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# Cutaneous Mucormycosis in Solid Organ Transplant Recipients after Hurricane Harvey: Short- and Long-term Management

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**Summary:** In the fall of 2017, Hurricane Harvey, one of the most costly hurricanes in American history, ravaged the Texas Gulf Coast, interrupting basic sanitation systems to hundreds of thousands of Texas residents. In the aftermath of Hurricane Harvey, our Houston hospitals noted an uptick in the incidence of cases of mucormycosis. Among the most vulnerable and affected have been immunocompromised transplant recipients. Here, we describe the successful management of 2 patients with atypical presentations of mucormycosis, 2 cutaneous infections after liver transplantation. Our comprehensive treatment strategy based upon guidelines and experience included coordinating aggressive surgical and medical therapies. We discuss our approach to surgical management including the extent and frequency of debridement, the methods of assessing disease-free margins, and minimizing the morbidity of radical debridement with temporary coverage and forethought to long-term reconstruction. Additionally, we describe the concurrent medical management, including type, route, and duration of antifungal therapy, minimizing suppression of the innate immune system, and optimizing the wound healing environment through maintaining nutritional status. *(Plast Reconstr Surg Glob Open 2019; 7:e2041; doi: 10.1097/GOX.0000000000002041; Published online 15 January 2019.)*

## INTRODUCTION

In the fall of 2017, Hurricane Harvey, one of the most costly hurricanes in American history, ravaged the Texas Gulf Coast, interrupting basic sanitation systems to hundreds of thousands of Texas residents.[1] Natural disasters, including tornadoes, earthquakes, tsunamis, and hurricanes, can cause massive population displacement and an interruption of normal sanitary services. The problem is further compounded by the reported ability to disturb and distribute naturally occurring fungal spores, leading to sometimes devastating infections.[2] In the month after Hurricane Harvey, our Houston hospital noted an uptick in the incidence of cases of mucormycosis. Five patients presented with acute invasive infections: 2 diabetic patients with rhinocerebral infections (both deceased), 1 cystic fibrosis who presented with visceral mucormycosis of the stomach (underwent gastrectomy), and the 2 transplant patients discussed here. Treatment regimens can be complex and come with significant morbidity.[3,4] Here, we describe the successful management of 2 patients with atypical presentations of mucormycosis, 2 cutaneous infections after liver transplantation.

Our comprehensive treatment strategy based upon guidelines and experience included coordinating aggressive surgical and medical therapies.[4] We discuss our approach to surgical management including the extent and frequency of debridement, the methods of assessing disease-free margins, and minimizing the morbidity of radical debridement with temporary coverage and forethought to long-term reconstruction. Additionally, we describe the concurrent medical management, including type, route, and duration of antifungal therapy, minimizing suppression of the innate immune system, and optimizing the wound healing environment through maintaining nutritional status.

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*Received for publication June 30, 2018; accepted October 10, 2018.*



DOI: 10.1097/GOX.0000000000002041

**Disclosure:** *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*

## CASE REPORTS

**Case 1**

A severely ill 13-month girl with biliary atresia underwent orthotopic liver transplantation after a failed Kasai procedure at age 2 months (pediatric model for end-stage liver disease: 19). Before transplantation, her liver disease was complicated by encephalopathy, ascites, coagulopathy, and bleeding varices resulting in multiple hospitalizations. Her early postoperative course was complicated by respiratory failure, vasopressor requirement, and the need for continuous renal replacement therapy. On postoperative day 16, a wound from an infiltrated leg IV was debrided and revealed fungal hyphae (Fig. 1). Intravenous liposomal amphotericin (5 mg/kg) was immediately added to her antimicrobial regimen and she was in the operating room within 2 hours of confirming the diagnosis. Serial debridements were undertaken over the ensuing week and when negative margins were achieved, the final wound measured 60 $cm^2$ with the deep margin comprising the tibial periosteum. The wound was managed initially with amphotericin soaked wet-to-dry dressing changes, transitioning eventually to an amphotericin-impregnated biologic skin substitute and negative-pressure wound therapy (NPWT). Final re-construction of her leg wound consisted of a split-thickness skin graft onto the granulated biologic skin substitute 2 months following the initial debridement. Nutrition was maintained with total parenteral nutrition in the early postoperative period and transitioned to naso-jejunal tube feeding that continued until 1 week before discharge. Supplemental tube feeding was weaned in a very gradual manner over the course of 2 weeks: from 24-hour continuous, to 18 hours, to nocturnal only until all caloric intake was oral. Intravenous posaconazole was introduced after 4 months and continued alongside amphotericin while tube feeding was weaned. After oral intake was stable, posaconazole was transitioned to PO and IV Amphotericin was continued until the posaconazole level was consistently greater than 1.0 ug/mL. Five months after her transplant, she was discharged home on posaconazole for 1-year duration.

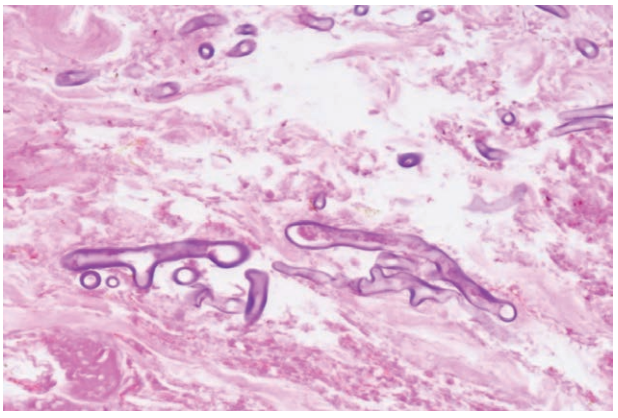

**Fig. 1.** Case 1: 13-month-old girl left leg H&E-stained section. Broad, hyaline, ribbon-like fungal hyphae with wide–angle branching (600× magnification).

**Case 2**

A 46-year-old man with diabetes, hepatitis C, and Laennec's cirrhosis (model for end-stage liver disease: 38) was admitted to the intensive care unit for variceal bleeding before orthotopic liver transplant. Two days before orthotopic liver transplant, patient underwent incision and drainage of a chest wall cutaneous abscess; fungal cultures were not sent at this time. The lesion progressed postoperatively and was debrided with concern for necrotizing soft-tissue infection. Tissue culture revealed fungal angioinvasion and amphotericin was added to his microbial coverage. Serial debridements were undertaken and when negative margins were achieved, the final wound measured 430 cm2. The deep margin included the sternal periosteum medially and the excision of the eighth rib (Fig. 2). The wound was managed initially with amphotericin soaked wet-to-dry dressing changes, transitioning eventually to an amphotericin impregnated biologic skin substitute and NPWT. The vasculature of the ipsilateral axilla and arm were preserved for possible future flap coverage. Maintenance of nutrition consisted of total parenteral nutrition weaned to a combination of tube feeds and ad lib per oral feeding. Three months into his hospital stay, he was discharged home with a naso-gastric feeding tube, NPWT dressing, and oral posaconazole.

## DISCUSSION

**Surgical Management**

Principles of surgical management include extensive and frequent debridement, diligent assessment of margins, and minimizing the morbidity of radical debridement with temporary coverage and forethought to long-term reconstruction.

***Extent and Frequency of Debridement***

Prompt radical debridement of all grossly abnormal tissue is the mainstay of treatment of cutaneous mucormycosis.[2] Although one must be cognizant of which tissues are involved, mucormycetes can spread directly into bowel and solid organs, the retroperitoneum, skin, fascia, muscle, and bone, seemingly without predilection and so debridement must be aggressive up front. When bone is suspected to be involved, shaving the bone layer by layer is our approach if it is structurally necessary (sternum, tibia) with total excision in the case of an expendable bony structure (rib). If disease is locally advanced in a patient with extremis, sacrificing a limb to save a life may be a consideration. Debridement of visceral infections should include sacrifice of nonvital blood vessels and allowance of intestinal discontinuity if needed. All debridements should take place in the operating room and the frequency of debridement should be based initially on the gross wound appearance, followed by further debridements guided by culture and histology results. Review of the tissue slides by pathologist to identify fungal elements is integral in early identification. For cutaneous lesions, we perform intraoperative imbedding of amphotericin pow-

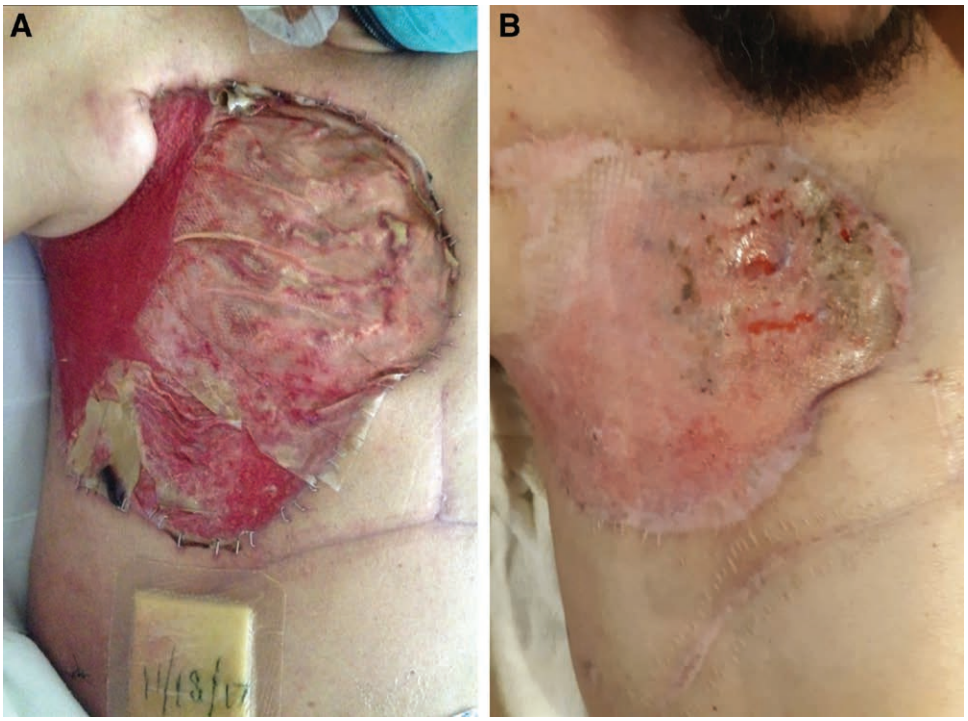


**Fig. 2.** A, Case 2: 46-year-old man right chest early debridement. B, Case 2: 46 year-old man right chest skin graft.

der into the wound in addition to dressing the wound with amphotericin soaked gauze, eventually transitioning to an impregnated skin substitute bilayer. Intraperitoneal amphotericin powder is used as well. We check for culture updates twice daily and collaborate with Infectious Disease specialists to assess for evidence of fungal elements in specimens.

***Assessing Margins***

Ensuring margins are truly clear of disease requires diligence and planning. Early in the treatment process, margins are expanded to include all grossly abnormal tissue. Involved soft tissue may appear necrotic and gray/black or may be inflamed and erythematous. Exudates may be minimal. Involved bone or cartilage may appear grossly normal. In the operating room, margins are sent for frozen and permanent sectioning and culture. Although frozen specimens may be low-yield, the presence of fungal elements such as hyphae necessitates immediate re-excision. Specialized methods including sliver-based staining (GMS, Gomori Methenamine-Silver) is used to detect fungi in permanent specimens. Tissue cultures can take between 2 days to 2 weeks to grow depending on the fungal burden. As mentioned previously, we collaborate closely with Infectious Disease specialists who give priority to these cases, given the potential for rapid deterioration. During debridement, we label multiple margins beyond the usual "deep, medial, lateral, etc." to minimize the defect size and to better localize areas in need of re-excision. Clear descriptions of the locations of these margins are necessary to keep track of the multitude of specimens created over the course of treatment. The same surgeon performs all debridements for a given patient given the complexities and subjective components of wound assessment.

***Coverage***

We utilize plastic and reconstructive surgery specialists from the time of diagnosis to have an early and ongoing plan for reconstruction. During the stage of daily planned debridements, we manage the wound with twice daily wet-to-dry dressing changes consisting of amphotericin-soaked gauze. This allows frequent wound assessment and action to be taken if needed. In latter stages, wound management consists of a biologic skin substitute impregnated with amphotericin sutured directly to the skin that can be left in place indefinitely.

Our product of choice is Integra (Plainsboro, New Jersey), a bilayer wound barrier consisting of a combination of porcine tendon elements, shark cartilage, and silicone. The high concentration of glycosaminoglycans resembles the normal extracellular matrix environment and seems to allow favoring of an anabolic over catabolic state to promote wound healing and conserve systemic resources. Additionally, the porous nature of this membrane allows for ready impregnation and controlled release of amphotericin over 36 hours.

Approximately 1 month after the final cultures are negative, we transition to NPWT coverage over the dermal substitute with changes 3 times weekly. Depending on the degree of wound healing achieved, definitive coverage may consist of skin grafting or myocutaneous coverage.

**Medical Management**

*Although invasive mucormycosis is commonly referred to as a "surgical disease," concurrent medical management must be regimented and follow several principles:* using amphotericin early as a first line therapy, minimizing suppression of the innate immune system, and optimizing nutritional status.

***Antifungal***

Amphotericin is the antifungal of choice in invasive mucormycosis; it has fungicidal properties necessary for this rapidly spreading disease.[5,6] Given that mucormycosis causes necrosis and micro thrombosis in tissue, achieving reliable tissue concentrations can be difficult. Therefore, both topical and systemic administration is preferred, given the difficulty of tissue penetration with IV administration alone. We give intravenous amphotericin for at 2–3 months past clinical improvement and then transition to oral posaconazole for a duration of 1 year. Using the liposomal preparation of amphotericin, we have experienced few renal side-effects so far. As mentioned previously, topical amphotericin is administered initially via wet-to-dry dressing changes with gauze and eventually via an impregnated dual-layer skin substitute. The transition to oral posaconazole is made only after gastric feeding is reliable and blood levels are confirmed stable (>1.0 ug/mL). When gastric feeding is not feasible, such as after total gastrectomy, much higher doses of enteral posaconazole are needed to achieve adequate plasma concentrations.

***Innate Immunity***

Liver transplant recipients are at risk for this opportunistic infection not only because of the immunosuppression administered, but also because of the immunologic consequences of the underlying disease. Minimizing steroid use during the treatment period is paramount, allowing the innate immune system to recover. In our patients, we quickly taper the corticosteroid dose to zero and continue calcineurin inhibitors, titrating to a moderate level. We have had no threatened grafts with this approach. Indeed, transplant patients with invasive mucormycosis are severely ill and are at a relatively low risk of rejection. Tight control of blood glucose with insulin and appropriate nutrition (enteral and/or parenteral) is also an important maneuver to help the innate immune system. High blood glucose serves as metabolic substrate to microorganisms and impairs host neutrophil function.[7]

***Nutrition***

Underlying all attempts to achieve convalescence is the necessity of adequate nutrition. We employ early aggressive enteral nutrition when possible in our liver transplant recipients and doubly so while treating infection. The preferred route is enteral over parenteral, but interruptions to enteral feeding can be substantial with frequent operative debridements. Although institutional policies vary, the use of a nasojejunal feeding tube has been shown to allow continuous feeding through surgery without interruption in such cases.[8] The calculation of caloric needs should resemble that of a severely burned patient given the combination infection and a large wound in the posttransplant setting. Our protein goal is 1.5–2 g/kg/d.[9]

## CONCLUSIONS

The posttransplant recovery following large-scale natural disasters can be challenging and the risk of opportunistic infection is increased beyond those already associated with commonly used immunosuppressive regimens.[10] To our knowledge, these 2 cases are the first reports of solid organ transplant recipients victimized by invasive fungal infection after a natural disaster.

Given that the incidence of invasive fungal infection following solid organ transplantation has been reported between 5% and 42%, with aspergillosis being more common than mucormycosis,[11–14] knowing which patients are at risk and having a high degree of suspicion are paramount to early diagnosis and timely initiation of the correct treatment of this devastating disease. Excellent outcomes can be achieved with a comprehensive, multi-disciplinary treatment strategy that includes consideration of the extent and frequency of debridement, the methods of assessing disease-free margins, minimizing the morbidity of radical debridement with temporary coverage and forethought to long-term reconstruction, and concurrent medical management for optimal wound healing.

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