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profoundly hypoxemic and critically ill, many clinicians favor beginning therapy with an amphotericin B formulation combined with an oral triazole antifungal. The triazole antifungal therapy is continued alone once clinical improvement occurs and should be continued for 6 months to 1 year. The nodules that may occur after primary pulmonary coccidi oidomycosis do not require treatment. As noted above, these nod ules are not easily distinguished from pulmonary malignancies by means of radiographic imaging. Close clinical follow-up and biopsy may be required to separate these two entities. Most pulmonary cavities do not require therapy. Antifungal treatment should be con sidered in patients with persistent cough, pleuritic chest pain, and hemoptysis. Occasionally, pulmonary coccidioidal cavities become secondarily infected (see above). This development is often mani fested by an air-fluid level within the cavity. Bacterial oral flora or Aspergillus species are commonly involved, and therapy directed at these organisms should be considered. Surgical removal of the cavity may be required in cases of persistent productive cough and hemoptysis or in those cases of a persistently growing cavity. In addition, cavities >4 cm in diameter are unlikely to resolve sponta neously, and surgical extirpation should be considered. Surgery is always required in cases of pyopneumothorax. For chronic pulmo nary coccidioidomycosis, prolonged antifungal therapy—lasting for at least 1 year—is usually required, with monitoring of symptoms, radiographic changes, sputum cultures, and serologic titers. Most cases of disseminated coccidioidomycosis require pro longed antifungal therapy. The duration of treatment is based on clinical improvement in conjunction with a significant decline in serum CF antibody titer. Such therapy routinely is continued for at least several years. Relapse occurs in 15–30% of individuals once therapy is discontinued and it is important to continue to monitor such patients on a regular basis (e.g., every 3–4 months) after anti fungal therapy is discontinued. Coccidioidal meningitis poses a special challenge. While most patients with this form of disease respond to treatment with oral tri azoles, 80% experience relapse when therapy is stopped. Therefore, lifelong therapy is recommended. In cases of triazole failure, intra thecal or intraventricular amphotericin B may be used. Installation requires considerable expertise and should be undertaken only by an experienced health care provider. Shunting of CSF in addition to appropriate antifungal therapy is required in cases of meningitis complicated by hydrocephalus. It is prudent to obtain expert con sultation in all cases of coccidioidal meningitis. PREVENTION There are no proven methods to reduce the risk of acquiring coccid ioidomycosis among residents of an endemic region, but avoidance of inhalation of uncultivated soil or dust is a reasonable measure. For individuals with suppressed cellular immunity, the risk of developing symptomatic coccidioidomycosis is greater than that in the general population. Among those about to undergo allogeneic solid-organ transplantation, antifungal therapy is appropriate prior to transplantation when there is evidence of active or recent coc cidioidomycosis. Several transplant centers in the endemic region provide universal antifungal prophylaxis for 6 months to 1 year after solid-organ

and allogeneic stem cell transplantation, and lifelong universal prophylaxis has been advocated after lung trans plantation to prevent the development of coccidioidomycosis after transplantation. Cases of donor-transmitted coccidioidomycosis have been reported. Donors who are living or have lived in a coccidioidal endemic region should be screened serologically for coccidioido mycosis before transplantation and organ donation deferred if there is evidence of active infection. Data on the use of antifungal agents for prophylaxis in other situations are limited. The administration of prophylactic anti fungals is not recommended for HIV-1-infected persons who live in an endemic region. Most experts would administer a triazole antifungal to patients with a history of active coccidioidomycosis

or a positive coccidioidal serology in whom therapy with tumor necrosis factor-α antagonists or other biological response modifiers is being considered.

There are recent efforts to develop a vaccine for coccidioido mycosis, and a live avirulent product has demonstrated promising results in a canine model. Future studies will determine if this is a viable strategy for preventing or ameliorating coccidioidal infection in humans. ■ ■FURTHER READING Galgiani JN et al: 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis 63:e112, 2016. Gorris ME et al: Expansion of coccidioidomycosis endemic regions in the United States in response to climate change. Geohealth 3:308, 2019. Shubitz LF et al: Δcps1 vaccine protects dogs against experimentally induced coccidioidomycosis. Vaccine 39:6894, 2021. Taylor JW, Barker BM: The endozoan, small-mammal reservoir hypothesis and the life cycle of Coccidioides species. Med Mycol 57:S16, 2019. Troung CN et al: Universal lifelong fungal prophylaxis and risk of coccidioidomycosis in lung transplant recipients living in an endemic area. Clin Infect Dis 74:1966, 2021. CHAPTER 220 Gregory M. Gauthier, Bruce S. Klein

Blastomycosis Blastomycosis ■ ■DEFINITION Blastomycosis is a pyogranulomatous disease that follows the inhalation of Blastomyces conidia or hyphal fragments. Typically, Blastomyces causes pulmonary infection; however, a subset of patients will have dissemi nated disease that involves organs such as the skin, bone, brain, or geni tourinary system. Blastomycosis is considered a primary fungal infection because it affects persons with either intact or impaired immune systems. A delay in diagnosis is common because blastomycosis mimics other diseases such as bacterial pneumonia, tuberculosis, and malignancy. Diagnosis involves culture- and nonculture-based tests. Amphotericin B formulations and triazoles are the drugs of choice for treatment. ■ ■ETIOLOGY Blastomyces is a species complex comprising B. dermatitidis, B. gil christii, B. helicus, B. percursus, B. emzantsi, B. silverae, and B. parvus. B. silverae and B. parvus are not known to commonly infect humans. Blastomyces species exhibit thermal dimorphism, which involves the ability to convert between hyphal and yeast morphologies in response to temperature. In the soil (22–25°C), Blastomyces grows as septate hyphae that produce infectious conidia. Among the Blastomyces spe cies, B. helicus is unique because its hyphae grow in a coiled pattern and it does not sporulate under in vitro growth conditions. In organs and tissues (37°C), Blastomyces grows as a pathogenic yeast (Fig. 220-1) that elicits pyogranulomatous inflammation. The yeast form of all Blas tomyces species grows as broad-based budding yeast cells, with subtle differences in size among the different species (4–29 μm). ■ ■EPIDEMIOLOGY Although the majority of Blastomyces infections occur in North America, blastomycosis is a systemic fungal infection of global importance, with infections also occurring in Africa and Asia. In the United States, the traditional geographic range

for Blastomyces includes the Mississippi

FIGURE 220-1 Blastomyces yeast at 37°C, with broad-based budding between mother and daughter cells (arrow). Bar = 10 µm. (Gregory M. Gauthier, MD, MS.) and Ohio River basins, the St. Lawrence River basin, states bordering the Great Lakes, and southeastern states. In Canada, the traditional geographic range includes the provinces of Saskatchewan, Manitoba, Ontario, and Quebec. In North America, B. dermatitidis is located throughout the traditional geographic range. B. gilchristii is geographi cally restricted to Minnesota, Wisconsin, Canada, and areas along the St. Lawrence River. B. dermatitidis and B. gilchristii are thought to have diverged 1.9 million years ago during the Pleistocene epoch, with

B. gilchristii restricted to formerly glaciated areas. B. dermatitidis is found in glaciated and nonglaciated areas. In the environment, B. dermatitidis and B. gilchristii are not uniformly distributed; rather, they grow in eco logic niches often referred to as microfoci, which are characterized by acidic, sandy soils that are found near water and that contain decaying organic matter such as vegetation or wood. In upstate New York State, blastomycosis is an emerging pathogen in the Capitol District and upper Susquehanna River Subbasin with B. dermatitidis (88.4%) more com mon than B. gilchristii (11.6%). In Canada, blastomycosis is an emerging pathogen in the province of Saskatchewan. B. helicus infections have been reported in the western United States (California, Montana, Idaho, Colorado, Nebraska, Texas) and Canada (Saskatchewan, Alberta); their ecologic niche has yet to be defined. The geographic range and ecologic niche for B. parvus and B. silverae are unknown. PART 5 Infectious Diseases Outside of North America, blastomycosis has been reported in Africa (>100 cases), India (<10 cases), and Israel. On the basis of mor phologic analysis, nearly all clinical isolates of Blastomyces in Africa were originally thought to be B. dermatitidis. However, molecular phylogenetic analysis of human clinical isolates has demonstrated that multiple Blastomyces species exist in Africa, including B. derma titidis, B. gilchristii, B. percursus, and B. emzantsi. A combination of internal transcribed spacer (ITS) sequencing, multilocus sequence typing (MLST), and whole genome sequencing was used to identify a new species, B. emzantsi, and to differentiate B. percursus from other Blastomyces species. MLST has identified a B. dermatitidis isolate from Rwanda and B. gilchristii from Zimbabwe and South Africa. Analysis of 20 isolates from South Africa collected over a 40-year period identified them as either B. emzantsi or B. percursus. The geographic distribu tion and ecologic niche of the four Blastomyces species in Africa are unknown. In India, there have been fewer than 10 autochthonous cases of blastomycosis, with the majority identified by morphologic analysis. One autochthonous case (caused by B. percursus) with molecular con firmation has been reported from Israel. Epidemiologic information about blastomycosis derives primar ily from passive laboratory surveillance, retrospective studies, and

outbreak investigations. The lack of sensitive skin testing and serologic testing, along with difficulty in isolating Blastomyces from the envi ronment by culture or molecular methods, has limited an in-depth epidemiologic understanding of blastomycosis. In North America, blastomycosis is reportable in five U.S. states (Minnesota, Wisconsin, Michigan, Arkansas, and Louisiana) and two Canadian provinces (Manitoba, Ontario). The annual incidence of blastomycosis in the tra ditional endemic area ranges from 0.11 to 2.17 cases/100,000 persons. In older persons (Medicare beneficiaries, 1999–2008), the nationwide annual incidence of blastomycosis was 0.7/100,000, with the highest rates in the midwestern and southern regions of the United States. Analysis of Healthcare Cost and

Utilization Project (HCUP) data esti mated that 11,776 persons were hospitalized for blastomycosis in the United States from 2010 through 2020, with the majority of patients from midwestern (58.8%) and southern (31.4%) states. In certain places, such as Vilas County, Wisconsin, and Kenora, Ontario, blas tomycosis is hyperendemic, with annual incidence rates ranging from 40 to 117 cases/100,000 persons. Incidence data likely underestimate the true burden of infection because they are limited to persons with clinically apparent infection. Patients with asymptomatic or subclinical infections are undercounted. Most Blastomyces infections are sporadic and can occur in either rural or urban areas. There have been at least 20 outbreaks of blastomy cosis in the United States since the mid-1950s. Wisconsin, Minnesota, and North Carolina have had multiple outbreaks. The majority of outbreaks have been in rural areas, but several have occurred in urban settings. Activities associated with outbreaks include construction (of homes, cabins, factories, and roads), excavation of dirt, participation in water sports (canoeing, tubing on a river, and fishing), and exposure to a community compost pile or to beaver dams. Blastomyces infection is typically acquired from disturbed soil, which liberates infectious particles that are then inhaled into the lungs. An investigation of a blastomycosis outbreak in Marathon County, Wisconsin (2009–2010), found that 45% of patients were of Hmong ethnicity. A retrospective study from the Marshfield Clinic in Wiscon sin (1999–2014) found that 14.4% of patients with blastomycosis were of Asian ethnicity—a figure higher than was anticipated given that <2.5% of the population within the catchment area is Asian, includ ing a large Hmong population. These findings suggest that persons of Hmong ethnicity have an increased risk of acquiring blastomycosis. A combination of whole genome sequencing and immunologic analyses indicated that polymorphisms in the interleukin 6 (IL-6) gene in the Hmong population result in decreased IL-6 production, which in turn impairs development of IL-17-producing CD4+ T lymphocytes. IL-17 is a critical cytokine for recruitment and activation of innate immune cells such as neutrophils and macrophages active against Blastomy ces. Thus, alterations in IL-6 production may be responsible for the increased risk of blastomycosis in the Hmong population. Although data are limited, persons of Hmong ethnicity do not appear to be at increased risk for disseminated blastomycosis. Increased incidence rates of blastomycosis have also been reported in indigenous people of Canada and the United States. Compared with Caucasians, Asian and indigenous persons with blastomycosis tend to have fewer underlying medical conditions and to be younger. ■ ■PATHOGENESIS A defining feature of the Blastomyces species complex is the ability to respond to shifts in temperature by switching between hyphal and yeast forms. In the soil, Blastomyces grows as mold cells with hyphae that produce conidia. Hyphal growth promotes environmental sur vival, genetic diversity through mating, and production of infectious conidia that facilitate transmission of Blastomyces from the environ ment to mammals, including humans. At 37°C (the core temperature of mammals), Blastomyces hyphae and conidia convert into patho genic yeast that upregulate yeast phase–specific virulence factors and downregulate host immune defenses, thereby facilitating infection. Virulence traits that Blastomyces shares with Histoplasma, Coccidioides, Sporothrix, and Paracoccidioides are thermotolerance at 37°C, intracel lular survival, and capacity to cause infection in persons with either

healthy or impaired immune defenses. Although Emergomyces and Talaromyces marneffei (formerly Penicillium marneffei) exhibit thermal dimorphism, growth as yeast at 37°C, and intracellular survival, these dimorphic fungi tend to cause infection primarily in immunocompro mised persons. The morphologic switch from hyphae to yeast at 37°C is driven chiefly by temperature and is coupled with the uptake of exogenous cysteine. Cysteine uptake is required to

complete the transition to the yeast form because it helps restart mitochondrial respiration, which ceases during the morphologic switch. Over the past two decades, knowledge about the genetic mechanisms that promote the tempera ture-dependent transition between hyphae and yeast has substantially increased. The discovery of dimorphism-regulating kinase 1 (DRK1), which encodes a group III hybrid histidine kinase that is part of the high-osmolarity glycerol (HOG) signaling pathway, provided genetic proof that that the transition to yeast is essential for virulence of the thermally dimorphic fungi. Disruption of DRK1 by gene deletion or RNA interference resulted in Blastomyces cells that grew as hyphae at 37°C instead of yeast. Although viable at 37°C, these cells had altered cell-wall composition, failed to upregulate the Blastomyces adhesin 1 (BAD1, formerly WI-1) virulence factor, and were avirulent in a mouse model of lethal pulmonary infection. Subsequent studies of Histoplasma and Talaromyces demonstrated that the function of DRK1 is conserved with regard to thermal dimorphism and virulence. The temperature-dependent transition in the other direction—from yeast to hyphae—is regulated in part by a GATA-transcription factor encoded by siderophore biosynthesis repressor in Blastomyces (SREB), which influences neutral lipid metabolism. In addition, sensing of chitin by NGT1 and NGT2 N-acetylglucosamine transporters accelerates the conversion to hyphae following a drop in temperature from 37°C to 22°C. These two mechanisms are conserved in Histoplasma capsulatum. As a primary fungal pathogen, Blastomyces is one of the few fungi that can infect immunocompetent persons. In its yeast form, Blastomy ces evades and modulates immune defenses. Following disruption of soil, conidia that are aerosolized and inhaled into the lungs are phago cytosed by pulmonary macrophages, in which a subset of the conidia germinate as yeast and replicate during the early phases of infection. Blastomyces is also capable of replicating outside of macrophages. Upon conversion to the yeast phase, an essential virulence factor encoded by BAD1 is upregulated. BAD1 encodes a multifunctional 120-KDa cellsurface protein that facilitates yeast adherence to lung epithelial cells via interaction with heparin sulfate, attachment to host immune cells by binding to CR3 and CD14 complement receptors, and downregulation of tumor necrosis factor alpha (TNF-α) in macrophages and neutro phils. In addition, the BAD1 protein impairs activation of CD4+ T lym phocytes, thereby decreasing the production of IL-17 and interferon gamma (IFN-γ). In vivo transcriptional profiling of B. dermatitidis yeast during pulmonary infection demonstrated that BAD1 is the most highly upregulated gene. Deletion of BAD1 renders B. dermatitidis avirulent in a murine model of pulmonary infection. Thus, BAD-1 is essential for virulence in B. dermatitidis and likely in B. gilchristii as well. In contrast, BAD1 is absent from the sequenced genomes of

B. helicus, B. parvus, B. silverae, B. percursus, and B. emzantsi. Additional factors that contribute to the virulence of Blastomyces yeast include relative resistance to oxidative stress, upregulation of catalase and superoxide dismutase during infection, active uptake of zinc by a PRA1-encoded zincophore and transmembrane transporter (ZRT1), and cleavage of granulocyte-macrophage colony-stimulating factor by dipeptidyl peptidase IVA, which blocks activation of innate immune cells (macrophages, neutrophils) and their recruitment to the lung. APPROACH TO THE PATIENT Blastomycosis On the basis of outbreak investigations, it is estimated that 50% of persons exposed to Blastomyces develop symptomatic infec tion after a 3-week to 3-month incubation period. The relatively long incubation period means that patients can be diagnosed with

blastomycosis throughout the year. Blastomycosis has been referred to as the “the great pretender” because it can mimic infectious and noninfectious diseases. Blastomycotic pneumonia clinically and radiographically resembles community-acquired bacterial pneu monia, viral

pneumonia, tuberculosis, and lung cancer. Patients often receive two or three courses of antibiotics before pulmonary blastomycosis is diagnosed. Without fungal stain and culture, cuta neous lesions can mimic skin cancer, sarcoidosis, and pyoderma gangrenosum. Rarely, blastomycosis can mimic laryngeal cancer. The most important aspect of the approach to a patient with a compatible illness is the consideration of Blastomyces as an etiologic agent in the differential diagnosis. This awareness facilitates early diagnosis and treatment, enhancing the potential for improved clinical outcomes. Clinical clues to blastomycosis, especially in persons who reside in or visit endemic regions, include pneumonia that does not improve with antibiotic treatment, pneumonia with extrapulmonary manifestations (e.g., skin lesions, osteomyelitis, central nervous system [CNS] involvement), and skin ulcers that do not respond to standard therapy. Blastomycosis should also be considered in persons from (or visited) an endemic area who have unexplained respiratory failure or acute respiratory distress syn drome (ARDS). In addition, a detailed exposure history can elevate blastomycosis in the differential diagnosis; approximately 50–60% of patients will have environmental risk factors for blastomycosis. This history should also include inquiries about a pet or family member with blastomycosis; these factors have been reported in 7.7–10% and 4–9% of patients, respectively. CHAPTER 220 ■ ■CLINICAL MANIFESTATIONS Pulmonary Blastomycosis Pulmonary manifestations occur in 69–93% of patients with symptomatic blastomycosis and are the most common clinical feature of infection. Signs and symptoms can include fever, chills, productive or nonproductive cough, shortness of breath, hemoptysis, malaise, and decreased appetite. Pulmonary blastomycosis also can manifest as asymptomatic infection, a brief influenza-like ill ness, acute pneumonia, chronic pneumonia, or ARDS. Radiographic findings in the lungs include lobar consolidation, a mass lesion, inter stitial infiltrates, nodule(s), a miliary pattern, cavitary disease, and dif fuse involvement of multiple lobes. Hilar adenopathy, pleural effusion, and empyema are uncommon. No distinctive features differentiate blastomycosis from other pulmonary diseases. Diabetes, receipt of a solid organ transplant, immunosuppression, and multilobar pneumo nia are risk factors for severe pulmonary blastomycosis. Approximately 4–15% of patients with pulmonary blastomycosis develop ARDS, which is characterized by a fulminant course and high mortality rates ranging from 40 to 89% in most studies. The mortality rate in ARDS is increased when the diagnosis is delayed. Blastomycosis Disseminated Blastomycosis Disseminated blastomycosis occurs in 15–48% of patients and has the potential to involve nearly any organ in the body. The most common site of dissemination is the skin, in which the infection can manifest as papules, ulcers, verrucous lesions, or abscesses. The second most common site is bone, with consequent osteomyelitis characterized by bone pain, soft tissue swelling, soft tissue abscess, and sinus tract formation. Typically, a single bone is involved; however, multifocal osteomyelitis can occur. The most common sites for osteomyelitis include the spine, long bones, and ribs. Dissemination to the CNS (e.g., manifesting as meningitis, an abscess, or a mass lesion), the larynx, or the genitourinary system (e.g., to the prostate or epididy mis) occurs in fewer than 10%; the majority of the affected patients have concomitant involvement of other organs, such as the lung or the skin. Factors that influence dissemination include the infecting Blasto myces species, the duration of pulmonary symptoms, and concomitant AIDS. Multiple studies from Wisconsin, a state in which B. derma titidis and B. gilchristii are endemic, have demonstrated that B. der matitidis is more likely to cause disseminated infection (31.4–47.8% of cases), whereas B. gilchristii tends to remain localized to the lung (90.7–92.2%). Surprisingly, immunosuppression has only a minimal

influence on dissemination, an observation suggesting that Blastomyces virulence factors have a greater impact than host immune defenses. The frequency of disseminated blastomycosis among solid organ transplant recipients, persons receiving cancer chemotherapy, and patients under going pharmacologic immunosuppression is similar to that among patients with intact immune systems. Although patients treated with TNF-α antagonists are considered at risk for blastomycosis, the clinical manifestations and frequency of disseminated disease are unknown in this group because of a paucity of published data. Persons with AIDS and CD4+ T lymphocyte counts of <100/μL are an exception: they are at increased risk for CNS dissemination. Blastomycosis in pregnancy is uncommon, is typically diagnosed in the second or third trimester (91%), and most frequently manifests as pneumonia (74%) or dis seminated infection (48%). Transmission to the neonate by either the transplacental route or aspiration of infected vaginal secretions is rare. Persons infected with B. helicus can have localized pulmonary infection or disseminated disease; they are typically immunosuppressed (e.g., as a result of solid organ transplantation, chemotherapy, HIV infection, or lupus) and have a high mortality rate (71.4% in seven patients). In contrast to B. dermatitidis and B. gilchristii, B. helicus commonly causes fungemia. Infections with B. percursus and B. emzantsi are often of long duration (persisting for 4 weeks to 5 years) and can involve the lungs or become disseminated (skin, bone, brain).

■ ■DIAGNOSIS Timely diagnosis of blastomycosis requires a high degree of clinical suspicion because its clinical and radiographic presentations mimic more common etiologies, such as community-acquired pneumonia, malignancy, and tuberculosis. Laboratory findings such as leukocy tosis, mild anemia, increased C-reactive protein level, and elevated erythrocyte sedimentation rate are nonspecific. Once suspected, the diagnosis of blastomycosis is straightforward and involves microscopic examination of stained specimens, fungal culture, and antigen testing. The poor sensitivity of complement fixation (9%) and immunodiffu sion (28%) renders serologic testing diagnostically dispensable. How ever, a recently developed serologic test designed to detect antibodies to BAD1 has a sensitivity of 87% and a specificity of 94–99%. PART 5 Infectious Diseases A presumptive diagnosis of blastomycosis can be made by staining of clinical specimens and looking for broad-based budding yeast with a doubly refractile cell wall. Along with the broad-based budding pat tern, yeast size (4–29 μm) allows Blastomyces to be distinguished from other fungi. An exception is B. helicus, which has the potential to be confused with Histoplasma because of its small-sized yeast. Respiratory tract specimens such as sputum, tracheal aspirate, and bronchoalveolar (BAL) fluid can be stained with calcofluor, 10% potassium hydroxide, or Papanicolaou stain. Purulent drainage can be stained in a similar manner. The sensitivity of staining of respiratory samples ranges from 50 to 90%. Tissue samples for histopathology should be stained with Gomori methenamine silver or periodic acid–Schiff stain and assessed for pyogranulomatous inflammation and broad-based budding yeast. Traditional stains, such as Gram’s stain or hematoxylin and eosin, do not permit optimal visualization of Blastomyces yeast. Growth of Blastomyces in cultures of respiratory tissue or body fluid samples provides a definitive diagnosis of blastomycosis but typically requires 5–28 days of incubation. Special media such as Sabouraud dextrose, potato dextrose, and brain–heart infusion are required because Blastomyces does not grow well on standard bacterio logic media. Most clinical microbiology laboratories incubate fungal cultures at 25–30°C, a temperature that results in hyphal growth of Blastomyces. Unfortunately, Blastomyces hyphae are not morphologi cally distinct enough to confirm diagnosis. Thus, fungal identification and diagnosis are commonly confirmed via chemiluminescent DNA probe or, less commonly, via conversion to yeast upon incubation at 37°C. Diagnosis can also be

confirmed by polymerase chain reaction. Neither the chemiluminescent DNA probe nor morphologic analysis of yeast by light microscopy differentiates among the different species of Blastomyces. Moreover, some species, such as B. emzantsi, are difficult to convert to yeast at 37°C. The species of Blastomyces is not typically determined in clinical labs because DNA sequencing is required.

An antigen test that detects a conserved galactomannan component in the Blastomyces cell wall has supplanted serologic testing. This test can be performed on urine, blood, BAL fluid, and cerebrospinal fluid. The sensitivity of the antigen test is 85–93% for urine and 57–82% for serum. Infection burden appears to influence test sensitivity, with a lower burden of infection resulting in reduced sensitivity. The antigen test can detect B. dermatitidis, B. gilchristii, and B. helicus; however, its utility for detection of other Blastomyces species is unknown. Crossreactions in the antigen test occur during infection with other dimor phic fungi, including H. capsulatum (96%), Paracoccidioides species (100%), and T. marneffei (70%). Among these, only H. capsulatum is found in the same endemic region as Blastomyces. Rare cross-reactions can occur with Aspergillus and Cryptococcus infections. Antigen levels in urine and blood decline with successful treatment, and their mea surement can be used to monitor the response to antifungal therapy. TREATMENT Blastomycosis Guidelines for the treatment of blastomycosis have been published by the Infectious Diseases Society of America (2008), the American Thoracic Society (2011), the American Society of Transplanta tion (2019), and European Confederation of Medical Mycology (2021). Although there are isolated reports of self-limited pul monary blastomycosis, there are no criteria to determine which patients will experience a resolution of infection. Thus, treatment is recommended for all patients with blastomycosis in order to prevent progressive infection, respiratory failure, and disseminated disease. Antifungal selection is influenced by immune status, CNS involvement, pregnancy, medical comorbidities (e.g., congestive heart failure, prolonged QT interval), and drug–drug interactions. Antifungal drugs active against Blastomyces include amphotericin B

(AmB) formulations and triazoles. The minimal amount of beta- (1,3)-glucan in the Blastomyces yeast cell wall renders echinocan dins ineffective, and they should not be used to treat blastomycosis. Hematologic, hepatic, and renal function should be assessed prior to initiation of antifungal therapy, and possible drug–drug interac tions should be evaluated. In addition, patients should be educated about proper administration of triazole antifungals. For example, itraconazole capsules require an acidic gastric environment for optimal absorption and should be taken with food and an acidic beverage to improve bioavailability; they cannot be used by persons taking antacids, H2 antagonists, or proton pump inhibitors. In con trast, itraconazole solution can be given to patients receiving gastric acid–lowering therapies and should be taken without food. Treatment for blastomycosis is summarized in Table 220-1. For immunocompetent patients with pulmonary or disseminated blasto mycosis of mild or moderate severity (e.g., treatable in the outpatient setting), itraconazole therapy for 6 months is recommended. For severe blastomycosis (e.g., that requiring hospitalization), induction therapy with lipid AmB for 7–14 days (or until clinical improve ment), followed by itraconazole treatment for 6–12 months, is recommended. Although not well studied, combination antifungal therapy with lipid AmB and itraconazole (or another azole) can be considered for patients with severe pulmonary blastomycosis. In patients with ARDS, prednisone can be considered; however, the benefits of steroids are unclear. Osteomyelitis due to blastomycosis requires at least 12 months of antifungal therapy, and some patients may require surgical debridement. For blastomycosis involving the CNS, lipid AmB is administered for 4–6 weeks and is followed by treatment with voriconazole, itraconazole, or fluconazole for at least 12

months. Although fluconazole has excellent CNS penetration, its minimum inhibitory concentration (MIC) against B. dermatitidis and B. gilchristii is higher than that of either itraconazole or vori conazole. Emerging data suggest that isavuconazonium sulfate can be used for treatment of CNS blastomycosis. Immunosuppressed patients should be treated with 7–14 days of lipid AmB followed by 12 months of itraconazole. For patients

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