

CLINICAL MYCOLOGY COURSE

A 25-YEAR-OLD CAMP COUNSELLOR WITH RESPIRATORY FAILURE

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Initial Presentation

A 25-year-old male camp counsellor from Ontario, Canada presented to the emergency department with rapidly progressing shortness of breath. One week earlier, he had been assessed by rheumatology for a 6-week history of a swollen right knee. An arthrocentesis demonstrated 60,000 white blood cells, 85% of which were neutrophils. There were no crystals seen, and bacterial cultures were negative. A serum auto-antibody panel was negative for antinuclear antibody and rheumatoid factor. He was diagnosed with seronegative arthritis and two days prior to his presentation he was started on prednisone 50 mg by mouth daily. Over the ensuing 24 hours, he felt progressively weak and breathless.

The patient had no other notable past medical history.

In the emergency room, he was profoundly hypoxic and hypotensive. The patient was intubated, and mechanical ventilation was initiated.

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A chest X-ray is shown below (see Figure 1).



Figure 1. Chest X-ray showing diffuse bilateral opacities. Image courtesy of Alexandre Carignan, MD.

The combination of acute pulmonary disease and subacute osteoarticular disease in a patient with outdoor exposure in an area of geographic risk for blastomycosis is concerning for this diagnosis.

Challenge Question 1. What is the single best diagnostic test in this patient?

- A. Repeat arthrocentesis for fungal stains and culture
- B. Urine *Blastomyces* antigen
- C. Fungal blood cultures
- D. Bronchoscopy for fungal stain and culture

Discussion

- A. **Repeat arthrocentesis for fungal stains and culture.** Given the sequence of events and temporal relationship between the arthritis and the pulmonary disease upon starting corticosteroids, a unifying infectious diagnosis that involves the knee and lung is likely. The knee synovial fluid is readily accessible. The fluid was previously sent for bacterial culture, but atypical pathogens including fungi and mycobacteria should be considered. Synovial fluid should be sent for fungal and mycobacterial stains and cultures; the former could provide results within several hours, although the latter could take several weeks before positive results would be expected.
- B. **Urine *Blastomyces* antigen.** A urinary antigen test for blastomycosis is commercially available. The sensitivity in urine is reported to range from 76-93%¹⁻³.
- C. **Fungal blood cultures.** Blastomycosis is very rarely, if ever, diagnosed by blood culture, even with centrifugation-lysis procedures. The exception to this is disease caused by *Blastomyces helicus*, a recently described and rarely encountered pathogen in western parts of North America⁴.
- D. **Bronchoscopy for fungal stain and culture.** Given that the main problem is hypoxic respiratory failure, it makes sense to focus diagnostics on the respiratory tract. Bronchoscopy for bronchial samples to test for bacterial, fungal, and mycobacterial culture is appropriate. While growth of *Blastomyces* on fungal culture is slow (taking at minimum 5-10 days, and often up to 28 days), fungal stains (KOH or calcofluor) can secure the diagnosis if the organism is visualized.

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Correct answer: D.

A bronchoscopy was performed, and bronchoalveolar lavage (BAL) fluid was sent for bacterial, fungal, and mycobacterial cultures. A calcofluor stain of BAL fluid is shown below (see Figure 2).

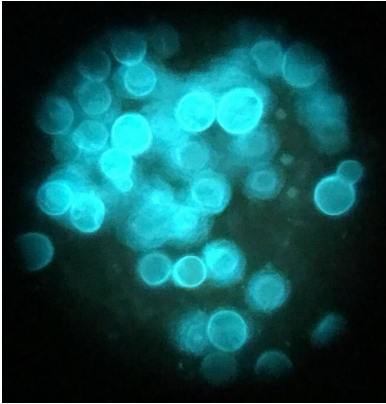


Figure 2. Calcofluor stain on bronchial alveolar fluid showing round, broad-based budding yeast-like cells. Image courtesy of Alexandre Carignan, MD.

Discussion

The appearance of broad-based budding yeasts consistent with *Blastomyces* in BAL can be considered diagnostic and warrants initiation of antifungal therapy.

Challenge Question 2. What is the most appropriate treatment?

- A. Micafungin 150 mg IV daily
- B. Liposomal amphotericin B (3-5 mg/kg IV daily)
- C. Amphotericin B deoxycholate (0.7-1 mg/kg IV daily)
- D. Isavuconazole 372 mg IV Q8H x 6 doses, then 372 mg IV daily
- E. Itraconazole 200 mg PO Q8H x 6 doses, then 200 mg PO Q12H

Discussion

This patient has severe pulmonary blastomycosis. Let's review the management.

- A. **Micafungin.** As mentioned previously, echinocandins, including micafungin, do not have meaningful activity against dimorphic fungi like *Blastomyces*. They do not have a role in treating blastomycosis.
- B. **Liposomal amphotericin B (3-5 mg/kg IV daily).** Liposomal amphotericin B is the drug of choice in moderately severe-to-severe blastomycosis⁵.
- C. **Amphotericin B deoxycholate (0.7-1 mg/kg IV daily).** Amphotericin B deoxycholate has a considerably worse toxicity profile than liposomal or lipid complex formulations. For the most part, its use should be restricted to settings in which liposomal or lipid complex formulations are unavailable.
- D. **Isavuconazole.** Isavuconazole would not be an appropriate first-line treatment for severe blastomycosis, although it can be considered in step down.

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- E. **Itraconazole.** Itraconazole is the azole of choice in the management of blastomycosis. However, it is used as initial or sole therapy in patients with *mild to moderate disease*, and as a step-down option in patients with non-CNS blastomycosis who first require amphotericin B⁵.

Correct answer: B.

Treatment

The patient is treated with liposomal amphotericin B (5 mg/kg/day). However, he continues to deteriorate. On 80% FiO₂, the patient's partial pressure of arterial O₂ was 75 mm Hg.

Case Management

Challenge Question 3. What is the most important next step in management?

- A. Corticosteroids
- B. Add itraconazole
- C. Add flucytosine
- D. Venovenous extracorporeal membrane oxygenation (vv-ECMO)

Discussion

Blastomycosis-associated acute respiratory distress syndrome (ARDS) complicates approximately 8-15% of symptomatic cases of blastomycosis that require hospitalization⁶⁻⁸ and carries a staggering mortality of up to 75%⁹. In this case, the ratio of arterial oxygen concentration to fraction of inhaled oxygen (PaO₂:FiO₂) is <100, which is indicative of severe ARDS.

The management of blastomycosis-associated ARDS is very difficult. Rescue therapy has been attempted with several adjunctive modalities, including combination therapy¹⁰, corticosteroids^{11,12}, and vv-ECMO¹²⁻¹⁴.

- A. **Corticosteroids.** Corticosteroids are frequently prescribed for blastomycosis-associated ARDS in some centers, although support for the practice remains anecdotal and expert consensus is lacking¹². This patient was already on corticosteroids, which likely triggered the development of ARDS due to impaired control of undiagnosed pulmonary and extrapulmonary blastomycosis. In this case, the corticosteroids should be discontinued.
- B. **Add itraconazole.** It is unlikely that a second antifungal would be of additional benefit, and there are theoretical reasons to avoid addition of a triazole including potential antagonism, risk of toxicity, and drug-drug interactions.
- C. **Add flucytosine.** Flucytosine is not active against *Blastomyces* and does not have a role in the management of blastomycosis¹⁵.
- D. **Venovenous extracorporeal membrane oxygenation (vv-ECMO).** Like for other causes of ARDS, vv-ECMO has been used successfully for blastomycosis-associated ARDS¹²⁻¹⁴ and should be considered for rescue therapy at centers where capacity exists¹⁶. In the setting of severe ARDS, benefit from vv-ECMO may exceed that of other options listed here and thus this would be the preferred option.

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Correct answer: D.

Case Continued

Rescue vv-ECMO is initiated.

Challenge Question 6. What should be done regarding antifungals?

- A. Increase the dose of liposomal amphotericin B to 7.5 mg/kg/day
- B. Change to deoxycholate formulation of amphotericin B 1mg/kg/day
- C. Change to itraconazole
- D. Change to isavuconazole
- E. Add an echinocandin

Discussion

- A. **Increase the dose of liposomal amphotericin B to 7.5 mg/kg/day.** There are limited data on the use of antifungals with ECMO. However, several case reports have suggested that liposomal amphotericin B can become sequestered in ECMO circuits, which can reduce drug exposure and can also interfere with ECMO membranes^{10,17}. This is likely due to the lipophilic nature of the liposomal formulation, which would not be a problem with the deoxycholate. The exact dose adjustment required is unknown, and most centers do not use therapeutic drug monitoring to guide dosing. Although there is risk of toxicity, high doses of liposomal amphotericin B are typically well tolerated¹⁸. On the balance of risks of inadequate exposure vs toxicity, increasing the dose to 7.5 mg/kg is appropriate¹⁹.
- B. **Change to deoxycholate formulation of amphotericin B 1 mg/kg/day.** This would be a reasonable second option given the uncertain pharmacokinetics with liposomal amphotericin B in a patient on ECMO. Amphotericin B deoxycholate does not appear to be sequestered in ECMO circuits²⁰. In general, nephrotoxicity of amphotericin B deoxycholate makes it less desirable. However, given the life-threatening nature of this infection and the importance of achieving appropriate drug exposure, this formulation could be considered. Some experts recommend continuous infusion of amphotericin B for this indication²¹.
- C. **Change to itraconazole.** Changing to itraconazole would not be recommended given the severity of illness.
- D. **Change to isavuconazole.** Changing to isavuconazole would not be recommended given the severity of illness.
- E. **Add an echinocandin.** Given that echinocandins are not active against *Blastomyces*, adding this medication would not be recommended¹⁴.

Correct answer: A.

Antifungal Treatment and Outcome

The patient was treated with liposomal amphotericin B 7.5 mg/kg daily while on ECMO. After 14 days, he was decannulated from ECMO, and the dosage of liposomal amphotericin B was lowered to 5 mg/kg daily. As he improved over the coming weeks, antifungal therapy was transitioned to itraconazole 200 mg PO twice daily with therapeutic drug monitoring. This was continued for 9 months.

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