosuppression. Optimal management requires a multidisciplinary approach with Infectious Disease and Otolaryngology input, as well as other potential specialists (ophthalmology, neurosurgery) depending on extent of infection.

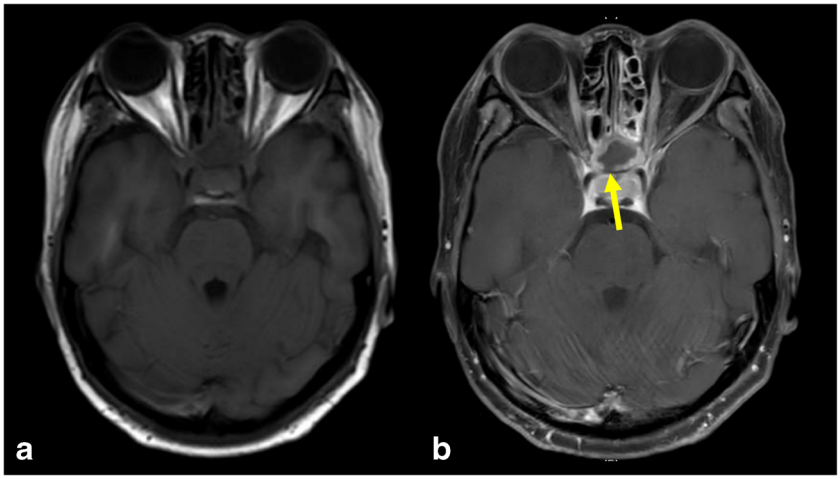

Fig. 3 MRI changes associated with AIFS. **a** Axial T1-weighted MRI demonstrates an isointense lesion within the superior aspect of the sphenoid sinus. **b** Axial T1-weighted fat-suppressed contrast-enhanced image shows similar lesion as in **a** and demonstrates loss of contrast enhancement

Antifungal Therapy

Empiric Therapy Empiric antifungal therapy should be started immediately as soon as there is clinical suspicion for AIFS; delay in therapy of ≥ 6 days is associated with a twofold increase in mortality [31]. For all patients, including those on azole prophylaxis, the authors recommend initial empiric therapy with liposomal amphotericin B, which is active against mucormycosis as noted below. Once a causative organism has been identified, targeted antifungal therapy should be initiated (Fig. 4).

Targeted Therapy for *Aspergillus* The three main classes of antifungal agents for the treatment of invasive *Aspergillosis* are the polyenes, the triazoles, and the echinocandins. Voriconazole is a first-line therapy with isavuconazole and liposomal amphotericin B considered alternative agents [32–34]. Posaconazole has been used for treatment in cases refractory or intolerant of first-line therapy. In contrast, echinocandins should only be considered as part of combination therapy or salvage therapy [33, 34].

Combination antifungal therapy for invasive *Aspergillosis* is not routinely recommended, but can be considered for salvage therapy or in very severe cases. In a randomized controlled trial of combination therapy of voriconazole plus anidulafungin versus voriconazole alone among 454 hematologic malignancy patients, there was a trend toward decreased mortality ($p = 0.09$) in the combination therapy group with similar safety profile [35]. Combination antifungal therapy with triazole and echinocandin as well as liposomal amphotericin and echinocandin has been used, but triazole and liposomal amphotericin are often favored for central nervous system infections [33, 34].

Therapeutic drug monitoring should be performed for all patients on azole antifungals, particularly when there is concern about gastrointestinal absorption, clinical or laboratory evidence of toxicity, co-administration of interacting drugs, and severe disease. Therapeutic voriconazole serum concentrations are predictive of clinical treatment success, with a trough < 1 associated with failure and >2 mg/L is recommended for severe infections [36, 37]. Doses should be adjusted to maintain levels < 5.5 mg/L to reduce voriconazole toxicity, including vision changes and hallucinations. Posaconazole levels > 1.0 mg/L should be targeted for treatment. In contrast, clinical evidence has not demonstrated a relationship between isavuconazole level and efficacy or safety, though some experts recommend therapeutic drug monitoring to ensure patient does not fall into 10% who have levels < 1 mg/L. [38]

The Clinical & Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing have established clinical breakpoints for voriconazole, itraconazole, and posaconazole against *Aspergillus* spp., and epidemiologic cutoff values and wild-type distributions for isavuconazole and echinocandins. Overall, voriconazole and isavuconazole exhibit reduced efficacy against *Aspergillus* isolates with MICs ≥ 16 μg/mL, including non-fumigatus *Aspergillus* species such as *A. ustus* and *A. niger* [39]. Below this threshold, there is limited understanding about susceptibility and clinical outcomes. Of note, recent evidence indicates there is increasing prevalence of azole-resistant isolates in the environment. A global survey reported that 3.2% of *Aspergillus* isolates are azole-resistant, with notably higher resistance rates in certain European countries [40]. Liposomal amphotericin B–based or combination regimens are recommended for patients with azole resistance.

Targeted Therapy for *Mucorales* Liposomal amphotericin B is the initial drug of choice for AIFS caused by *Mucorales*. The optimal dose of liposomal amphotericin has not been established in randomized clinical trials. Preclinical data suggested that higher doses (e.g., 10 mg/kg) of liposomal amphotericin might be needed to treat invasive mucormycosis [41]. However, in the AmBizygo trial, a prospective trial of liposomal amphotericin at 10 mg/kg/day for treatment of patients with mucormycosis, there was no survival benefit

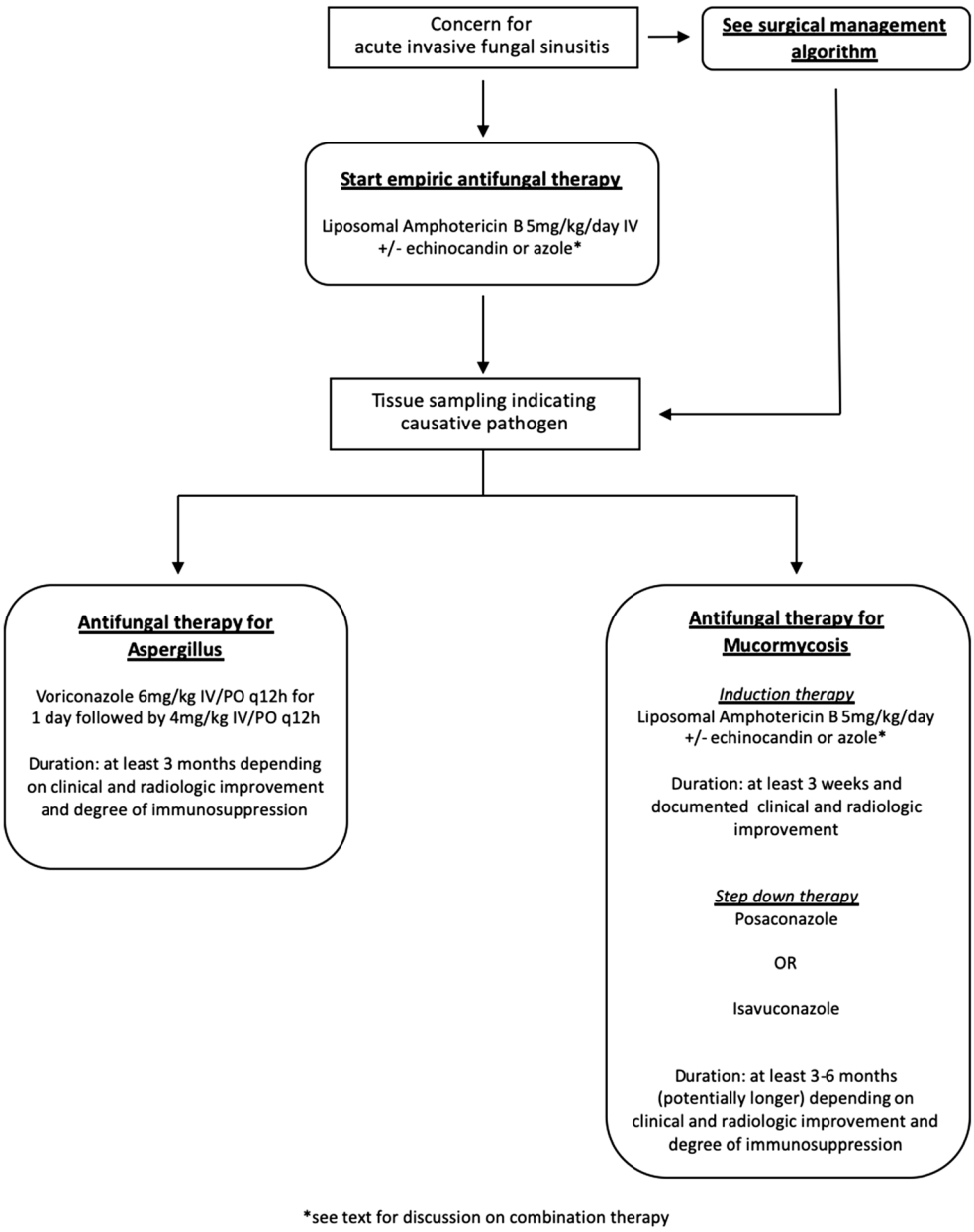

Fig. 4 Acute invasive fungal sinusitis medical management algorithm

compared with historical controls and patients had high rates of nephrotoxicity [42]. The most recent guidelines from the European Conference on Infections in Leukemia recommend starting liposomal amphotericin at a dose of 5 mg/kg/day [43], as do other experts within the USA [44]. A dose increase can be considered in patients failing standard therapy and/or who have significant central nervous system involvement [44].

For patients who are intolerant or refractory to liposomal amphotericin, isavuconazole and posaconazole are both potential options with activity against *Mucorales* spp. While both drugs have been shown to be effective as salvage therapy [45, 46], only isavuconazole has been shown, in a small number of patients in the VITAL study, to be effective as primary treatment for mucormycosis [46].

There is significant debate over the benefit of combination therapy in the initial treatment of mucormycosis. A small retrospective study in 2008 showed a survival benefit for combination therapy with amphotericin and an echinocandin compared with amphotericin alone, although the number in the combination group was small [47]. However, a larger retrospective study in 2016 showed no survival benefit with this combination [48]. There is also interest in using an azole with activity against mucormycosis (posaconazole or isavuconazole) as the drug to use in combination with amphotericin. The benefit of such a strategy remains unclear, as a small retrospective study of posaconazole plus amphotericin as salvage therapy did not show a survival benefit compared with historical controls treated with amphotericin monotherapy [49]. One benefit of early

combination therapy with an azole is that if patients are intolerant of liposomal amphotericin, this can be held or stopped and the patient will still be on active therapy, without needing to wait several days to reach steady-state levels if an azole was only started at that point.

Induction therapy with liposomal amphotericin is usually continued for at least 3 weeks [44] before stepping down to an oral azole. Oral azole therapy is then continued for a prolonged duration of therapy, at least 3–6 months [45, 46] and often much longer depending on the immune status of the patient (e.g., if immunosuppression is reversible). The decision as to which azole for stepdown therapy should be made on an individual basis, taking into consideration the side effect profile of the drugs (e.g., isavuconazole does not prolong the QT interval), need to monitor levels (e.g., there is more data and clinical experience for therapeutic drug monitoring with posaconazole), fungal MICs if available (although these are not clearly associated with outcomes), and whether or not there is concern for development of breakthrough invasive fungal infections while on chronic azole therapy. This latter point is notable since isavuconazole has recently been linked to breakthrough fungal infections, in particular in patients who are solid organ transplant or hematologic malignancy patients [14, 50].

AIFS Due to Other Organisms AIFS caused by rare or atypical fungal pathogens such as *Fusarium*, *Scedosporium*, *Alternaria*, *Paecilomyces*, and *Scopulariopsis* species should be treated in conjunction with an Infectious Diseases specialist and guided by existing expert consensus guidelines [51].

Duration of Therapy The optimal duration of antifungal therapy for AIFS should be individualized based on response to therapy, both clinical and radiological, and patient's underlying immune status. At minimum, therapy should be continued until all clinical and radiologic abnormalities have resolved and until no microbiologic evidence of infection (normalization of fungal biomarkers, negative cultures if resampling occurs). In an epidemiologic study of 89 hematologic malignancy patients with CNS and sinus invasive fungal infection, median duration of antifungal therapy was 60 days (range 5–835) [9].

Reversal of Immunosuppression

Reversing underlying disease process and decreasing immunosuppression is a mainstay of treatment in patients with AIFS, playing as an important role as surgical management and antifungal therapy [52, 53]. In a case series of 7 hematologic malignancy patients with AIFS, 5 were treated with combined medical and surgical therapy, of which only three survived—all three demonstrated substantial improvement after neutrophil recovery [54].

Alternative Therapies

Given increased risk for AIFS among patients with hematologic malignancy with neutropenia, granulocyte transfusion has been used in select cases. A recent multi-institutional review of 114 patients with AIFS showed that immune-stimulating therapies (G-CSF, GM-CSF, granulocyte transfusion, or a combination of these) resulted in a 70% reduction in 1-month mortality [5].

Case reports and series have reported survival benefit in patients with AIFS rhinosinusitis treated with hyperbaric oxygen [55, 56] with the theory that hyperbaric oxygen improves blood flow to ischemic tissues and acidosis. Other studies, however, have noted increased mortality among patients who received hyperbaric oxygen [15]. Overall, additional studies are needed to better clarify the role of these alternative therapies in AIFS and other invasive fungal infections.

Surgical Management

Surgical Candidacy

Whether to take a patient with suspected AIFS to the operating room (OR) is a critical decision that needs to be made by a multidisciplinary team made up of surgeons, Infectious Disease specialists, and the patient's primary providers (e.g., oncologist, transplant specialist, endocrinologist depending on patient's underlying immunosuppression).

Surgeons should first assess if the patient is a surgical candidate. Occasionally, patients are too sick or debilitated to be deemed proper candidates for general anesthesia, or their underlying disease has progressed beyond a reasonable chance for improvement. Performing a bedside biopsy is possible, but there are significant limitations to the anatomic structures that can be biopsied in an awake, inflamed patient, namely only the anterior portions of the inferior and middle turbinate or the nasal septum. If suspected AIFS disease is present within a sinus, or more posteriorly, these areas require sinus surgery to access for biopsy. Additionally, bedside biopsies run the risk of sampling error—missing the diseased tissue entirely or taking a biopsy of necrotic/non-viable tissue that cannot be properly interpreted by pathology. Because of these reasons, the authors' algorithm guiding surgical decision-making in these complex patients discourages the use of bedside biopsies (Fig. 5).

Once the decision is made to go to the OR, the next critical decision relates to timing of the procedure. Certainly, if there is evidence of an impending complication such as vision loss, prompt surgical intervention is important. If the clinical presentation is less concerning, it is often preferred to perform surgery when the patient is optimized and the proper surgical team is available. One study examining the urgency of surgery for AIFS found that surgical intervention within 6 days of

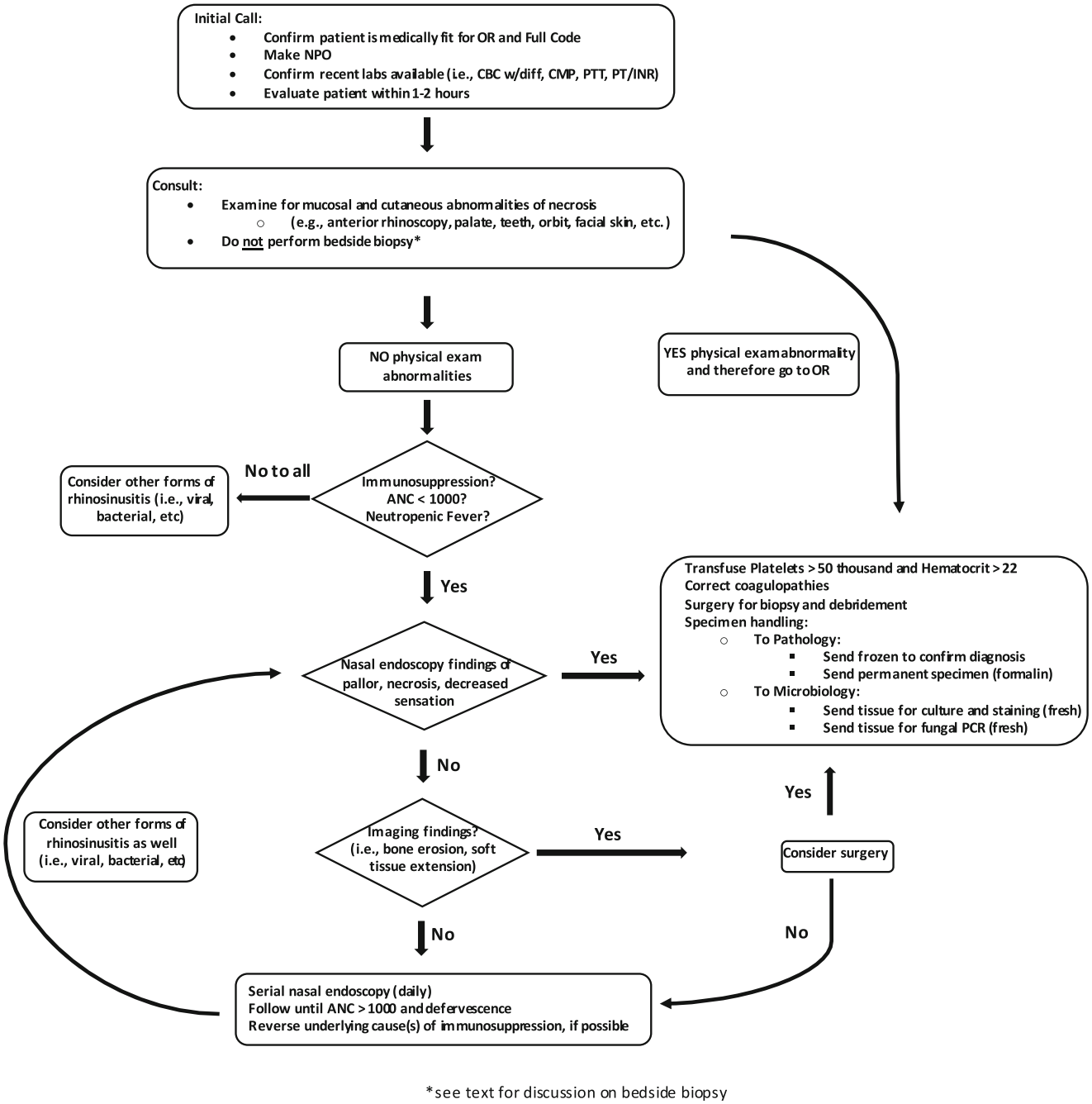

Fig. 5 Acute invasive fungal sinusitis surgical management algorithm

presentation of clinical symptoms led to improved survival compared to surgical intervention between 7 and 12 days or > 13 days [55].

Prior to surgery, it is important to ensure appropriate imaging (e.g., CT maxillofacial and/or MRI with gadolinium particularly if cranial neuropathies or ophthalmologic signs or symptoms present) has been obtained and patient has been properly prepared for surgery including NPO status and reversal of coagulopathy. Thrombocytopenia is common in patients with AIFS, and we recommend a target of at least 50,000 per microliter prior to surgical intervention.

Operative Technique

The initial steps of operative intervention involve relatively routine sinus surgery with the primary goal of establishing a definitive diagnosis by obtaining representative diseased tissue for histopathologic analysis, pathogen identification, and tissue cultures that permit antifungal sensitivity analysis. Tissue immediately adjacent to the areas of necrosis often yields superior H&E results compared with examining frankly necrotic tissue. Secondary objectives include removing all necrotic tissue and opening up any obstructed sinuses. If sub-

total resection of necrotic tissue is performed, then revision surgery should be considered in the near future by a qualified surgeon comfortable with advanced rhinologic procedures.

Neurosurgical and Ophthalmology Involvement

Due to the complex nature of head and neck anatomy, the disease process of AIFS often extends to places that require the expertise of several different specialists. When there is concern for optic or orbit involvement, ophthalmology should be consulted. If there is concern for intracranial involvement, neurosurgery should be consulted. Additionally, if the teeth are found to be involved (loose dentition), oral surgery should be consulted.

Kennedy et al. reported survival did not improve if aggressive debridement of tissue is performed "outside the box" of the sinonasal cavity [57]. Specifically, if there is intracranial involvement, it would be uncommon for a neurosurgeon to recommend surgical debridement. Similarly, if vision loss has occurred, it is uncommon for an ophthalmologist to recommend initial orbit exenteration. Delayed exenteration may be needed to alleviate ophthalmoplegia or as part of an approach for palliation of pain.

Monitoring

After the initial surgical encounter, the patient should be evaluated by focused physical exam daily. This includes a full cranial nerve examination, gross visual field and acuity examination, facial skin evaluation, and palate and dental evaluation. Nasal endoscopy within the first week after surgery is generally not informative or encouraged given the recent trauma to the sinonasal mucosa during surgery that will challenge any helpful clinical observation. Frequent nasal sterile saline irrigations using a low-pressure/high-volume device with or without the addition of antifungal medications are beneficial to facilitate wound healing and clearing of retained mucus and blood. This is commonly recommended starting post-operative day 1 and performed 3–4 times per day.

A "second look" surgery 1–2 weeks later in clinic or the operating room may be helpful to facilitate additional resection of concerning tissue or debridement of obstructing crusts or debris. This may be of greater importance if the clinical picture related to sinus AIFS is not improving. In general, repeat imaging with a CT scan is performed at short intervals only if there is a plan to return to the operating room for additional resection of tissue or if the patient's clinical picture is not improving.

Conclusion

Despite improvements in medical and surgical management of AIFS, mortality continues to approach 50%. Early diagnosis of this disease entity followed by aggressive surgical and medical management are important. However, reversal of the underlying source for immunosuppression is likely the primary predictor of survival. Immune-stimulating therapies may improve short-term survival, but require additional study.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Wilson AL, Plebanski M, Stephens AN. New trends in anti-cancer therapy: combining conventional chemotherapeutics with novel immunomodulators. Curr Med Chem. 2018;25(36):4758–84. https://doi.org/10.2174/0929867324666170830094922.
2. Transplant trends. https://unos.org/data/transplant-trends/. Accesed Jul 1 2019
3. deShazo RD, Chapin K, Swain RE. Fungal sinusitis. N Engl J Med. 1997;337(4):254–9. https://doi.org/10.1056/NEJM199707243370407.
4. 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. https://doi.org/10.1002/lary.23912.
5. Wandell GM, Miller C, Rathor A, Wai TH, Guyer RA, Schmidt RA, et al. A multi-institutional review of outcomes in biopsy-proven acute invasive fungal sinusitis. Int Forum Allergy Rhinol. 2018;8(12):1459–68. https://doi.org/10.1002/alr.22172.
6. Montone KT. Pathology of fungal rhinosinusitis: a review. Head Neck Pathol. 2016;10(1):40–6. https://doi.org/10.1007/s12105-016-0690-0.
7. 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 http://www.ncbi.nlm.nih.gov/pubmed/9604977.
8. Chen CY, Sheng WH, Cheng A, Chen YC, Tsay W, Tang JL, et al. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. BMC Infect Dis. 2011;11:1–9. https://doi.org/10.1186/1471-2334-11-250.
9. Candoni A, Klimko N, Busca A, et al. Fungal infections of the central nervous system and paranasal sinuses in onco-haematologic patients. Epidemiological study reporting the diagnostic-therapeutic approach and outcome in 89 cases. Mycoses. 2019;November 2018:252–60. https://doi.org/10.1111/myc.12884.
10. Husain S, Silveira FP, Azie N, Franks B, Horn D. Epidemiological features of invasive mold infections among solid organ transplant recipients: PATH Alliance® registry analysis. Med Mycol. 2017;55(3):269–77. https://doi.org/10.1093/mmy/myw086.
11. 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. https://doi.org/10.1093/jac/dkv198.
12. Bakhshaee M, Bojdi A, Allahyari A, Majidi MR, Tavakol S, Najafzadeh MJ, et al. Acute invasive fungal rhinosinusitis: our experience with 18 cases. Eur Arch Oto-Rhino-Laryngology. 2016;273(12):4281–7. https://doi.org/10.1007/s00405-016-4109-z.
13. Lamoth F, Chung SJ, Damonti L, Alexander BD. Changing epidemiology of invasive mold infections in patients receiving azole prophylaxis. Clin Infect Dis. 2017;64(11):1619–21. https://doi.org/10.1093/cid/cix130.
14. Fung M, Schwartz BS, Doernberg SB, Langelier C, Lo M, Graff L, et al. Breakthrough invasive fungal infections on isavuconazole prophylaxis and treatment: what is happening in the real-world setting? Clin Infect Dis. 2018;67(7):1142–3. https://doi.org/10.1093/cid/ciy260.
15. Trief D, Gray ST, Jakobiec FA, Durand ML, Fay A, Freitag SK, et al. Invasive fungal disease of the sinus and orbit: a comparison between mucormycosis and Aspergillus. Br J Ophthalmol. 2016;100(2):184–8. https://doi.org/10.1136/bjophthalmol-2015-306945.
16. Orlowski HLP, McWilliams S, Mellnick VM, et al. Imaging spectrum of invasive fungal and fungal-like infections. Radiographics. 37(4):1119–34. https://doi.org/10.1148/rg.2017160110.
17. Choi YR, Kim J-H, Min HS, Won JK, Kim HJ, Yoo RE, et al. Acute invasive fungal rhinosinusitis: MR imaging features and their impact on prognosis. Neuroradiology. 2018;60(7):715–23. https://doi.org/10.1007/s00234-018-2034-0.
18. Kim JH, Kang BC, Lee J-H, Jang YJ, Lee B-J, Chung Y-S. The prognostic value of gadolinium-enhanced magnetic resonance imaging in acute invasive fungal rhinosinusitis. J Inf Secur. 2015;70(1):88–95. https://doi.org/10.1016/j.jinf.2014.07.027.
19. Silveira MLC, Anselmo-Lima WT, Faria FM, Queiroz DLC, Nogueira RL, Leite MGJ, et al. Impact of early detection of acute invasive fungal rhinosinusitis in immunocompromised patients. BMC Infect Dis. 2019;19(1):310. https://doi.org/10.1186/s12879-019-3938-y.
20. Badawy MS, Badawy BS, Yousef LM, El Sherief N. Evaluation of pulmonary fungal diseases in patients with fungal rhino-sinusitis. Egypt J Chest Dis Tuberc. 2013;62(3):493–500. https://doi.org/10.1016/j.ejcdt.2013.06.004.
21. Hennessy M, McGinn J, White B, Payne S, Warrick JI, Crist H. Frozen section as a rapid and accurate method for diagnosing acute invasive fungal rhinosinusitis. Otolaryngol Head Neck Surg. 2018;159(3):576–80. https://doi.org/10.1177/0194599818770615.
22. Mmg L, Yj D, Wang J, et al. Galactomannan detection for invasive Aspergillosis in immunocompromised patients (review). Summary of findings for the main comparison. 2017;12. https://doi.org/10.1002/14651858.CD007394.pub2 www.cochranelibrary.com.
23. Mardani M, Faghani Y, Tabarraee M, Abolghasemi S. Clinical manifestation and diagnosis of invasive fungal sinusitis in patients with hematological malignancy. Arch Clin Infect Dis. 2016;11(4). https://doi.org/10.5812/archcid.36566.
24. Melancon CC, Lindsey J, Russell GB, Clinger JD. The role of galactomannan Aspergillus antigen in diagnosing acute invasive fungal sinusitis. Int Forum Allergy Rhinol. 2019;9(1):60–6. https://doi.org/10.1002/alr.22225.
25. 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. https://doi.org/10.1093/cid/ciq206.
26. Payne SJ, Mitzner R, Kunchala S, Roland L, McGinn JD. Acute invasive fungal rhinosinusitis: a 15-year experience with 41 patients. Otolaryngol Head Neck Surg (United States). 2016;154(4):759–64. https://doi.org/10.1177/0194599815627786.
27. Zaman K, Rudramurthy SM, Das A, et al. Molecular diagnosis of rhino-orbito-cerebral mucormycosis from fresh tissue samples. J Med Microbiol. 2017;66(8):1124–9. https://doi.org/10.1099/jmm.0.000560.
28. Gholinejad-Ghadi N, Shokohi T, Seifi Z, et al. Identification of Mucorales in patients with proven invasive mucormycosis by polymerase chain reaction in tissue samples. Mycoses. 2018;61(12):909–15. https://doi.org/10.1111/myc.12837.
29. Liberman J, Mathias P, Sengupta DJ, Cookson B, Schmidt RA, Bryan A. When speed counts: molecular diagnosis of invasive fungal sinusitis. Am J Pathol. 2018;149:S169–70.
30. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) C. Clin Infect Dis. 2008;46(12):1813–21. https://doi.org/10.1086/588660.
31. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis. 2008;47(4):503–9. https://doi.org/10.1086/590004.
32. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347(6):408–15. https://doi.org/10.1056/NEJMoa020191.
33. Husain S, Camargo JF. Invasive Aspergillosis in solid-organ transplant recipients: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transpl. 2019. https://doi.org/10.1111/ctr.13544.
34. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of Aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1–e60. https://doi.org/10.1093/cid/ciw326.
35. Marr KA, Schlamm HT, Herbrecht R, Rottinghaus ST, Bow EJ, Cornely OA, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. Ann Intern Med. 2015;162(2):81–9. https://doi.org/10.7326/M13-2508.
36. Luong M-L, Al-Dabbagh M, Groll AH, et al. Utility of voriconazole therapeutic drug monitoring: a meta-analysis. J Antimicrob Chemother. 2016;71(7):1786–99. https://doi.org/10.1093/jac/dkw099.
37. Hamada Y, Seto Y, Yago K, Kuroyama M. Investigation and threshold of optimum blood concentration of voriconazole: a descriptive statistical meta-analysis. J Infect Chemother. 2012;18(4):501–7. https://doi.org/10.1007/s10156-011-0363-6.
38. Andes D, Kovanda L, Desai A, Kitt T, Zhao M, Walsh TJ. Isavuconazole concentration in real-world practice: consistency with results from clinical trials. Antimicrob Agents Chemother. 2018;62(7). https://doi.org/10.1128/AAC.00585-18.
39. Van Der Linden JWM, Warris A, Verweij PE. Aspergillus species intrinsically resistant to antifungal agents. Med Mycol. 2011;49(S1):S82–9. https://doi.org/10.3109/13693786.2010.499916.
40. van der Linden JWM, Arendrup MC, Warris A, Lagrou K, Pelloux H, Hauser PM, et al. Prospective multicenter international surveillance of azole resistance in Aspergillus fumigatus. Emerg Infect Dis. 2015;21(6):1041–4. https://doi.org/10.3201/eid2106.140717.
41. Lewis RE, Albert ND, Liao G, Hou J, Prince RA, Kontoyiannis DP. Comparative pharmacodynamics of amphotericin B lipid complex and liposomal amphotericin B in a murine model of pulmonary mucormycosis. Antimicrob Agents Chemother. 2010;54(3):1298–304. https://doi.org/10.1128/AAC.01222-09.
42. Lanternier F, Poiree S, Elie C, Garcia-Hermoso D, Bakouboula P, Sitbon K, 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. https://doi.org/10.1093/jac/dkv236.
43. Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017;102(3):433–44. https://doi.org/10.3324/haematol.2016.152900.
44. Sipsas NV, Gamaletsou MN, Anastasopoulou A, Kontoyiannis DP. Therapy of mucormycosis. J Fungi. 2018;4(3):1–17. https://doi.org/10.3390/jof4030090.
45. van Burik J-AH, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis. 2006;42(7):e61–5. https://doi.org/10.1086/500212.
46. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16(7):828–37. https://doi.org/10.1016/S1473-3099(16)00071-2.
47. Reed C, Bryant R, Ibrahim AS, Edwards J Jr, Filler SG, Goldberg R, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008;47(3):364–71. https://doi.org/10.1086/589857.
48. Kyvernitakis A, Torres HA, Jiang Y, Chamilos G, Lewis RE, Kontoyiannis DP. Initial use of combination treatment does not impact survival of 106 patients with haematologic malignancies and mucormycosis: a propensity score analysis. Clin Microbiol Infect. 2016;22(9):811.e1–8. https://doi.org/10.1016/j.cmi.2016.03.029.
49. Pagano L, Cornely OA, Busca A, Caira M, Cesaro S, Gasbarrino C, et al. Combined antifungal approach for the treatment of invasive mucormycosis in patients with hematologic diseases: a report from the SEIFEM and FUNGISCOPE registries. Haematologica. 2013;98(10):127–30. https://doi.org/10.3324/haematol.2012.083063.
50. Rausch CR, Dipippo AJ, Bose P, Kontoyiannis DP. Breakthrough fungal infections in patients with leukemia receiving isavuconazole. Clin Infect Dis. 2018;67(10):1610–3. https://doi.org/10.1093/cid/ciy406.
51. Tortorano AM, Richardson M, Roilides E, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. Clin Microbiol Infect. 2014;20(Suppl 3):27–46. https://doi.org/10.1111/1469-0691.12465.
52. 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. https://doi.org/10.1016/j.otohns.2010.08.017.
53. Duggal P, Wise SK. Chapter 8: Invasive fungal rhinosinusitis. Am J Rhinol Allergy. 27(Suppl 1):S28–30. https://doi.org/10.2500/ajra.2013.27.3892.
54. Zappasodi P, Rossi M, Castagnola C, Pagella F, Matti E, Cavanna C, et al. Resolution of invasive fungal sinusitis in immunocompromised patients: neutrophil count is crucial beside a combined medical and surgical approach. Ann Hematol. 2010;89(7):737–9. https://doi.org/10.1007/s00277-009-0854-z.
55. Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. Surv Ophthalmol. 39(1):3–22 http://www.ncbi.nlm.nih.gov/pubmed/7974189.
56. Simmons JH, Zeitler PS, Fenton LZ, Abzug MJ, Fiallo-Scharer RV, Klingensmith GJ. Rhinocerebral mucormycosis complicated by internal carotid artery thrombosis in a pediatric patient with type 1 diabetes mellitus: a case report and review of the literature. Pediatr Diabetes. 2005;6(4):234–8. https://doi.org/10.1111/j.1399-543X.2005.00118.x.
57. Kennedy CA, Adams GL, Neglia JR, Giebink GS. Impact of surgical treatment on paranasal fungal infections in bone marrow transplant patients. Otolaryngol Head Neck Surg. 1997;116(6):610–6. https://doi.org/10.1016/S0194-5998(97)70236-5.