BLASTOMYCOSIS: PATHOPHYSIOLOGY, MANAGEMENT AND TREATMENT OF A UNIQUE EPIDEMIC DISEASE IN NORTH AMERICA

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While most endemic diseases are directly correlated with environmental factors or climate factors, there are also others that do not demonstrate the aforementioned factors. One such example is that of blastomycosis, also known as North American blastomycosis, which is a fungal infection primarily associated with the soil in the Great Lakes Basin, encompassing territory from Southern Canada throughout most of the Midwest United States [1][2]. The clinical manifestations of pulmonary blastomycosis range from asymptomatic infection to severe pulmonary infection, which can lead to the development of acute respiratory distress syndrome (ARDS) requiring the use of extracorporeal membrane oxygenator (ECMO) [5]. In addition, pulmonary blastomycosis can also cause extrapulmonary manifestations, also known as disseminated blastomycosis, which in turn can lead to infections within the skin, bone, and central nervous system [3][4]. The pharmacological treatment of pulmonary and disseminated blastomycosis is directly dependent upon the degree of severity, the host immune status, and whether the central nervous system has been implicated. This paper will explore the new guidelines in regards to the treatment of blastomycosis, as well as the mechanisms of action of the drugs involved in its treatment.

A disease unique to the Midwest yet little known among its residents, the geographical region impacted by blastomycosis extends eastward along the south shore of the St. Lawrence River Valley, southward along the central Appalachian Mountains in the east, and to the Mississippi River Valley in the west (Figure 1) [4].

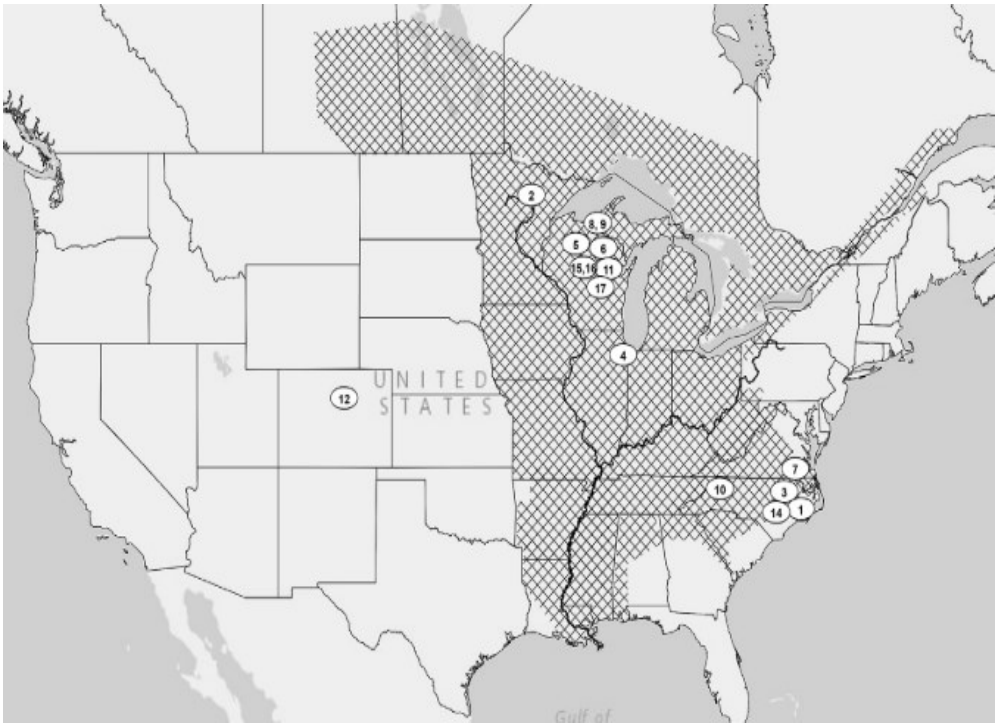

Figure 1 – Map of Distribution of Endemic Blastomycosis in North America. The numbers represent the distribution of the cases [4].

Blastomycosis is caused by dimorphic microfungus blastomyces *dematitidis*, a member of the *ascomycota* phylum, within the *ajellomycetaceae family* [7][8]. In order to begin to explore how blastomycosis is treated, it is necessary to first explore the pathogenesis of this infection. Recent analyses categorized blastomyces into either the *blastomyces dermatitidis* category or the *blastomyces gilchristii* category, which are both present in the soil and are aerosolized during activities that cause soil disruption [3][4][6]. When blastomyces are present within the soil, they undergo critical transformations when soil temperatures reach 22°C to 25°C, and later begin to produce infectious spores known as conidia. Conidia can be converted into yeast when exposed to temperatures ranging from 35°C to 37°C, which is what occurs in affected patients when inhaled [3][4]. When the conidia is inhaled, it is phagocytized by lung macrophages and neutrophils, and the portion of the conidia that survives at phagocytosis matures into yeast, as the lungs provide the perfect environment for conversion [3]. The transformation of the conidia into yeast is crucial, as it also causes a change in the composition of the cell membrane, increasing the amount of α (1-3) glucan within the cell wall [3][4]. In addition, blastomycosis yeast have high virulence and immune evasion from the innate and adaptive immune system. The transformation of the conidia into yeast allows the infection to transcend into the lungs parenchyma and vascular system, which in turns allows it to spread to many other vital organs. Also, when blastomycosis presents in the form of yeast, it is also able to inhibit host cell cytokine production, impair $CD4^+$ T-lymphocyte activation, and suppress nitric oxide production [3][4]. It is also important to note that blastomycosis yeast is resistant to reactive oxygen species produced by neutrophils and macrophages. For this reason, blastomycosis yeast is very difficult to treat within the human body, and it often causes organ damage in those affected ranging from asymptomatic subclinical infection to fulminant pulmonary infection [3][4].

The lungs are the primary entry point for the blastomycosis conidia, and pulmonary infection is typically reported in more than 79% of all documented cases [3]. Generally, the incubation period can vary from two to six weeks, during which time patients are asymptomatic. On the other hand, when patients begin to exhibit symptoms there is a high risk the patient has developed extrapulmonary dissemination, which generally involves an infection in the skin, bones, genitourinary tract, and central nervous system [3][4]. The spectrum of pulmonary infection can vary from subclinical pneumonia to ARDS. Although the treatment of pulmonary blastomycosis is highly case dependent, the Infectious Diseases Society of America (IDSA) recommends that all affected patients receive treatment, specifically antifungal therapy, regardless of the presence of symptoms [7]. Hospitals generally adopt two different treatment protocols in the treatment of blastomycosis: one for patients with mild or moderately pulmonary or disseminated blastomycosis, and a second protocol for patients with moderate-severe or severe pulmonary or disseminated blastomycosis with symptoms [3][4][7]. Generally, the first-line treatment for mild and moderate forms of pulmonary or disseminated blastomycosis is the use of the drug itraconazole, although it can be substituted by the less active drugs such as fluconazole or voriconazole. Differently, moderate-severe to severe forms of pulmonary or disseminated blastomycosis, as well as cases involving the central nervous system are generally treated with the administration of amphotericin B, which can be substituted with itraconazole or voriconazole in case of intolerance to itraconazole [4][7]. Pulmonary blastomycosis represents both a diagnostic and therapeutic challenge, due to its non-specific and wide spectrum of illness that can vary from asymptomatic infection to acute respiratory distress syndrome. The development of pulmonary blastomycosis in ARDS frequently is treated with specific antifungal drugs coupled with the use of ECMO [5]. The IDSA guidelines released in 2008 highly recommend the use of lipid amphotericin B as a first-line treatment for patients with moderate-severe to severe pulmonary blastomycosis, as well as several triazole drugs for patients with mild to moderate blastomycosis [7]. Despite more than fifty years of documented outbreaks, the IDSA guidelines are only based on clinical experiences, de-

scriptive studies, and reports of expert committees. A clinical trial has not yet been conducted to develop deeper knowledge of the infection, mainly due to the infrequency of outbreaks and small population size affected [7]. Despite the rarity of outbreaks, further research must be conducted to improve treatment plans, due to the relatively high mortality rate ranging from 4% - 6% associated with the infection [10]. In fact, the mortality rate can reach up to 89% in patients with ARDS, even when the appropriate antifungal treatment is received [10]. Continued research on blastomycosis and its therapeutic treatments is promising, and it will remain a fascinating infection due to its rarity and localization to a contained region of North America.

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