Battling Pediatric Mold Infections: Invasive Aspergillosis and Invasive Mucormycosis

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Interview Summary

Mold species are inhaled by people every day and, typically, infection is locally curtailed by the immune system. However, in people who are immunocompromised, invasive aspergillosis (IA) or invasive mucormycosis (IM) can lead to great morbidity and even mortality. Although many studies have been conducted in adults regarding diagnosis and treatment of IA and IM, infections in children have been investigated to a much lower extent. Surabhi Vora is a pediatrician based in Seattle who specializes in treating immunocompromised children with fungal infections. Here, she discusses several issues around IA and IM in these populations, including the importance of detecting and treating these infections early. Diagnosis of IA and IM may be problematic in children as symptoms can be non-specific, such as repeated bouts of fever; chest CTs and laboratory tests may not be as accurate as needed; and accessing tissue for biopsy can be difficult. Treatment of IA and IM can depend on a number of factors, such as the specific pathogen, drug–drug interactions, and a child's age and ability to consume a medication. Education is needed for both patients and caregivers, especially with regard to the need to take medication for extended periods of time and be on guard for both further IA or IM symptoms and for medication side effects.

INTRODUCTION

The genus *Aspergillus* includes several pathogenic mold species, including the most common invasive species *A. fumigatus*.[1] Genera under the order *Mucorales* include *Rhizopus*, the most common to cause IM.[2] Sources of both of these include soil and decaying vegetation,[1,2] with reports of *Aspergillus* also being air- or water-borne.[1] Following inhalation of *Aspergillus*[1] or *Mucorales*[2] spores, local colonization can occur, with subsequent invasion of the vascular system and widespread dissemination, leading to IA[1] or IM.[2] Morbidity and mortality associated with these infections can be high in people who are immunocompromised.[1,2] As such, awareness regarding infection signs and symptoms, as well as of suitable treatment, is paramount, especially considering that incidence/prevalence of both IA[3] and IM[4] is increasing.

Treatment for IA and IM has predominantly been studied in adults, with only a few studies conducted in pediatric populations.[5-10] To discuss these infections in children, the AMJ sat down with Surabhi Vora, a pediatric infectious diseases specialist with a particular interest in fungal infections in immunocompromised patients.

Invasive fungal infections such as IA and IM are most commonly seen in children with hematologic malignancies, especially acute myeloid leukemia[5,7,8,10] and relapsed/refractory acute lymphoblastic leukemia,[5-8,10] which may involve stem cell transplantation.[5-8,10] IA and IM may also develop in children undergoing solid organ transplant.[5,7,10] However, Vora explained, "most of our pediatric organ transplant patients are not significantly immunocompromised in the pre-transplant period. At the time of transplant, they are immunosuppressed intensely and continue on immune suppression, but not at the levels we sometimes see with stem cell transplants. Here, they may have had a fungal infection even before their transplant because they've had prolonged periods of profound neutropenia and immune suppression due to their underlying condition."

IA and IM may particularly occur in children with prolonged neutropenia or high steroid doses.[5,7,10] For example, in an IA study including 139 children, neutropenia was present for ≥3 days in 59% of patients and lasted for ≥30 days in ~30%. Corticosteroid therapy for the period prior to detection of IA was administered to 69% of patients and immunosuppressive therapies to 43%.[5]

PRESENTATION AND PROGRESSION OF INVASIVE *ASPERGILLUS* OR INVASIVE *MUCORMYCOSIS*

The spectrum of clinical manifestations of IA and IM is highly dependent on the individuals' risk factors, including immune system status. Greater immune suppression is associated with increased risk for invasive disease.[1,2] Infection with *Aspergillus* most commonly leads to invasive pulmonary aspergillosis (IPA), with symptoms including pulmonary infiltrates, pleural effusion, dyspnea, progressive cough, hemoptysis, pneumothorax, fever, and pleuritic chest pain. Other syndromes associated with IA include tracheobronchitis and sinusitis, and disseminated disease to other organs, bone, skin, and the central nervous system.[1] Clinical forms of IM include pulmonary, cutaneous, gastrointestinal, and rhinocerebral infections, and/or it can also be disseminated. Symptoms are site dependent; for example, symptoms of rhinocerebral mucormycosis can include facial pain, edema, and headache, whereas patients with pulmonary mucormycosis may experience chest pain, dyspnea, cough, and fever.[2]

Based on Vora's experience, a typical presentation in a pediatric patient with IA or IM "is a child who has been neutropenic for an extended period of time and then has fevers that do not go away despite antibiotic therapy. Depending on the infection site, they can also have skin lesions, sinus symptoms, sinus or face pain, headaches, respiratory symptoms, cough, shortness of breath, or chest pain." In her clinical experience, Vora

explained, the rate of progression of IA or IM "really depends on the individual and their immune system. Some can be fine one day and the next can have rapid progression, especially with IM. Others, more commonly, progress over weeks to months." She continued: "Even with early diagnosis, there's a risk of mortality.[1,2] It's pretty rare because we have more options for treatment and we're vigilant about progression and spread, but we still have to be very careful."

DIAGNOSING INVASIVE *ASPERGILLUS* OR INVASIVE *MUCORMYCOSIS*

Vora explained how immunocompromised children "are generally at risk for bacterial and viral infections,[11] not just fungal infections, so we look holistically at what could be causing symptoms. If it's just a fever, it can be very non-specific. We tend to start with treatment for bacterial infections, because we see those more commonly. If symptoms persist or are very severe, we look for other things, including viruses and fungal infections."

When discussing pulmonary manifestations of IM and IA, Vora explained how "one of our first diagnostic strategies is to image the lungs with a chest CT, because a regular X-ray doesn't usually pick up the subtle findings of a mold infection."[1,2] In IPA, such scans may reveal multiple, diffuse, nodules; focal consolidation; isolated masses; wedge-shaped densities or cavitary lesions; and pleural effusions.[1] In IM, findings may be similar including multiple nodules, consolidation nodules, cavities, abscesses, micronodules, and pleural effusions.[2] A chest CT may be able to distinguish pulmonary symptoms of IA from IM, with the former showing a halo sign[1] and the latter showing a reversed halo sign.[2] However, discussed Vora, "in reality we don't always see those things; the imaging findings really may be quite non-specific in children, but a nodular or cavitary lesion would certainly raise our suspicion for fungal infection."

Diagnosis of IA or IM may be challenging as there are no simple blood tests available,[1] with definitive diagnosis necessitating a bronchoscopy or biopsy.[1,2] Of note though, emphasized Vora from her clinical experience, "getting a bronchoscopy is a big deal in pediatric patients because they require sedation and may not tolerate the procedure.[1,2] They're already sick and have a lot of other things going on and they're fragile. There may be a lot of risk associated." Not being able to obtain a sample can be problematic, noted Vora, because "we're often in a situation where we think there's a probable or a presumed fungal infection, but we haven't been able to confirm it because of diagnostic limitations." It may also be the case that there is no absolute diagnosis even after an invasive procedure, explained Vora.

If a sample is collected, advanced techniques may be used to examine specimens, such as fungal PCR testing and metagenomic next-generation sequencing.[1,2,6] "However," said Vora regarding the latter, "it's relatively new and very expensive so it remains to be seen how useful it will be in this setting."

TREATMENT

There are various antifungal agents for treatment of IA and IM.[1,2] "Using [an agent with] the appropriate spectrum of activity is very important," remarked Vora. However, she also explained that there are only a few clinical studies investigating the efficacy and safety of treatments for pediatric patients with invasive molds.[8,9,12]

One trial that examined the pharmacokinetics and safety of an antifungal agent in this population was a Phase I, open-label, multicenter study of isavuconazonium sulfate including 46 immunocompromised pediatric patients. Participants were stratified by age to receive intravenous (aged 1–17 years) or oral (aged 6–17 years) formulations. At the studied dose, these formulations were well tolerated and resulted in exposure in pediatric patients that was similar to adults.[8]

In a subsequent open-label, non-comparative, Phase II study, 31 pediatric patients were administered oral (aged 6–17 years, weighing ≥12 kg) or intravenous (aged 1–17 years) formulations of isavuconazonium sulfate for treatment of at least possible IM or IA. Overall response rate at the end of treatment was 54.8%. Isavuconazole was well tolerated, with adverse events and exposure consistent with adult studies.[13] In these studies, the most frequently reported adverse reactions were diarrhea (26%), abdominal pain (23%), vomiting (21%), elevated liver chemistry tests (18%), rash (14%), nausea (13%), pruritus (13%), and headache (12%).[12]

Vora discussed how there are other factors to consider with regard to treatment choice, such as drug–drug interactions.[1] Additionally, "the site of infection can make a difference. If we have an infection in the brain, for instance, we want to make sure we have a drug that penetrates the CNS." Also of consideration, Vora discussed, is "what we think the patient can tolerate and their underlying renal or liver status. We also look at the age of the patient and whether we have dosing we're comfortable with." Another consideration Vora described is whether the drug of choice has an age-appropriate formulation. "If it's a young child, then we're limited by what they can take orally."

It was noted by Vora that, "if you suspect a mold infection, you really have to treat immediately and aggressively even when diagnosis is not confirmed."[2,14] She explained that "this means that sometimes we're treating a bit blindly because we don't know if it's IA or IM or a different organism." Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy, though it may be instituted before results of cultures and other laboratory studies are known. Once results are available, antifungal therapy should be adjusted accordingly.[14]

When prescribing a medication, Vora discussed how consideration needs to be given regarding treatment duration. She described how there is potential for using an intravenous drug initially, but then switching to an oral medication when the child has to take it at home for an extended period of time. Such time spans were evidenced by a pediatric study of treatment for invasive fungal infections where isavuconazonium sulfate was administered for a median 81 days, with a range of 15–356 days.[9]

Treatment for IM or IA can also include surgery, growth factors, or granulocyte transfusions.[1,2] "Surgery is a really important part of treatment in some of these infections, especially when they're focal and very aggressive. For IM especially, surgery is a critical part of reducing mortality. When there is something we can debride, we do that urgently to try and decrease the load of infection we need to treat," Vora said.[2]

EDUCATIONAL NEEDS FOR PATIENTS AND CARERS

Vora also discussed patient and family education regarding fungal infections in pediatric patients. "These infections can be very scary and it's tricky, because there's such a range of presentations and outcomes. You can be pretty convinced that a patient will be fine if they take their treatment for a very long time, or you can be very worried for a patient's life on Day 1. What the conversation is going to be like really depends on the situation."

Vora explained how "there's a lot of very specific education around diagnostics" when suspicious for IA or IM. Conversations may be challenging, she said, "especially when you've convinced someone to have a bronchoscopy then you don't have a diagnosis, but you're still going to treat them as if they have a fungal infection, because it would be too dangerous not to treat them." Once a treatment regimen has been established, Vora explained that education then centers around the importance of taking antifungals every day for a long time,

as well as regarding potential side effects and symptoms to look out for at home.

A final aspect of IA and IM Vora discussed was professional networks that, she explained, "are often all we have in pediatrics." She highlighted the International Pediatric Fungal Network[15] who "work together to do studies on fungal infections in children, trying to answer questions that no single site can answer alone because these are relatively rare infections." For example, they are currently undertaking a study looking at better strategies to diagnose IA and IM in the lungs.[15,16]

CONCLUSION

Vora concluded by reminding people that "there's a lot of morbidity and mortality associated with both IA and IM,[1,2] so we have to be very vigilant about looking for them in high-risk patients. Even with the limitations of diagnostics, we have to treat aggressively if there's even suspicion that that's what's going on. The more antifungal treatment options we have, the more chance we have of achieving better outcomes."

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IMPORTANT SAFETY INFORMATION AND INDICATIONS AND USAGE OF CRESEMBA (isavuconazonium sulfate)

CONTRAINDICATIONS

- CRESEMBA is contraindicated in persons with known hypersensitivity to isavuconazole
- Coadministration of strong CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir (400 mg every 12 hours), with CRESEMBA is contraindicated because strong CYP3A4 inhibitors can significantly increase the plasma concentration of isavuconazole
- Coadministration of strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates with CRESEMBA is contraindicated because strong CYP3A4 inducers can significantly decrease the plasma concentration of isavuconazole
- CRESEMBA shortened the QTc interval in a concentration-related manner. CRESEMBA is contraindicated in patients with familial short QT syndrome

WARNINGS AND PRECAUTIONS

Hepatic Adverse Drug Reactions (e.g., elevations in ALT, AST, alkaline phosphatase, total bilirubin) have been reported in clinical trials and were generally reversible and did not require discontinuation of CRESEMBA. Cases of severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with azole antifungal agents, including CRESEMBA. Evaluate liver tests at the start and during therapy. Monitor patients who develop liver abnormalities during CRESEMBA therapy for severe hepatic injury. Discontinue if clinical signs and symptoms consistent with liver disease develop that may be attributable to CRESEMBA.

Infusion-Related Reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of CRESEMBA. Discontinue the infusion if these reactions occur.

Hypersensitivity Reactions: Anaphylactic reactions, with fatal outcome, have been reported during treatment with CRESEMBA. Serious skin reactions, such as Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA if anaphylactic or serious skin reactions occur, and initiate supportive treatment as needed.

Embryo-Fetal Toxicity: During pregnancy, CRESEMBA may cause fetal harm when administered, and CRESEMBA should only be used if the potential benefit to the patient outweighs the risk to the fetus. Women who become pregnant while receiving CRESEMBA are encouraged to contact their physician.

Drug Interactions: Coadministration of CRESEMBA with strong CYP3A4 inhibitors such as ketoconazole or high-dose ritonavir and strong CYP3A4 inducers such as rifampin, carbamazepine, St. John's Wort, or long acting barbiturates is contraindicated.

Drug Particulates: Following dilution, CRESEMBA intravenous formulation may form precipitate from the insoluble isavuconazole. Administer CRESEMBA through an in-line filter.

ADVERSE REACTIONS

In adult patients, the most frequently reported adverse reactions among CRESEMBA-treated patients were nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), cough (12%), peripheral edema (11%), and back pain (10%).

In adult patients, the adverse reactions which most often led to permanent discontinuation of CRESEMBA therapy during the clinical trials were confusional state (0.7%), acute renal failure (0.7%), increased blood bilirubin (0.5%), convulsion (0.5%), dyspnea (0.5%), epilepsy (0.5%), respiratory failure (0.5%), and vomiting (0.5%).

In pediatric patients, the most frequently reported adverse reactions were diarrhea (26%), abdominal pain (23%), vomiting (21%), elevated liver chemistry tests (18%), rash (14%), nausea (13%), pruritus (13%), and headache (12%).

In general, adverse reactions in pediatric patients (including serious adverse reactions and adverse reactions leading to permanent discontinuation of CRESEMBA) were similar to those reported in adults.

INDICATIONS AND USAGE

CRESEMBA (isavuconazonium sulfate) is an azole antifungal indicated for the treatment of **invasive aspergillosis and invasive mucormycosis** as follows:

- **CRESEMBA for injection:** adults and pediatric patients 1 year of age and older
- **CRESEMBA capsules:** adults and pediatric patients 6 years of age and older who weigh 16 kg and greater

Specimens for fungal culture and other relevant laboratory studies (including histopathology) to isolate and identify causative organism(s) should be obtained prior to initiating antifungal therapy. Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Please see full Prescribing Information for CRESEMBA (isavuconazonium sulfate).