The breadth of fungi causing human disease and the spectrum of clinical presentations associated with these infections has widened. Epidemiologic trends display dramatic shifts with expanding geographic ranges, identification of new at-risk groups, increasing prevalence of resistant infections, and emergence of novel multidrug-resistant pathogenic fungi. Certain fungi have been transmitted between patients in clinical settings. Major health events not typically associated with mycoses resulted in larger proportions of the population susceptible to secondary fungal infections. Many health care-related, environmental, and socioeconomic factors have influenced these epidemiologic shifts. This review summarizes updates to clinically significant fungal pathogens in North America.

Various uncommon fungal pathogens have been increasingly identified as causes of disseminated and invasive fungal disease (IFD) worldwide. Growing recognition and clinical knowledge of these emerging fungal pathogens has occurred through improved molecular diagnostics, nucleic sequence databases, and taxonomic reclassification of medically significant fungi. However, emerging fungal diseases carry significant morbidity and mortality and, due to a paucity of published literature, the collective clinical experience with these fungi is often limited. In this review, we focus on unusual emerging fungal pathogens not extensively covered elsewhere in this issue of Infectious Diseases Clinics of North America.

Pathogenic fungi have several mechanisms of resistance to antifungal drugs, driven by the genetic plasticity and versatility of their homeostatic responses to stressful environmental cues. We critically review the molecular mechanisms of resistance and cellular adaptations of pathogenic fungi in response to antifungals and discuss the factors contributing to such resistance. We offer suggestions for the translational and clinical research agenda of this rapidly evolving and medically important field. A better understanding of antifungal resistance should assist in developing better detection tools and inform optimal strategies for preventing and treating refractory mycoses in the future.
Antifungal Susceptibility Testing and Identification 313
Sarah E. Kidd, Lucy C. Crawford, and Catriona L. Halliday

The requirement for antifungal susceptibility testing is increasing given the availability of new drugs, increasing populations of individuals at risk for fungal infection, and emerging multiresistant fungi. Rapid and accurate fungal identification remains at the forefront of laboratory efforts to guide empiric therapy. Antifungal susceptibility testing methods have greatly improved, but are subject to variation in results between methods. Careful standardization, validation, and extensive training of users is essential to ensure susceptibility results are clinically useful and interpreted appropriately. Interpretive criteria for many drugs and species are still lacking, but this will continue to evolve.

Antifungals in Clinical Use and the Pipeline 341
Melissa D. Johnson

Over the past 15 years, there has been an increase in the development and utilization of newer antifungal agents. The ideal antifungal, however, in regard to spectrum of activity, pharmacokinetic/pharmacodynamic properties, development of resistance, safety, and drug interaction profile remains elusive. This article reviews pharmacologic aspects of Food and Drug Administration–approved polyenes, flucytosine, azoles, and echinocandins as well as promising pipeline antifungal agents. Unique properties of these newer agents are highlighted. The clinical role of established and investigational antifungal agents as treatment and/or prevention of invasive fungal infections is discussed.

Immunology of Fungal Infections 373
Oscar A. Fernández-García and Jennifer M. Cuellar-Rodríguez

Complex processes mediate immunity to fungal infections. Responses vary depending on the organism, morphogenic state, and infection site. Innate immune effectors such as epithelia, phagocytes, and soluble molecules detect pathogens, kill fungi, release cytokines, and prime the adaptive response. Adaptive responses to mucocutaneous or invasive disease are markedly different but intersect at certain pathways (molecules required for IL-23 and IL-12 signaling). Many of these pathways have been elucidated from the study of inborn errors of immunity. This review explores the general aspects of antifungal immunity and delves into the mechanisms that mediate protection from frequently encountered fungi.

Candidemia and Invasive Candidiasis 389
Todd P. McCarty, Cameron M. White, and Peter G. Pappas

Invasive candidiasis (IC) is a collective term that refers to a group of infectious syndromes caused by a variety of species of Candida, 6 of which cause most cases globally. Candidemia is probably the most commonly recognized syndrome associated with IC; however, Candida can cause invasive infection of any organ, especially visceral organs, vasculature, bones and joints, the eyes and central nervous system. Targeted prevention and empirical therapy are important interventions for patients at high
risk for IC, and the current approach should be based on a combination of clinical risk factors and non–culture-based diagnostics, when available.

**Aspergillosis: Epidemiology, Diagnosis, and Treatment**

Jose Cadena, George R. Thompson III, and Thomas F. Patterson

The spectrum of disease produced by Aspergillus species ranges from allergic syndromes to chronic pulmonary conditions and invasive infections. Invasive aspergillosis is a major cause of morbidity and mortality in immunocompromised patients. Risk factors continue to evolve and include newer biological agents that target the immune system and post-influenza infection; and it has been observed following COVID-19 infection. Diagnosis remains a challenge but non–culture-based methods are available. Antifungal resistance has emerged. Voriconazole remains the treatment of choice but isavuconazole and posaconazole have similar efficacy with less toxicity. Combination therapy is used with extensive infection and in severe immunosuppression.

**Mucormycosis**

Julie M. Steinbrink and Marisa H. Miceli

Mucormycosis is a rare but aggressive fungal disease that mainly affects patients with poorly controlled diabetes mellitus and those who are severely immunocompromised, including patients with hematological malignancies and solid organ transplant recipients. Early recognition of infection is critical for treatment success, followed by prompt initiation of antifungal therapy with lipid formulation amphotericin B. Posaconazole and isavuconazole should be used for stepdown and salvage therapy. Surgical debridement is key for tissue diagnosis and treatment and should be pursued urgently whenever possible. In addition to surgery and antifungal therapy, reverting the underlying risk factor for infection is important for treatment response.

**Coccidioidomycosis**

Derek J. Bays and George R. Thompson III

Coccidioidomycosis, caused by the dimorphic pathogenic fungi Coccidioides immitis and Coccidioides posadassi, is endemic to the southwestern United states and Central and South America. The incidence of coccidioidomycosis continues to increase. Coccidioidomycosis is typically a self-limiting influenza-like respiratory illness; however, it can lead to disseminated disease outside of the lungs. Not all nondisseminated cases require therapy, but antifungal therapy is typically beneficial requiring treatment ranging from months to lifelong. Clinical factors related to treatment decisions include severity of symptoms, radiography, coccidioidomycosis serologic results, and concurrent medical problems including immunosuppression. This review summarizes the epidemiology, clinical manifestations, and treatment options.

**Histoplasmosis**

Ana Belén Araúz and Padmasayee Papineni

Histoplasmosis is one of the commonest endemic mycoses in the Americas yet is often underdiagnosed and neglected as a public health priority.
This review outlines the evolving understanding of its epidemiology and the clinical syndromes of histoplasmosis, in addition to up-to-date diagnostic and treatment guidelines. A focus on histoplasmosis in advanced HIV is included. The challenges pertinent to histoplasmosis management in Latin America, with recommendations made through international expert consensus are discussed.

Cryptococcosis

Alexis C. Gushiken, Kapil K. Saharia, and John W. Baddley

Cryptococcosis is an invasive fungal infection of global significance caused by yeasts of the genus Cryptococcus. The prevalence of HIV in certain areas of the world and the expanding population of immunocompromised patients contribute to the ongoing global disease burden. Point-of-care serologic testing has allowed for more rapid diagnosis and implementation of screening programs in resource-limited settings. Management involves therapy aimed at reduction in fungal burden, maintenance of intracranial pressure, and optimization of host immunity. Despite diagnostic and therapeutic advances, cryptococcosis continues to be a disease with unacceptably high incidence and mortality, particularly in resource-limited settings.

Blastomycosis

Patrick B. Mazi, Adriana M. Rauseo, and Andrej Spec

Blastomycosis is the fungal disease caused by thermally dimorphic fungi in the genus Blastomyces, with B dermatitidis complex causing most cases. It is considered hyperendemic in areas adjacent to the Great Lakes and along the St. Lawrence, Mississippi, and Ohio rivers, but definitive geographic distribution of blastomycoses remains obscure. Clinical presentation is variable. Disseminated blastomycosis with extrapulmonary manifestations is more common in immunosuppressed individuals. Culture positivity is required for definitive diagnosis, but compatible histology is often sufficient for presumptive diagnosis and initiation of treatment. Treatment should be provided to all symptomatic cases to prevent progression or recurrence.