

## Blasting Blasto – treatment of blastomycosis

### Transcript:

1	GG: Hello and welcome to Think Blasto! I am Dr. Greg Gauthier, an infectious diseases specialist at the University of Wisconsin.
2	JM: Yes, welcome to Think Blasto! I am Dr. Joe McBride, an infectious diseases specialist at the University of Wisconsin. This podcast series is designed to describe and outline a disease that is more common in Wisconsin than in most parts of the world: an infection called blastomycosis.
3	GG: The title of today's podcast is "Blasting Blasto - treatment of blastomycosis". In this podcast, we will discuss how blastomycosis is treated, what medications are used, medication side effects, and how successful treatment is.
4	JM: Thus, we will be talking about how blastomycosis is treated in human patients. In a separate podcast we will discuss treatment of blastomycosis in animals. So Greg, tell me how do we treat blastomycosis?
5.	GG: When most people think of treating an infection, they think of using antibiotics; however, antibiotics will not work against <i>Blastomyces</i> because it is a fungus not a bacteria. Rather antifungal medications, which can be given taken by mouth or administered intravenously are required for treatment of blastomycosis.
6.	JM: What antifungals can be used to treat it?
7.	GG: The major antifungal drugs used to treat blastomycosis are amphotericin B and itraconazole. The second drug, itraconazole is better known as Sporonox. Other antifungal drugs that can be used to treat blastomycosis include voriconazole, posaconazole, and isavuconazonium sulfate. Another antifungal drug, fluconazole, is not commonly used because it is not as potent as the other antifungal drugs
8.	JM: Okay Greg those are some really strange sounding names. On the Think Blasto! Website, we have the names of these antifungal drugs spelled that out.  One of the things I find fascinating about the field of infectious diseases is how the drugs that we use to treat infections were discovered. Greg, can you tell me a little bit about how the antifungal drugs used to treat blastomycosis were discovered?
9.	GG: Yes. The first drug you mentioned, Amphotericin B, was discovered in the 1950's by 4 researchers at the Squibb Institute for Medical Research in New Brunswick, New Jersey. Amphotericin B is a natural product, which means it is derived from a biological source, in this case, it is a bacteria that grows in the soil known as <i>Streptomyces nodosus</i> . The bacterial strain from which Amphotericin B was originally discovered was collected near a river in the country of Venezuela. In 1960, Amphotericin B became routinely available to treat invasive fungal infections like blastomycosis. In the 1990's newer formulations of Amphotericin B were developed that improved its tolerability and side effect profile.  Drugs such as itraconazole and voriconazole end with the word "azole" and are known as

	<p>azole antifungals. Unlike Amphotercin B, azoles are not considered natural products, rather they are made in chemistry lab. In the 1940's, Dr. Dilworth W. Woolley at the Rockefeller Institute for Medical Research in New York discovered that azole-based compounds could inhibit the growth of the fungus known as <i>Saccharomyces cerevisiae</i>. This fungus, <i>Saccharomyces cerevisiae</i>, is better known as brewers or bakers yeast, which is used to brew beer or make bread. However, it was not until 1958 that the 1<sup>st</sup> azole antifungal became available for human use. The primarily azole used to treat blastomycosis is itraconazole and was approved the Food &amp; Drug Administration in 1992. Since then, 3 other antifungal azole drugs have been approved by the Food and Drug Administration that have activity against <i>Blastomyces</i>.</p>
10.	<p>JM: Greg, that is an interesting historical perspective. So, amphotericin B originally came from a bacteria found in soil, whereas azole antifungals were originally made in a chemistry lab.</p> <p>Now that we know that there are quite a number of antifungal drugs that can be used to treat blastomycosis, how do doctors and other healthcare providers determine who should be treated and with what antifungals?</p>
11	<p>GG: Excellent question Joe. Currently there are 3 medical societies that have put forth treatment guidelines for blastomycosis. These include the Infectious Diseases Society of America, the American Thoracic Society, and the American Society for Transplantation. Fortunately the recommendations from these 3 medical societies are similar.</p>
12.	<p>JM: Greg, should all patients diagnosed with blastomycosis be treated?</p>
13.	<p>GG: Yes it is strongly recommended that all patients diagnose with blastomycosis be treated with antifungals. In the medical literature, there are a few reports of spontaneous resolution of symptomatic pneumonia due to blastomycosis, however, this likely a rare event. Moreover, it is impossible to predict the rare patient that will have spontaneous resolution of symptomatic pneumonia. A much more common scenario is that an untreated patient will develop progressive infection which puts them at risk for respiratory failure, dissemination other organs such as the skin, bone, or brain, and even death. Thus all 3 medical societies recommend treatment.</p>
14.	<p>JM: OK, now that we know all patients with blastomycosis should be treated how do you go about determining which antifungal drug should be used?</p>
15.	<p>GG: That is a great question. Antifungal drugs selection is influenced on whether the patient has a healthy or impaired immune system, whether the infection has spread from the lungs to other organs such as the brain, the overall severity of the infection, underlying medical conditions such as congestive heart failure, and potential for antifungal drugs to interact with medications the patient is currently taking. Thus, selection of the appropriate antifungal drug should be individualized.</p> <p>So Joe, tell me about what antifungal therapy would you recommend for a person with blastomycosis pneumonia that is severe enough to result in hospitalization.</p>
16.	<p>JM: For hospitalized patients, intravenous amphotericin B, our strongest drug, is typically</p>

	administered. This antifungal is considered fungicidal, which means it kills <i>Blastomyces</i> yeast. Typically, it is administered until there is clinical improvement, often 7 – 14 days, before the patient is switched to an azole antifungal, which can be given by mouth to complete the course of treatment.
17.	GG: Joe, since Amphotericin B is the most powerful drug against <i>Blastomyces</i> , is it given to all patients with blastomycosis.
18.	JM: No, it is not. We typically reserve it for persons with severe pulmonary blastomycosis because persons on Amphotericin B require close monitoring of the kidney function and electrolytes such as potassium and magnesium. Amphotericin B can be hard on the kidneys; however, there are several things we can do to keep the kidneys happy including using lipid formulations of amphotericin, administering normal saline intravenously before and after Amphotericin B infusions, and stopping other medications that can be hard on the kidneys. Amphotericin B can cause loss of potassium and magnesium through increased excretion of these electrolytes in the urine; we can replace these electrolytes either by mouth or intravenously to maintain normal blood levels of potassium and magnesium.
19.	GG: Thus, we reserve Amphotericin B for situations in which the benefits of its strong antifungal killing power outweigh the risks for side effects. We mentioned that hospitalized patients with severe pneumonia typically receive Amphotericin B. Joe, are there other situations in which Amphotericin B is recommended?
20.	JM: Yes, Amphotericin B, typically the lipid formulations, are recommended as initial therapy for persons with blastomycosis that involves the brain such as meningitis or brain abscesses. Lipid formulations of Amphotericin B are also recommended as initial therapy for immunocompromised patients with blastomycosis. Immunocompromised patients have a weakened immune system and are at higher risk for severe blastomycosis. Immunocompromise can be caused by organ transplantation, chemotherapy to treat cancer, high-dose steroids, or a group of medications known TNF-alpha inhibitors that are used to treat autoimmune disorders such as rheumatoid arthritis, lupus, ulcerative colitis, and Crohn's disease.  In addition, Amphotericin B is recommended for the entire duration for pregnant women with blastomycosis because azole antifungals can have adverse effects on the developing fetus, especially in the 1 <sup>st</sup> trimester. Thus, it is important that prior to starting therapy for blastomycosis that a woman of childbearing age undergoes a pregnancy test because this will influence the medications used to treat blastomycosis.
21	GG: To summarize, Amphotericin B is recommended in 4 scenarios: 1) for persons hospitalized with severe pneumonia, 2) infection that has spread to the brain, 3) those who are immunocompromised, and 4) women who are pregnant. Joe, we mentioned earlier in the podcast that azole antifungals such as itraconazole are used to treat blastomycosis. Tell me a little bit more about azole antifungals.
22.	JM: Azole antifungals are fungistatic against <i>Blastomyces</i> yeast, which means azoles inhibit the ability of <i>Blastomyces</i> yeast to grow but do not kill it quickly. This is why azole antifungals are reserved for persons with less severe blastomycosis or as therapy after a course of Amphotericin B is administered.

23.	GG: What do you mean by less severe blastomycosis?
24.	JM: This would be blastomycosis that can be treated in the outpatient clinic and does not require hospitalization.
25.	GG: We mentioned that itraconazole is the most common azole antifungal used to treat blastomycosis, could you tell me more about this drug?
26.	JM: Itraconazole can only be given by mouth, the intravenous version was discontinued from production about 20 years ago. There are two different formulations of itraconazole with one being a capsule and the other being a liquid solution. The capsule should be taken with food and an acidic beverage such as soda or orange juice. This will optimize absorption the capsule and result in improved levels itraconazole in the blood and the site of infection. For patients who are on stomach acid blockers for conditions such as heartburn or gastric acid reflux, the liquid solution is a better option because it does not require an acidic environment for optimal absorption into the bloodstream. In addition the liquid solution should be taken on an empty stomach.
27.	GG: That's pretty complicated so let me reiterate what you just said. Itraconazole capsules are taken with food and with an acidic beverage. Itraconazole liquid solution is the exact opposite, It is taken on an empty stomach and without an acidic beverage. If a person has concerns about how best to take itraconazole, they should talk with their pharmacist or health care provider.  We mentioned that Amphotericin B can be hard on the kidneys and cause wasting of electrolytes. What should health care providers and patients be aware about itraconazole?
28.	JM: In my experience, most, but not all patients tolerate itraconazole pretty well. Like almost any medication, it can cause GI upset such as nausea or diarrhea. Although itraconazole is very gentle to the kidneys, it can cause the liver to become irritated, but fortunately, that is uncommon in my experience. Thus, it is important to avoid alcohol when taking itraconazole or any azole antifungal medication. Rarely, itraconazole can cause blood potassium levels to be low, which can be corrected with oral supplementation of potassium.
29.	GG: Are there certain conditions in which itraconazole should be used with caution or avoided?
30.	JM: In persons with underlying congestive heart failure, itraconazole should be used with caution or an alternative azole antifungal should be used. This is because itraconazole has the potential to exacerbate congestive heart failure. This is unique to itraconazole and does <i>not</i> occur with other azole antifungals such as voriconazole, posaconazole, or isavuconazonium sulfate.  Greg, earlier in the podcast, you mentioned that drug-drug interactions influence selection of antifungals. Joe, could you tell a bit more about this?
31.	GG: Yes, for patients on Amphotericin B we want to avoid other medications that can be

	<p>hard on the kidneys or cause additional excretion of electrolytes in the urine.</p> <p>For patients on azole antifungals, there are a lot of drug-drug interactions and thus, it is important for health care providers and pharmacists to look for drug-drug interactions. One of the most common interactions we see in the clinic is between azole antifungals and statin medications, which are used to lower cholesterol. The azole antifungals can result in high levels of the statin drug in the blood, which increases the risk for muscle breakdown. Fortunately, there is one statin drug, known as pravastatin that can be used safely with the azole antifungals. Thus, we often have patients switch their statin drug to pravastatin to allow their cholesterol to continue to be treated during antifungal therapy.</p>
32.	JM: How long does treatment for blastomycosis last?
33.	<p>GG: That is a great question. Treatment duration for blastomycosis as well as other fungal infections is quite long and ranges from 6 – 12 months and in some cases, longer. For persons with a healthy immune system, treatment is generally a total of 6 months. Some exceptions include brain or bone infection, which requires 12 months. For a person with a weakened immune system, 12 months of therapy is recommended.</p> <p>For the majority of the treatment course, an oral azole antifungal is used. As mentioned previously, Amphotericin B, which is given intravenously, is reserved as initial therapy for persons with severe blastomycosis and is typically only used for the first 1-2 weeks of therapy. However, persons with blastomycosis involving the brain require longer rather than shorter courses of Amphotericin B, typically 4-6 weeks before switching to an oral azole antifungal. Also, women who are pregnant are generally treated for 6-8 weeks with Amphotericin B and oral azole therapy is avoided given potential for adverse effects on the fetus and the pregnancy.</p>
34.	JM: With such a long course of therapy, how do you monitor how the infection is responding to therapy?
35.	<p>GG: During treatment, I assess for improvement in symptoms, labs, and radiographic imaging findings. I also get routine monitoring labs such as a complete blood count, blood electrolytes, kidney function, and liver function tests.</p> <p>For many azole antifungals, drug levels in the blood can be obtained, which lets me know how well the antifungal drug is working. The frequency of obtaining these lab tests are individualized for each patient.</p> <p>I also monitor <i>Blastomyces</i> antigen levels in either the urine or blood. With successful therapy, the <i>Blastomyces</i> antigen levels decline and become undetectable. We mentioned the <i>Blastomyces</i> antigen test in our “Broad-Based budding yeast” podcast in which we discussed the diagnosis of blastomycosis. Thus, the antigen test can be used both for diagnosis and for monitoring response to treatment.</p>
36.	JM: In general, how good are the treatment outcomes in persons with blastomycosis.
37.	GG: Overall, the treatment outcomes are very good for blastomycosis. In general, more than 90% of patients are cured of their infection. But there are exceptions to this. In

	persons with severe blastomycosis pneumonia that requires care in the intensive care unit, outcomes are not as good as we would like because the infection is either overwhelming or there was a significant delay in recognizing the illness was due to blastomycosis or both. This is why it is always important to Think Blasto!, which can lead to earlier diagnosis and earlier initiation of treatment.
38.	JM: Once a person has completed treatment for blastomycosis, what is their chance of having the infection relapse?
39.	GG: When treatment guidelines are followed, relapse of infection is uncommon for persons with a healthy or weakened immune system. In a recently published study from the University of Wisconsin, which included 106 patients from the years 2004 – 2016, only 7 patients or 6.6% experienced relapse. A few of these cases of relapsed infection were due to short duration of therapy. Thus, the vast majority of persons treated for blastomycosis do not experience a relapse of infection.
40.	JM: So lets summarize what we have learned today
41.	GG: Antifungal drugs, not antibiotics are used to treat blastomycosis.
42.	JM: All patients with blastomycosis should be treated.
43.	GG: Antifungal drug selection for treatment of blastomycosis should be individualized for each patient.
44.	JM: In persons with severe blastomycosis or those who have weakened immune systems, Intravenous Amphotericin B is administered for 1 – 2 weeks before therapy is switched to an oral azole antifungal.
45.	GG: For patients with blastomycosis that can be treated in the outpatient clinic and does not require hospitalization, oral azole fungal can be used for the entire treatment course
46.	JM: Azole antifungal drugs should not be used in women who are pregnant. Any women of childbearing age should have a pregnancy test before antifungal therapy is started.
47.	GG: Treatment of blastomycosis is generally 6 – 12 months in duration.
48.	JM: While on treatment, clinical symptoms, labs, radiographic imaging, <i>Blastomyces</i> antigen levels, and antifungal drug levels are monitored to assess response to therapy.
49.	GG: Overall, treatment outcomes are very good for blastomycosis and risk for relapse of infection is quite low.
50.	JM: To our audience, thank you very much for your time and interest. Greg, I look forward to discussing more aspects of blastomycosis with you in the future.
51.	GG: And until next time, Think Blasto!