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Endemic Mycoses: Underdiagnosed and Underreported

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Blastomycosis, coccidioidomycosis, and histoplasmosis are the endemic mycoses that are most prevalent in North America. Exposure within the focal endemic regions is often unavoidable, and patients are frequently unaware of activities that increase individual risk. These fungi have traditionally had distinct geographic distributions, although these regions are expanding and the organisms are probably much more widespread. They occupy a specific ecological niche in the environment and are able to cause disease in healthy hosts. After the infectious “spores” are inhaled, these fungal pathogens often survive macrophage ingestion and escape, thereafter replicating and producing clinical illness.

Presenting symptoms of endemic mycoses are myriad, although pulmonary symptoms are most common. Systemic symptoms (fever, chills, cough, night sweats, fatigue) are nonspecific and thus may be attributed to a viral or bacterial cause given their often overlapping clinical similarity. When an endemic mycosis is erroneously diagnosed as a bacterial infection, antibiotics are frequently prescribed—often multiple times as patients fail to improve. This exposes patients to unneeded, inefficacious prescription medications and contributes to the development of antimicrobial resistance in the community. Delays in diagnosis can also contribute to increased health care costs and adverse outcomes ranging from prolongation of symptoms to hospitalization and even death in some cases (1).

Climatic temperatures and precipitation patterns play significant roles in the ecology of these environmentally acquired fungi. Climate change projections suggest that endemic regions are likely to expand, and current epidemiology indicates that expansion has already occurred. Coccidioidomycosis has been identified in Washington State, far north of the

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traditionally accepted endemic region (2). Similarly, an investigation of coccidioidomycosis cases in nontravelers residing in Nebraska is currently ongoing, suggesting eastward expansion. The range of histoplasmosis either is expanding or was not fully identified, with more cases locally acquired in the North and West and cases identified in Alberta, Minnesota, Wisconsin, and Michigan. In fact, histoplasmosis is probably ubiquitous worldwide, with some “hot spots” where it is clearly more endemic than in other areas. Cases of blastomycosis have also been observed outside its traditional region, although it remains unclear whether a new *Blastomyces* species (*B helicus*) plays a role in westward expansion (3).

The true range of these endemic mycoses therefore remains uncertain, but the traditional maps are clearly no longer useful. More than 10% of these infections are diagnosed outside their traditional region of endemicity, emphasizing the need for a travel history and increasing the likelihood that clinicians who are not familiar with these organisms will encounter them during daily practice. Even those who practice within traditionally endemic regions may have little prior experience with their recognition and treatment, given that almost 50% of U.S.-trained physicians begin their practice outside their state of residency training (4).

Although these infections are increasing in geographic reach and frequency, current guidelines on community-acquired pneumonia from the American Thoracic Society and the Infectious Diseases Society of America (5) do not offer specific testing or treatment recommendations. These guidelines serve a global audience, and comprehensive recommendations for specific geographic regions may not be feasible. However, in regions that are hyperendemic for endemic mycoses, the diagnosis and testing should be considered in all patients with suggestive illness. In patients who do not respond to initial antibacterial agents, a thorough travel history and additional diagnostic testing should be undertaken before a trial of a second antibacterial agent.

Missed opportunities to diagnose blastomycosis, histoplasmosis, or coccidioidomycosis are common, even when patients are seen within the endemic regions. For example, within the hyperendemic regions of California and Arizona, about 20% of all community-acquired pneumonia may be caused by coccidioidomycosis (6). Despite the frequency of infection, the median time between symptom onset and diagnosis often exceeds 3 weeks, leading to substantial increases in coccidioidomycosis-related health care costs (7), with antibiotics inappropriately prescribed to more than 70% of patients (8).

Similar observations have been made for histoplasmosis. In a study of patients diagnosed with histoplasmosis, the mean duration from initial presentation to diagnosis was 39 days, with one third of patients experiencing a delay of 50 days or more (9), and antibiotics were frequently prescribed to patients before their diagnosis. Blastomycosis has also been noted to be underdiagnosed, with a median of 23 days from initial presentation to diagnosis and a median of 2.5 antibiotic courses prescribed before the diagnosis (10).

Multiple factors contribute to these diagnostic and treatment delays. Knowledge of disease diagnosis and management varies widely among practitioners. Coupled with the increasing

travel of our patients, it is easy to envision the reasons for missed diagnostic opportunities. Directed continuing medical education improves diagnostic and treatment practices, although mandatory training on these regional infections has not been proposed. The lack of point-of-care diagnostics may also play a role in delayed diagnosis. Multiplexed platforms used for the diagnosis of respiratory infections do not include the endemic mycoses, and serum antibody and urinary antigen tests for the endemic mycoses are typically available only from reference laboratories, causing diagnostic delays. Some patients require invasive procedures (bronchoscopy or biopsy), leading to additional cost and delay. Few practitioners treat the endemic mycoses empirically in the outpatient setting while awaiting specific diagnostic tests.

Compounding these factors, most of the endemic mycoses are not uniformly reportable to public health agencies, frustrating attempts to define the true burden of infection. Improvements in our epidemiologic understanding of disease and the ability to capture changes in disease incidence at the county level would enable directed educational efforts, public health campaigns, and quality improvement initiatives to reduce the time to diagnosis and receipt of appropriate antifungal therapy. Reporting of veterinary disease would similarly help alleviate these issues and aid our understanding of the evolving epidemiology. Veterinary patients may assist in defining geographic spread by serving as “sentinels” indicating disease expansion.

Although these diseases have geographic niches, their ranges remain poorly characterized and seem to be expanding. We suggest the following: 1) national surveillance and disease reporting of endemic mycoses in both human and veterinary patients, 2) educational efforts directed at patients and providers, 3) inclusion of endemic mycoses in future community-acquired pneumonia guidelines, 4) development of point-of-care diagnostics to decrease the time to diagnosis and receipt of effective therapy, and 5) exploration of a pan–endemic mycoses vaccine to prevent infection. This multifaceted approach to the growing problem of the endemic mycoses may help with preventive efforts and the timely recognition and treatment of these diseases.

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