Epidemiology of Systemic Fungal Diseases: An Overview

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The epidemiology of systemic fungal diseases has evolved rapidly over the past 2 decades. Advances in medical treatment have led to improved survival in the general population, but these advances have also led to larger numbers of individuals (including those who have indwelling catheters, who are in intensive care, who have received various immunosuppressive therapies, and who are undergoing organ or stem cell transplantation) being at risk for fungal infection. The global human immunodeficiency virus (HIV) pandemic has led to unprecedented numbers of opportunistic fungal infections, including candidiasis, cryptococcosis, histoplasmosis, and penicilliosis. While the numbers have dropped dramatically in developed nations [1–4], many countries in sub-Saharan Africa [5–7] and parts of Asia [8–10] remain highly affected by these and other fungal diseases. Migration patterns, land use, and climate factors are thought to have contributed to a marked increase in the incidence of coccidioidomycosis [11] in the endemic areas of the southwestern USA and in the emergence of *Cryptococcus gattii* infections [12, 13] in British Columbia, Canada, and the Pacific northwestern USA.

This chapter will focus on public health aspects of systemic fungal diseases. It will discuss principles of epidemiology, risk factors, and prevention of infection by using specific fungal diseases as examples of broader public health principles. Major public health issues will be discussed, including potential strategies for minimizing morbidity and mortality related to fungal diseases.

Cycle of Disease Prevention

Prevention of disease is the ultimate goal of public health. Prevention measures may include limiting risk factors, developing educational campaigns, and administering vaccination programs, but can also include improved methods for early diagnosis or improved treatment strategies to prevent disease sequelae. Once measures are identified it is important to act to reduce disease and disease-related morbidity and mortality.

In order to achieve the ultimate goal of prevention, public health activities need to encompass a wide array of interrelated issues, including understanding disease occurrence or incidence (the number of new cases of a disease during a period of time), performing surveillance to identify disease, investigating outbreaks to determine the source and stop disease transmission, defining risk factors for disease, and ultimately implementing prevention strategies. Some in public health refer to these activities as the cycle of disease control and prevention (Fig. 1).

As depicted in Fig. 1, activities of public health are related and lead from one to another. For example, surveillance can determine the incidence of disease in a given population. Surveillance may also help identify outbreaks of disease and may lead to further epidemiologic investigation. These activities are useful to identify risk factors or prevention measures, as well as to guide applied research projects so that epidemiologic findings can be better understood. Applied research may in turn identify useful prevention tools, such as new vaccine candidates.

Finally, an important role of public health is to measure the effect of prevention measures and to determine how to improve the effectiveness of any prevention effort. This is performed through continued surveillance for the disease, thus beginning the cycle anew.

Surveillance

Public health surveillance is defined as the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health [14, 15]. It is one of the most vital functions of public health agencies. Surveillance data are used to measure the burden and trends of diseases, to detect new pathogens, and

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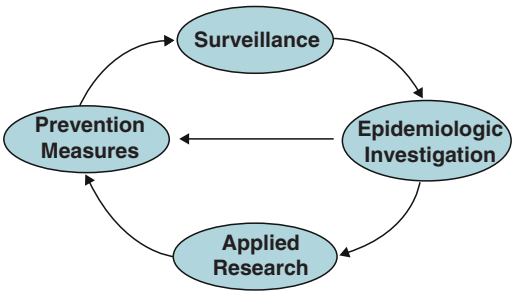

Fig. 1 The cycle of disease control and prevention

to evaluate quality of care [15]. It is also essential to determine the effectiveness of interventions such as prevention guidelines and vaccination programs. Various epidemiologic surveillance systems (to be distinguished from microbiologic surveillance) have been used to examine systemic fungal diseases [3, 7, 16–25].

Surveillance systems can vary by the population under surveillance (population-based surveillance vs sentinel surveillance), or by the method of data collection (active vs passive surveillance).

Population-Based Surveillance

Population-based surveillance is a type of surveillance performed within a well-defined catchment area where data on the population are accessible. This catchment area is often a geographic location, such as a city, county, state, or province, because a reliable population can be derived from census data. In population-based surveillance programs, all cases of the disease under surveillance in the catchment area are identified. However, only cases occurring among residents of the catchment area are counted toward the incidence calculation because the denominator (population as defined by census) only includes residents of that geographic area. Incidence can then be calculated as the number of new cases occurring in the population during a defined time period, divided by the total population (i.e., cases of disease per 100,000 residents of the surveillance area per year).

Population-based surveillance programs for a number of systemic fungal diseases have now been conducted in a number of different countries worldwide. For example, the Centers for Disease Control and Prevention (CDC) conducted population-based surveillance for *Candida* bloodstream infections (candidemia) at different sites in the USA during 1992–1994, and again during 1998–2000. These studies were conducted in metropolitan San Francisco and Atlanta (1992–1994) [26], Baltimore City/County, and the state of Connecticut (1998–2000) [20] and showed that the annual incidence of candidemia was 8–10 cases per 100,000 population [20, 26]. Another population-based surveillance conducted in the state of Iowa between 1998 and 2001 demonstrated an annual incidence of candidemia of 6 cases per 100,000 population [27]. Population-based surveillance has also been conducted in a number of European countries, where the annual incidence of candidemia has been lower, generally between 1.8 and 4.9 cases per 100,000 persons [16, 28–31].

Population-based surveillance has the advantage of providing the most representative description of the epidemiology of a disease in the area under surveillance, because large numbers of individuals may be included and because cases are detected in a multitude of settings, from small outpatient clinics to large tertiary-care centers. For example, in the population-based surveillance of candidemia in Connecticut and Baltimore, a total of 4.7 million persons were under surveillance in 47 hospitals [20]. However, performing such wide-scale surveillance often requires considerable expense and is difficult to sustain for long periods of time.

Another type of population-based surveillance is one in which the catchment area is not defined by geography, but by a common cohort (group) of persons. In such cohort studies, adequate follow-up is essential to determine the presence or absence of infection and therefore inclusion as a case of disease or as a noncase. Cohort studies, as opposed to geographically defined populations, are advantageous when only subsets of the general population are at risk for a certain infection. For example, a cohort study conducted among persons with HIV in Uganda during 1995–1999 determined an annual incidence of cryptococcosis of 4.0% [5].

Recently, a cohort strategy was used to determine incidence of fungal diseases in a transplant population. CDC, in partnership with academic transplant centers across the USA, conducted surveillance for invasive fungal infections among stem cell and organ transplant recipients between 2001 and 2006 [32]. This network of tertiary care transplant centers was appropriate for surveillance of this patient population because these procedures are generally only performed at these types of institutions. Data from this large network are more broadly representative of systemic fungal diseases following transplantation performed in the USA than studies from individual centers.

Sentinel Surveillance

Another important type of surveillance is sentinel surveillance. This is usually conducted at selected sites (often medical centers), rather than in the entire population of a geographic area. Sentinel surveillance is generally easier to perform and less costly than population-based surveillance, and as a result, is performed more frequently. Although it is not possible to estimate the total burden of disease in a population with this form of surveillance, it can

be helpful for diseases such as candidemia for which the at-risk population is captured.

Since candidemia is primarily a healthcare-associated infection, hospitals are good sites for sentinel surveillance, since hospital-based denominators such as hospital admissions and patient-days can be used. As a result, numerous sentinel surveillance studies for candidemia have been performed. Published incidence rates for candidemia have ranged from 2.0 cases per 10,000 hospital admissions in France during 1997–1999 [33] to 24.9 cases per 10,000 admissions in Brazil during 2003–2004 [17]. Explanations for these differences in incidence rates by geographic region are not obvious, but may be related to differences in the prevalence of particular risk factors in the population. Such factors likely include differences in antibacterial or antifungal agent use, differences in patient demographics, including race and sociodemographic factors, infection control practices, or medical care, such as frequency of central venous catheter utilization or abdominal surgery.

One particular benefit of performing surveillance over time is to be able to determine trends in incidence. In the examples we have noted earlier, studies conducted over time cannot only determine if the incidence of candidemia in general is changing, but can also detect changes in the incidence of individual pathogens. Some surveillance data from intensive care units in the USA have suggested that although the species distribution has shifted from predominantly *Candida albicans* in the 1980s to an increase in the proportion of non-*albicans* species during the 1990s, it was a decrease in the incidence of *C. albicans* that led to this shift [24]. Some reports from Europe have demonstrated stable incidence rates of both *C. albicans* and non-*albicans* candidemia [34], while others have actually demonstrated an increase in candidemia incidence overall [30, 31].

It is important to distinguish surveillance from disease registries, which are collections of cases. Registries can be useful sources of information about clinical details of cases, particularly for rare diseases, such as mucormycosis [35], or even for diseases occurring in special hosts, such as transplant recipients [36, 37]. However, for the purposes of public health surveillance, registries are of limited value. They do not provide information on incidence because meaningful and appropriate denominator data do not exist. Registries are also subject to ascertainment bias, in which selected participation or case finding can lead to biased data. As a result, registries may not be representative of broader populations and probably should not be interpreted as such.

Active Surveillance

Active surveillance is a surveillance method whereby data collection is initiated by the investigator or public health authority. In these systems, one or more components of the surveillance, such as case finding and detection, are performed consistently and periodically throughout the length of the surveillance period. An example of active surveillance is a system whereby microbiology laboratory records are reviewed and audited periodically to detect new cases of a disease. Clinical information about the cases may then be collected and recorded to describe the epidemiology.

Active surveillance for fungal diseases is expensive and often difficult to conduct, but it results in more complete and accurate information because virtually all cases of the disease in question are being counted. It has enabled accurate population-based incidence rates to be determined for several invasive fungal infections, including *Candida* bloodstream infections and cryptococcosis [3, 16, 17, 19, 20, 23, 26]. It has also permitted a more representative description of the epidemiology of these diseases.

One difficulty with performing active surveillance is the amount of resources required to sustain this effort for prolonged periods. Dedicated staff are generally needed to perform case finding and confirmation, as well as to recover clinical data. Isolates are often submitted to a central laboratory, which may perform species confirmation and antimicrobial susceptibility testing. Because of the resources required, surveillance may not be conducted continuously in order to measure trends in incidence. One strategy to overcome this is to repeat surveillance at periodic intervals in the same population. Active, population-based surveillance for candidemia is currently ongoing in Atlanta and Baltimore, where population-based surveillance was performed previously [20, 26]. These data will describe the changing epidemiology of candidemia in these populations and ascertain whether changes in incidence of antifungal susceptibility or species distribution have occurred.

Passive Surveillance

Passive surveillance systems are provider-initiated: the data are reported to public health authorities without being actively requested. The vast majority of public health surveillance is passive. The advantage of passive surveillance systems is their low cost, as fewer resources are required. However, the quality and completeness of the data are not as high as that collected through active systems.

An example of a passive surveillance system for a fungal disease is the notifiable disease surveillance system for coccidioidomycosis. In the endemic states of the southwest USA, cases of coccidioidomycosis are reported by providers or laboratories to state health departments. Data submitted generally include basic demographic data only. Total case counts are then submitted to CDC, which compiles and

reports state, regional, and national data in the Morbidity and Mortality Weekly Report (available at www.cdc.gov/mmwr.pdf).

These data show that the incidence of coccidioidomycosis has been increasing steadily, especially in the endemic states of Arizona and California [38, 39]. In Arizona, coccidioidomycosis is now the third-most-common infection reported to the state health department with an annual incidence of 91 per 100,000 population in 2006 [40]. In California, in 2006, the overall incidence in the state was 8 per 100,000 population, but in the highly endemic area of Kern County, the incidence was 150 per 100,000 population [39].

Passive surveillance data, while easier to collect, are often limited in scope. Clinical and demographic data, which would require more active methods to capture, are often sparse. In addition, case counts may not be complete, as the public health authority is not actively collecting cases or performing audits to ensure that all cases have been reported.

Issues with Surveillance

Case Definitions

In order to perform reliable surveillance for a disease, standard case definitions must be applied. Case definitions may vary depending on their purpose. For example, a definition used for surveillance purposes may not need to be as strict as a definition used for enrollment criteria in a clinical trial.

One example of this is the case definition used for invasive mould infections. Although consensus case definitions have been developed for clinical trial enrollment of immunocompromised patients with cancer and hematopoietic stem cell transplant recipients, [41, 42] these definitions are complicated and are therefore cumbersome for surveillance purposes.

Establishing accurate incidence estimates of invasive mould infections, such as aspergillosis and zygomycosis, remains a major challenge. CDC performed active population-based surveillance for mould infections as a part of a broader laboratory-based fungal surveillance conducted in San Francisco in 1992–1993 [23]. However, for case detection this study relied on laboratory reports of positive fungal cultures [23]. This case definition may not have been accurate: A positive mould culture has a poor positive predictive value because it fails to distinguish between colonization and infection. Furthermore, not all mould infections result in a positive culture result. Indeed, patients who are diagnosed with an invasive mould infection often have this diagnosis reached by a combination of approaches including culture, histopathology, and increasingly, antigenic markers, such as galactomannan. When future surveillance studies in the general population are performed, simpler and more reliable surveillance case definitions for mould infections will need to be developed.

Case definitions can be complicated, but public health authorities have sometimes been successful in simplifying these definitions for surveillance purposes. Prior to 2007, the serologic component of the case definition for coccidioidomycosis required a documented rise in IgG titer for a case to count as a reportable infection. After consulting with experts in the disease and considering the relative cost and benefit of a simplified definition, the Council of State and Territorial Epidemiologists in 2007 agreed to modify the case definition to include persons with a single positive serologic test result as adequate for definition of a case for surveillance purposes [43]. This simplified surveillance case definition may result in an increase in reported cases, but is likely to provide a better total estimate of the burden of disease, and this will be helpful for public health purposes.

Administrative data, such as International Classification of Diseases (ICD) codes, have also been used for fungal surveillance. These data are often used as the case definitions for surveillance. However, since administrative data are usually coded by personnel who are trained for reimbursement purposes, these criteria have been shown to have poor predictive value for fungal diseases, such as aspergillosis, when used as a case definition [44]. Their sensitivity for screening for fungal diseases is considerably more useful.

Burden of Disease

Understanding the actual burden of a disease as it relates to other diseases is one of the major challenges for public health. In most cases, surveillance systems do not accurately estimate the total burden of disease in a population. Often this occurs because there are many steps between the actual reporting of a case of disease and its occurrence in a population. To begin with, a person must have symptoms of disease; these must rise to the level of concern to initiate a visit to a clinician for evaluation. The clinician must then collect an appropriate sample and submit it to a capable laboratory. The laboratory must identify the causative organism by an appropriate methodology. Lastly, the case must be reported to public health authorities by the defined method used for surveillance. These steps, when taken together, constitute what can be described as the burden of illness pyramid (Fig. 2a) [45]. The shape of the pyramid varies for every disease and situation (Fig. 2b). For example, for a disease such as a viral hemorrhagic fever, it is likely that nearly all of the cases in a population will be

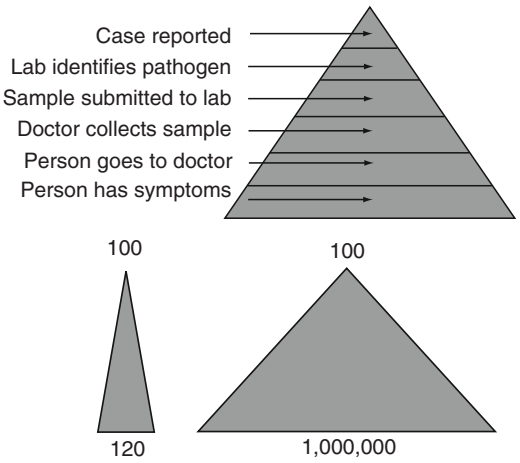

Fig. 2 (**a**) and (**b**) Pyramid of surveillance

detected; but for a disease such as salmonellosis, studies have demonstrated that only 1 in 38.6 cases are reported to public health authorities [46].

Because surveillance may not estimate the entire burden of a disease, it is helpful to estimate the incidence using burden of disease calculations. Burden of disease estimates allow for comparison with other disease burdens and help public health authorities determine disease priorities and resource allocation. CDC and the World Health Organization have conducted numerous studies to measure the burden due to specific diseases throughout the world [47–50].

One of the most striking estimates recently was the global burden of cryptococcal meningitis, including yearly cases and deaths, in persons with HIV infection [51]. According to the estimate, approximately 958,000 cases of cryptococcal meningitis occur each year (range, 371,700–1,544,000) (Table 1). The region with the greatest number of cases was sub-Saharan Africa, with 720,000 cases per year, followed by South and Southeast Asia, with 120,000 cases per year. Western and Central Europe (500 cases) and Oceania (100 cases) had the fewest number of estimated cases. In addition, an estimated 625,000 deaths were estimated to occur globally, with most deaths in sub-Saharan Africa, with over 500,000 deaths per year.

Similar burden of disease estimates have not been developed for other systemic fungal diseases. Such estimates would allow public health agencies to place particular diseases in the context of other diseases. In the case of cryptococcosis, the recent burden estimates showed that the disease is one of the leading causes of infection-related mortality in sub-Saharan Africa [51] and the most common cause of meningitis in that part of world. It is estimated to cause more deaths in this region than diseases such as tuberculosis, which are more common in the population (Fig. 3) [50].

Table 1 Estimated cryptococcal meningitis (CM) cases and deaths among 10 UN AIDS global regions by using published incidence rates from studies conducted in those regions (Adapted from [51])

Region	Estimated yearly CM cases (range), in 1,000 s	Estimated deaths (range), in 1,000 s
Sub-Saharan Africa	720 (144.0–1,296.0)	504.0 (100.8–907.2)
East Asia	13.6(2.7–24.5)	1.2 (0.2–2.2)
Oceania	0.1 (0.0–0.1)	0.009 (0.0–0.009)
South and Southeast Asia	120 (24.0–216.0)	66.0 (13.2–118.8)
Eastern Europe, Central Asia	27.2 (5.4–49.0)	15.0 (3.0–27.0)
Western and Central Europe	0.5 (0.1–1.0)	0.045 (0.009–0.09)
North Africa, Middle East	6.5 (1.3–11.6)	3.6 (0.7–6.4)
North America	7.8 (1.6–14.0)	0.7 (0.1–1.3)
Caribbean	7.8 (1.6–14.1)	4.3 (0.9–7.8)
Latin America	54.4 (10.9–97.9)	29.9 (6.0–53.8)
Global	957.9 (371.7–1,544)	624.7 (125.0–1,124.9)

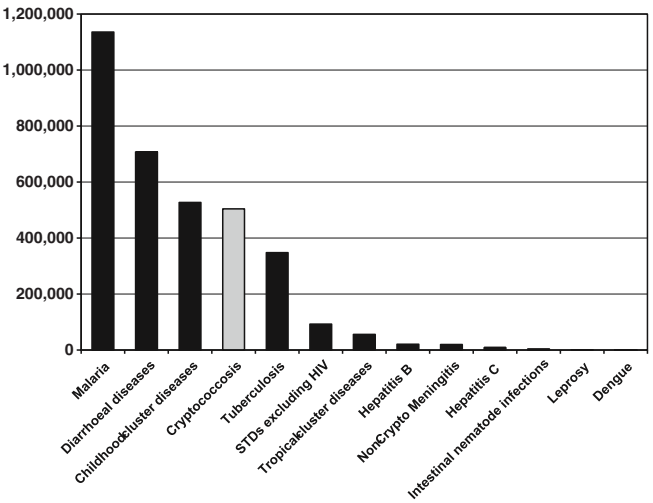

Fig. 3 Comparison of deaths in sub-Saharan Africa due to human immunodeficiency virus (HIV)-related cryptococcosis and common infectious diseases, excluding HIV, as estimated by WHO [51]

Reducing the Public Health Burden of Systemic Fungal Diseases

The ultimate goal of public health is to reduce morbidity and mortality related to a disease, either through reduction of the number of cases of a disease or by improving the outcomes associated with the infection. Prevention of some fungal infections may be performed by identifying outbreaks and eliminating the transmission of disease. Fungal outbreaks may be associated with hospital construction [52, 53],

point-sources from the community [54–56], and even novel medical devices [57, 58]. An adequate understanding of the mechanisms of transmission of these infections has important implications for prevention strategies, ranging from the need for specific containment and environmental control measures to the consideration of antifungal drug prophylaxis.

Environmental Control Measures

The ubiquitous occurrence of many opportunistic moulds in the environment and the ecology of others, such as the endemic pathogens *Histoplasma capsulatum* and *Coccidioides* species, make it difficult to prevent exposure. Environmental control measures designed to protect high-risk patients from exposure to moulds at home or in the hospital are difficult. Housing these individuals in rooms supplied with HEPA-filtered air has helped to prevent the acquisition of *Aspergillus* infection within the hospital. The CDC, in collaboration with the Hospital Infection Control Practices Advisory Committee (HICPAC), has published guidelines that describe many of these environmental measures for preventing aspergillosis in the hospital environment (available at: http://www.cdc.gov/ncidod/dhqp/hicpac_pubs.html).

In the case of *Candida* bloodstream infections, evidence from outbreak investigations has implicated carriage of organisms on the hands of healthcare providers as a cause of transmission of some *Candida* species in hospitals. Guidelines have been developed by the CDC and the Association for Professionals in Infection Control and Epidemiology (http://www.cdc.gov/ncidod/dhqp/hicpac_pubs.html) to enforce rigorous hand washing before and between all patient contacts, especially when dealing with high-risk patients.

Guidelines have also been developed for protection against some community-acquired infections in special risk groups. Examples include prevention of histoplasmosis among workers (http://www.cdc.gov/niosh/docs/2005-109/) and prevention of opportunistic fungal infections in persons with AIDS, developed in collaboration with the Infectious Diseases Society of America (IDSA) (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5108a1.htm).

Improving the Diagnosis of Fungal Infections

Although improved diagnostics may not prevent disease, simpler and easier diagnosis may lead to increased numbers of patients being treated for fungal infections, and this may in turn reduce the morbidity and mortality related to these diseases. Improved diagnostic tools would be beneficial in the diagnosis and early management of many systemic fungal infections.

The detection of cryptococcosis in resource-poor countries is a major concern and an area in which improved diagnostic capabilities could dramatically benefit patients. Currently, in many of the countries with the highest burden of this infection (e.g., sub-Saharan Africa and South and Southeast Asia) laboratory capacity is not uniformly capable of reliably detecting *Cryptococcus*. Many clinical laboratories in these countries are small and poorly equipped and may be staffed by persons with minimal training. Improving capacity for diagnosis, as well as development of simple diagnostic technologies, such as lateral flow assays for antigen detection, may be increasingly important in these areas.

Improved diagnostic practices are also being encouraged for coccidioidomycosis. Although the incidence of disease currently reported from the southwestern USA through passive surveillance is quite high, there is evidence that the actual burden is much higher. Only 2–13% of individuals with compatible respiratory illnesses are tested for *Coccidioides* antibodies, [59] despite prospective studies showing that 8–29% of cases of community acquired pneumonias in endemic regions may be caused by this organism [59–61]. To lessen this diagnostic gap, public health authorities are encouraging increased testing for coccidioidomycosis among persons in endemic areas presenting to clinical providers with community-acquired pneumonia.

Vaccination

Vaccination is the ultimate tool for prevention and control of disease. Unfortunately, few vaccines are being developed for fungal diseases. For coccidioidomycosis, a vaccine may be an attractive option because natural infection almost always confers lifelong immunity to reinfection [62]. Over the last decade, the Valley Fever Vaccine Project, a consortium of researchers coordinated by the California State University, Bakersfield campus, has identified candidate vaccines for further development. Despite an economic analysis published in 2001 which suggested that a vaccine would have substantial public health benefit [63] funding for research has been inconsistent. Nonetheless, numerous candidate vaccines have been developed [62, 64–66], and phase I or phase II trials may be possible in the near future.

Encouraging Improved Therapeutics

Just as improved diagnostics may help to reduce the morbidity and mortality related to disease, so can improved therapeutics. Clinical trials are being conducted for infections such as aspergillosis and candidiasis. Similar efforts

for diseases such as coccidioidomycosis and histoplasmosis, which have been given less attention, have been advocated by public health authorities.

Until prevention efforts such as a vaccine are available, prevention of coccidioidomycosis will prove to be challenging. The infective dose for *Coccidioides* is very low, and although dust-generating activities such as digging have been associated with outbreaks, the vast majority of cases that occur in the endemic area are sporadic. Because of this, public health officials are also focusing on strategies to reduce the morbidity and mortality of this disease. One potential intervention that has only been studied retrospectively is the utility of antifungal treatment for primary infection [67]. While studies have shown that the majority of cases resolve eventually without treatment, many persons may be ill for months and consequently may be absent from work or school [11]. It is not known if treatment of primary infection can reduce symptoms or quicken improvement, or if it can help to prevent disseminated disease, which is uniformly fatal when untreated. Further study should determine if rapid diagnosis and treatment of primary pulmonary infection can reduce the complications of infection, and which groups of patients, if any, benefit the most.

Another situation that warrants further study is the best approach to treatment of cryptococcosis in resource-limited areas. Although current IDSA guidelines recommend treatment of cryptococcal meningitis with amphotericin B and flucytosine [68], these medications are not available or are cost-prohibitive to use in many countries in sub-Saharan Africa. Additionally, the complex medical infrastructure required for the management of these patients (which includes frequent lumbar punctures to manage intracranial pressure and monitoring of renal function for those on amphotericin B) is often not available. Therefore, creative treatment and sustainable management solutions will need to be developed. One promising strategy is the use of fluconazole at high doses for treatment. Recent data have shown that fluconazole at dosages of up to 1,200 mg daily is safe and effective [69]. Additionally, combination therapy with fluconazole and amphotericin B is safe and may be effective [70].

In areas in which amphotericin B and/or flucytosine are not available, these treatment strategies may be considered. Public health officials should work with ministries of health to determine the most cost-effective strategies for prevention of cryptococcal disease given the numerous competing resources for HIV/AIDS care and treatment. This situation also offers an example of the interrelated nature of the cycle of disease prevention. Surveillance can offer an estimate of the burden of fungal infection in this patient population; such burden estimates can then be used to inform public health officials so that appropriate employment of health resources can be made.

Prophylaxis

The investment in organ and stem cell transplantation is large and increasing. Public health efforts are not only aimed at maintaining the safety and quality of transplanted tissues and organs, but also focus on reducing risk of infection after transplantation has occurred. Invasive fungal infections remain one of the leading causes of infection-related morbidity and mortality. In stem cell transplant populations, antifungal prophylaxis, in particular with fluconazole [71–73] and posaconazole [74, 75], has been shown to be effective at reducing systemic fungal infections. Of the few clinical trials that have been performed among organ transplant recipients, fluconazole and itraconazole have demonstrated efficacy in preventing fungal infections in liver transplant recipients [76–78]. Prophylaxis with trimethoprim-sulfamethoxazole for prevention of *Pneumocystis jiroveci* infection is standard of care for organ transplant recipients.

Candidemia is one of the most common health care-associated infections. The burden of candidemia among neonates and infants is particularly high, with an incidence as high as 160 cases per 100,000 population among black infants in Baltimore [20]. Clinical trials of fluconazole prophylaxis for the prevention of candidiasis have demonstrated efficacy, particularly among very-low-birth-weight neonates, against this disease [79–82]. Antifungal prophylaxis is not widely practiced in these infants, partly due to concerns for the emergence of resistant *Candida* species [83]. Recommendations for prophylaxis focus on those whose birth weight is <1,000 g and who are cared for in units that have high rates of invasive candidiasis.

Primary prophylaxis to prevent cryptococcosis in high-risk HIV patients merits further clinical study. Prophylaxis trials among HIV-infected persons performed in the 1990s in developed countries (USA, Europe, and Australia) using either fluconazole or itraconazole showed a reduction of risk for development of cryptococcal infection, but without an overall survival benefit [84–86]. As a result, primary prophylaxis was never recommended as a prevention strategy. However, these studies were all performed in developed countries in optimized clinical conditions where the incidence and attributable mortality from cryptococcal disease among the cohorts was low, relative to the current reality in resource-limited countries in which cryptococcosis has a higher incidence and higher case-fatality rate. In developing countries, trials may be more likely to achieve statistical significance in demonstrating a benefit for primary prophylaxis in selected HIV-infected populations.

Two studies have been performed recently in Thailand with differing results. The first study involved 129 HIV-infected patients with CD4 counts <300 cells/μL who received either itraconazole prophylaxis or placebo; this study did not show a survival benefit from receiving antifungal medication, but no

patients in the itraconazole arm developed cryptococcosis [87]. Another small study, which randomized 90 HIV-infected patients with CD4 <100 cells/μL to either fluconazole, 400 mg each week, or placebo, did suggest a survival benefit [88]. Overall, 3 of 44 (6.8%) patients on the fluconazole arm developed cryptococcal disease, compared with 7 of 46 (15.2%) in the placebo arm, although this outcome was not statistically different [88]. To date, no randomized trials to evaluate prophylaxis have been published from sub-Saharan Africa.

Empirical and Pre-Emptive Therapy

Empirical therapy consists of identifying persons at high risk for development of an invasive fungal infection by recognition of clinical signs and symptoms that are consistent with early fungal disease, and then initiating antifungal therapy. Empirical approaches have been studied extensively in high-risk neutropenic patients; amphotericin B deoxycholate, liposomal formulations of amphotericin B, voriconazole, itraconazole, and caspofungin are recommended as options for treatment of persistently febrile neutropenic patients by IDSA guidelines [89].

In contrast to empirical therapy, a pre-emptive therapy strategy is one in which patients with evidence of fungal infection are identified early in the course of disease, allowing early initiation of antifungal therapy. These strategies have been extensively studied in invasive aspergillosis. High levels of antigenic markers, such as galactomannan, have been shown to be helpful to identify persons who may benefit from early initiation of antifungal therapy, and certain radiographic findings on high-resolution chest computed tomography scans have been shown to be early predictors of worse disease in many cases [90–93]. Prospective studies have shown value in a pre-emptive approach to treatment of patients with prolonged neutropenia [90, 94].

Pre-emptive treatment may also be valuable in cryptococcal meningitis. Most patients with cryptococcal meningitis in sub-Saharan Africa present very late in the course of disease, often with very low CD4 counts and with signs of advanced cryptococcal infection; survival rates are extremely poor [5, 7, 95]. Pre-emptive treatment may be beneficial among asymptomatic or mildly symptomatic persons with a positive serum cryptococcal antigen test. Studies using prospective or retrospective serum antigen screening have reported a prevalence of cryptococcal antigenemia of 6–18% [96–100]. Antigenemia has also been shown to precede clinical disease and independently predict poor outcomes. In a study from Uganda, antigenemia preceded clinical symptoms of cryptococcosis by a median of 22 days (range, 5–234), with 11% of individuals demonstrating positivity for greater than 100 days [5]. Another study found that asymptomatic cryptococcal antigenemia was associated with a higher risk of death (RR 6.6, 95% CI 1.9–23.6), and had a population-attributable risk for mortality similar to that of active tuberculosis [98].

Identifying antigenemic persons with few or no symptoms would allow for early antifungal treatment using an oral agent, such as fluconazole, which is widely available and inexpensive. In a Cambodian study, 10 persons with asymptomatic antigenemia were treated with fluconazole, 200 mg daily for 12 weeks [100]. When evaluated after completion of therapy, none had developed cryptococcal meningitis. Early treatment may also help to prevent immune reconstitution inflammatory syndrome (IRIS), which may contribute substantially to early mortality among persons initiating antiretroviral medication.

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References

1. Dromer F, Mathoulin-Pelissier S, Fontanet A, et al. Epidemiology of HIV-associated cryptococcosis in France (1985–2001): comparison of the pre- and post-HAART eras. AIDS 2004;18:555-62.
2. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. Clin Infect Dis 2000;30(Suppl 1):S5-14.
3. Mirza SA, Phelan M, Rimland D, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. Clin Infect Dis 2003;36:789-94.
4. van Elden LJ, Walenkamp AM, Lipovsky MM, et al. Declining number of patients with cryptococcosis in the Netherlands in the era of highly active antiretroviral therapy. AIDS 2000;14:2787-8.
5. French N, Gray K, Watera C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS 2002;16:1031-8.
6. Mbanya DN, Zebaze R, Minkoulou EM, Binam F, Koulla S, Obounou A. Clinical and epidemiologic trends in HIV/AIDS patients in a hospital setting of Yaounde, Cameroon: a 6-year perspective. Int J Infect Dis 2002;6:134-8.
7. McCarthy KM, Morgan J, Wannemuehler KA, et al. Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence. AIDS 2006;20:2199-206.
8. Klotz SA, Nguyen HC, Van Pham T, Nguyen LT, Ngo DT, Vu SN. Clinical features of HIV/AIDS patients presenting to an inner city clinic in Ho Chi Minh City, Vietnam. Int J STD AIDS 2007;18:482-5.

9. Kong BN, Harwell JI, Suos P, et al. Opportunistic infections and HIV clinical disease stage among patients presenting for care in Phnom Penh, Cambodia. Southeast Asian J Trop Med Public Health 2007;38:62-8.
10. Kumarasamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, Mayer KH. Natural history of human immunodeficiency virus disease in southern India. Clin Infect Dis 2003;36:79-85.
11. Park BJ, Sigel K, Vaz V, et al. An epidemic of coccidioidomycosis in Arizona associated with climatic changes, 1998-2001. J Infect Dis 2005;191:1981-7.
12. Chambers C, MacDougall L, Li M, Galanis E. Tourism and specific risk areas for *Cryptococcus gattii*, Vancouver Island, Canada. Emerg Infect Dis 2008;14:1781-3.
13. MacDougall L, Kidd SE, Galanis E, et al. Spread of *Cryptococcus gattii* in British Columbia, Canada, and detection in the Pacific Northwest, USA. Emerg Infect Dis 2007;13(1):42-50.
14. Centers for Disease Control and Prevention. Guidelines for evaluating surveillance systems. MMWR – Morb Mortal Wkly Rep 1988;37(Suppl 5):1-18.
15. German RR, Lee LM, Horan JM, et al. Updated guidelines for evaluating public health surveillance systems: recommendations from the Guidelines Working Group. MMWR Recomm Rep 2001;50:1-35.
16. Almirante B, Rodriguez D, Park BJ, et al. Epidemiology and predictors of mortality in cases of *Candida* bloodstream infection: results from population-based surveillance, Barcelona, Spain, from 2002 to 2003. J Clin Microbiol 2005;43:1829-35.
17. Colombo AL, Nucci M, Park BJ, et al. Epidemiology of candidemia in Brazil: a nationwide sentinel surveillance of candidemia in eleven medical centers. J Clin Microbiol 2006;44: 2816-23.
18. Hajjeh RA, Brandt ME, Pinner RW. Emergence of cryptococcal disease: epidemiologic perspectives 100 years after its discovery. Epidemiol Rev 1995;17:303-20.
19. Hajjeh RA, Conn LA, Stephens DS, et al. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. Cryptococcal Active Surveillance Group. J Infect Dis 1999;179:449-54.
20. Hajjeh RA, Sofair AN, Harrison LH, et al. Incidence of bloodstream infections due to *Candida* species and in vitro susceptibilities of isolates collected from 1998 to 2000 in a population-based active surveillance program. J Clin Microbiol 2004;42:1519-27.
21. Pfaller MA, Diekema DJ, Gibbs DL, et al. Results from the ARTEMIS DISK global antifungal surveillance study, 1997-2007: 10.5-year analysis of susceptibilities of noncandidal yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. J Clin Microbiol 2009;47:117-23.
22. Pfaller MA, Messer SA, Boyken L, et al. Global trends in the antifungal susceptibility of *Cryptococcus neoformans* (1990 to 2004). J Clin Microbiol 2005;43:2163-7.
23. Rees JR, Pinner RW, Hajjeh RA, Brandt ME, Reingold AL. The epidemiological features of invasive mycotic infections in the San Francisco Bay area, 1992-1993: results of population-based laboratory active surveillance. Clin Infect Dis 1998;27: 1138-47.
24. Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP, National Nosocomial Infections Surveillance System H. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989-1999. Clin Infect Dis 2002;35:627-30.
25. Viscoli C, Girmenia C, Marinus A, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999;28:1071-9.
26. Kao AS, Brandt ME, Pruitt WR, et al. The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. Clin Infect Dis 1999;29:1164-70.
27. Diekema DJ, Messer SA, Brueggemann AB, et al. Epidemiology of candidemia: 3-year results from the emerging infections and the epidemiology of Iowa organisms study. J Clin Microbiol 2002;40:1298-302.
28. Asmundsdottir LR, Erlendsdottir H, Gottfredsson M. Increasing incidence of candidemia: results from a 20-year nationwide study in Iceland. J Clin Microbiol 2002;40:3489-92.
29. Laupland KB, Gregson DB, Church DL, Ross T, Elsayed S. Invasive *Candida* species infections: a 5 year population-based assessment. J Antimicrob Chemother 2005;56:532-7.
30. Poikonen E, Lyytikainen O, Anttila VJ, Ruutu P. Candidemia in Finland, 1995-1999. Emerg Infect Dis 2003;9:985-90.
31. Sandven P, Bevanger L, Digranes A, et al. Candidemia in Norway (1991 to 2003): results from a nationwide study. J Clin Microbiol 2006;44:1977-81.
32. Morgan J, Wannemuehler KA, Marr KA, et al. Incidence of invasive aspergillosis following hematopoietic stem cell and solid organ transplantation: interim results of a prospective multicenter surveillance program. Med Mycol 2005;43(Suppl 1):S49-58.
33. Tortorano AM, Peman J, Bernhardt H, et al. Epidemiology of candidaemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis 2004;23:317-22.
34. Marchetti O, Bille J, Fluckiger U, et al. Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991-2000. Clin Infect Dis 2004;38:311-20.
35. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005;41:634-53.
36. Horn DL, Fishman JA, Steinbach WJ, et al. Presentation of the PATH alliance registry for prospective data collection and analysis of the epidemiology, therapy, and outcomes of invasive fungal infections. Diagn Microbiol Infect Dis 2007;59:407-14.
37. Neofytos D, Horn D, Anaissie E, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis 2009;48:265-73.
38. Centers for Disease Control and Prevention. Increase in Coccidioi domycosis – Arizona, 1998-2001. MMWR – Morb Mortal Wkly Rep 2003;52:109-12.
39. Centers for Disease Control and Prevention. Increase in Coccidioi domycosis – California, 2000-2007. MMWR – Morb Mortal Wkly Rep 2009;58:105-9.
40. Sunenshine RH, Anderson S, Erhart L, et al. Public health surveillance for coccidioidomycosis in Arizona. Ann NY Acad Sci 2007;1111:96-102.
41. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7-14.
42. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813-21.
43. *Coccidioides* (*Coccidioides* spp., Valley fever) 2008 case definition: Centers for Disease Control and Prevention, 2008. (Accessed December 1, 2009, at http://www.cdc.gov/ncphi/disss/nndss/casedef/coccidioid2008.htm.)
44. Chang DC, Burwell LA, Lyon GM, et al. Comparison of the use of administrative data and an active system for surveillance of invasive aspergillosis. Infect Control Hosp Epidemiol 2008;29:25-30.

45. Hardnett FP, Hoekstra RM, Kennedy M, Charles L, Angulo FJ, Emerging Infections Program FoodNet Working Group. Epidemiologic issues in study design and data analysis related to FoodNet activities. Clin Infect Dis 2004;38(Suppl 3):S121-6.
46. Voetsch AC, Van Gilder TJ, Angulo FJ, et al. FoodNet estimate of the burden of illness caused by nontyphoidal Salmonella infections in the United States. Clin Infect Dis 2004;38(Suppl 3): S127-34.
47. Mead PS, Slutsker L, Dietz V, et al. Food-related illness and death in the United States. Emerg Infect Dis 1999;5:607-25.
48. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ 2004;82:346-53.
49. Crump JA, Youssef FG, Luby SP, et al. Estimating the incidence of typhoid fever and other febrile illnesses in developing countries. Emerg Infect Dis 2003;9:539-44.
50. Revised Global Burden of Disease (GBD) 2002 Estimates: World Health Organization, 2002. (Accessed December 1, 2009, at http://www.who.int/healthinfo/bodgbd2002revised/en/index.html.)
51. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS 2009;23:525-30.
52. Panackal AA, Dahlman A, Keil KT, et al. Outbreak of invasive aspergillosis among renal transplant recipients. Transplantation 2003;75:1050-3.
53. Vonberg RP, Gastmeier P. Nosocomial aspergillosis in outbreak settings. J Hosp Infect 2006;63:246-54.
54. Chamany S, Mirza SA, Fleming JW, et al. A large histoplasmosis outbreak among high school students in Indiana, 2001. Pediatr Infect Dis J 2004;23:909-14.
55. Huhn GD, Austin C, Carr M, et al. Two outbreaks of occupationally acquired histoplasmosis: more than workers at risk. Environ Health Perspect 2005;113:585-9.
56. Kauffman CA. Endemic mycoses: blastomycosis, histoplasmosis, and sporotrichosis. Infect Dis Clin North Am 2006;20:645-62.
57. Chang DC, Grant GB, O'Donnell K, et al. Multistate outbreak of *Fusarium* keratitis associated with use of a contact lens solution. JAMA 2006;296:953-63.
58. Grant GB, Fridkin S, Chang DC, Park BJ. Postrecall surveillance following a multistate *Fusarium* keratitis outbreak, 2004 through 2006. JAMA 2007;298:2867-8.
59. Chang DC, Anderson S, Wannemuehler K, et al. Testing for coccidioidomycosis among patients with community-acquired pneumonia. Emerg Infect Dis 2008;14:1053-9.
60. Kim MM, Blair JE, Carey EJ, Wu Q, Smilack JD. Coccidioidal pneumonia, Phoenix, Arizona, USA, 2000-2004. Emerg Infect Dis 2009;15:397-401.
61. Valdivia L, Nix D, Wright M, et al. Coccidioidomycosis as a common cause of community-acquired pneumonia. Emerg Infect Dis 2006;12:958-62.
62. Cox RA, Magee DM. Coccidioidomycosis: host response and vaccine development. Clin Microbiol Rev 2004;17:804-39.
63. Barnato AE, Sanders GD, Owens DK. Cost-effectiveness of a potential vaccine for *Coccidioides immitis*. Emerg Infect Dis 2001;7:797-806.
64. Capilla J, Clemons KV, Liu M, Levine HB, Stevens DA. *Saccharomyces cerevisiae* as a vaccine against coccidioidomycosis. Vaccine 2009;27:3662-8.
65. Tarcha EJ, Basrur V, Hung CY, Gardner MJ, Cole GT. Multivalent recombinant protein vaccine against coccidioidomycosis. Infect Immun 2006;74:5802-13.
66. Xue J, Chen X, Selby D, Hung CY, Yu JJ, Cole GT. A genetically engineered live attenuated vaccine of *Coccidioides posadasii* protects BALB/c mice against coccidioidomycosis. Infect Immun 2009;77:3196-208.
67. Ampel NM, Giblin A, Mourani JP, Galgiani JN. Factors and outcomes associated with the decision to treat primary pulmonary coccidioidomycosis. Clin Infect Dis 2009;48:172-8.
68. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010;50:291-322.
69. Longley N, Muzoora C, Taseera K, et al. Dose response effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in Southwestern Uganda. Clin Infect Dis 2008;47:1556-61.
70. Pappas PG, Chetchotisakd P, Larsen RA, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. Clin Infect Dis 2009;48:1775-83.
71. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 1992;326:845-51.
72. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood 2000;96:2055-61.
73. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation – a prospective, randomized, double-blind study. J Infect Dis 1995;171:1545-52.
74. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348-59.
75. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007;356:335-47.
76. Winston DJ, Pakrasi A, Busuttil RW. Prophylactic fluconazole in liver transplant recipients. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999;131:729-37.
77. Lumbreras C, Cuervas-Mons V, Jara P, et al. Randomized trial of fluconazole versus nystatin for the prophylaxis of *Candida* infection following liver transplantation. J Infect Dis 1996;174:583-8.
78. Sharpe MD, Ghent C, Grant D, Horbay GL, McDougal J, David Colby W. Efficacy and safety of itraconazole prophylaxis for fungal infections after orthotopic liver transplantation: a prospective, randomized, double-blind study. Transplantation 2003;76:977-83.
79. Kaufman D. Fluconazole prophylaxis decreases the combined outcome of invasive *Candida* infections or mortality in preterm infants. Pediatrics 2008;122:1158-9.
80. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Donowitz LG. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. N Engl J Med 2001;345:1660-6.
81. Kaufman D, Boyle R, Hazen KC, Patrie JT, Robinson M, Grossman LB. Twice weekly fluconazole prophylaxis for prevention of invasive *Candida* infection in high-risk infants of <1000 grams birth weight. J Pediatr 2005;147:172-9.
82. Kicklighter SD, Springer SC, Cox T, Hulsey TC, Turner RB. Fluconazole for prophylaxis against candidal rectal colonization in the very low birth weight infant. Pediatrics 2001;107:293-8.
83. Burwell LA, Kaufman D, Blakely J, Stoll BJ, Fridkin SK. Antifungal prophylaxis to prevent neonatal candidiasis: a survey of perinatal physician practices. Pediatrics 2006;118:e1019-26.
84. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Clin Infect Dis 1999;28:1049-56.
85. Powderly WG, Finkelstein D, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the

prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. N Engl J Med 1995;332:700-5.
86. Smith DE, Bell J, Johnson M, et al. A randomized, double-blind, placebo-controlled study of itraconazole capsules for the prevention of deep fungal infections in immunodeficient patients with HIV infection. HIV Med 2001;2:78-83.
87. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. Clin Infect Dis 2002; 34:277-84.
88. Chetchotisakd P, Sungkanuparph S, Thinkhamrop B, Mootsikapun P, Boonyaprawit P. A multicentre, randomized, double-blind, placebo-controlled trial of primary cryptococcal meningitis prophylaxis in HIV-infected patients with severe immune deficiency. HIV Med 2004;5:140-3.
89. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008;46:327-60.
90. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis 2005;41:1242-50.
91. Maertens J, Van Eldere J, Verhaegen J, Verbeken E, Verschakelen J, Boogaerts M. Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. J Infect Dis 2002;186:1297-306.
92. Maertens J, Verhaegen J, Lagrou K, Van Eldere J, Boogaerts M. Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. Blood 2001;97:1604-10.
93. Segal BH, Almyroudis NG, Battiwalla M, et al. Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. Clin Infect Dis 2007;44:402-9.
94. Cordonnier C, Pautas C, Maury S, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis 2009;48: 1042-51.
95. Hovette P, Soko TO, Raphenon G, Camara P, Burgel PR, Garraud O. Cryptococcal meningitis in AIDS patients: an emerging opportunistic infection in Senegal. Trans R Soc Trop Med Hyg 1999; 93:368.
96. Desmet P, Kayembe KD, De Vroey C. The value of cryptococcal serum antigen screening among HIV-positive/AIDS patients in Kinshasa, Zaire. AIDS 1989;3:77-8.
97. Lara-Peredo O, Cuevas LE, French N, Bailey JW, Smith DH. Cryptococcal infection in an HIV-positive Ugandan population. J Infect 2000;41:195.
98. Liechty CA, Solberg P, Were W, et al. Asymptomatic serum cryptococcal antigenemia and early mortality during antiretroviral therapy in rural Uganda. Trop Med Int Health 2007;12:929-35.
99. Tassie JM, Pepper L, Fogg C, et al. Systematic screening of cryptococcal antigenemia in HIV-positive adults in Uganda: JAIDS 2003;33:411-2.
100. Micol R, Lortholary O, Sar B, et al. Prevalence, determinants of positivity, and clinical utility of cryptococcal antigenemia in Cambodian HIV-infected patients. JAIDS 2007;45:555-9.

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