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Characteristics and Distribution of Fungal Meningitis: A Systematic Review

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ABSTRACT

Objective: Meningitis is one of the most severe manifestations of fungal infections in the central nervous system. Various microorganisms, including fungi, can cause the disease. Understanding the prevalence of fungal meningitis is crucial for identifying geographical areas with higher incidence rates and improving prevention, control, and treatment strategies. This study aimed to highlight gaps in understanding disease-causing factors and vulnerable populations.

Materials and Methods: This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to systematically review articles on fungal meningitis from 2014 to 2023. Relevant articles were screened for eligibility and quality-checked using the Joanna Briggs Institute (JBI) tools before inclusion in the final analysis.

Results: A total of 33 articles were included in the review. Most of the articles on the prevalence of fungal meningitis were published in 2015. The highest number of studies were conducted in the United States, southern African countries, and Brazil. *Cryptococcus* spp. was identified as the primary cause of fungal meningitis in 84.8% of the articles. Additionally, HIV was the most commonly associated medical condition.

Conclusion: This systematic review provides an overview of the global epidemiology of fungal meningitis and underscores its significant burden. While progress has been made in understanding the epidemiology of the disease, major challenges remain in early diagnosis, access to effective treatment, and management of complications. Continued research and improved access to healthcare resources are critical to mitigating the impact of this life-threatening condition worldwide.

Keywords: Meningitis, CNS fungal infections, fungal meningitis, fungal meningitides

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INTRODUCTION

In recent decades, fungal infections of the central nervous system (CNS) have increased significantly. Of more than 100,000 identified fungal species, approximately 10 to 15% are responsible for implicated fungal-related neurological diseases (1). A significant clinical manifestation of fungal infections of the CNS is meningitis, a serious condition marked by inflammation of the tissues surrounding the brain and spinal cord (2). Various fungi can cause this condition, including yeast species like *Cryptococcus neoformans, Candida* spp., *Cryptococcus* spp., and *Trychosporon* spp.; filamentous fungi such as *Aspergillus* spp., *Penicillium* spp., *Pseudallescheria* spp.; dimorphic fungi like *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides* spp., and *Sporothrix* spp.; and dematiaceous fungi such as *Cladophialophora bantiana* and *Exophiala dermatitidis* (3).

Cryptococcus spp. is the leading cause of fungal meningitis worldwide, particularly affecting individuals with HIV. Recent studies indicate an annual mortality rate of approximately 180,000 AIDS patients due to cryptococcal meningitis, constituting 15% of all AIDS-related deaths (4, 5). *C. neoformans* is the primary cause of most cryptococcal meningitis cases among the *Cryptococcus* genus. Additionally, reports indicate numerous cases of *Cryptococcus gattii* in the Pacific Northwest and certain provinces of Canada (6, 7). Individuals in high-risk groups, such as AIDS patients, transplant recipients, those with weakened immune systems due to corticosteroid drugs and chemotherapy, and patients with hematologic malignancies, are most susceptible to neurological infections caused by pathogenic fungi. Moreover, non-sterile and unsanitary surgical instruments pose significant risks for meningitis in neurosurgery (3).

While *Cryptococcus* spp. is the most common cause of fungal meningitis, *Candida* spp. remains the most prevalent fungal pathogen in humans. *Candida* spp. often induces meningitis in premature infants, possibly due to the incompleteness of their blood-brain barrier, and in children with immune system defects. In contrast, *Aspergillus* spp. rarely causes CNS infections in premature infants but is known to cause meningitis in infants and children with hematological disorders or impaired immune systems (8).

The originality of this research is rooted in its worldwide perspective and emphasis on epidemiological data from various global regions. In contrast to numerous studies on fungal meningitis that often concentrate on particular countries or areas, this review synthesizes a broad array of epidemiological literature, thereby facilitating a thorough and comparative analysis of the disease's prevalence, associated risk factors, and outcomes across different populations and healthcare systems. By investigating global trends and disparities, the study provides valuable insights into the geographic and demographic elements that affect the incidence and development of fungal meningitis, which can guide more focused public health initiatives and enhance the global healthcare response to this rising infectious challenge.

This article reviews the causative agents, demographic vulnerabilities, geographic variability, and diagnostic challenges of fungal meningitis, providing essential information for public health awareness. Diagnosing fungal meningitis presents numerous challenges, largely because its symptoms closely resemble those of meningitis caused by bacteria and viruses. Additional obstacles include the limitations of current diagnostic tests, which may involve the analysis of cerebrospinal fluid, the detection of fungal antigens, or the culture of fungi. These methods can be complex and time-

HIGHLIGHTS

- The most founded studies were published before 2018.
- *Cryptococcus* spp. is the main cause (84.8%) of fungal meningitis.
- Fungal meningitis prevalence was highest in the U.S., Southern Africa, and Brazil.
- HIV is a major risk factor, with immunocompromised individuals being most vulnerable.
- Diagnosis and treatment remain challenging, requiring better healthcare access and further research.

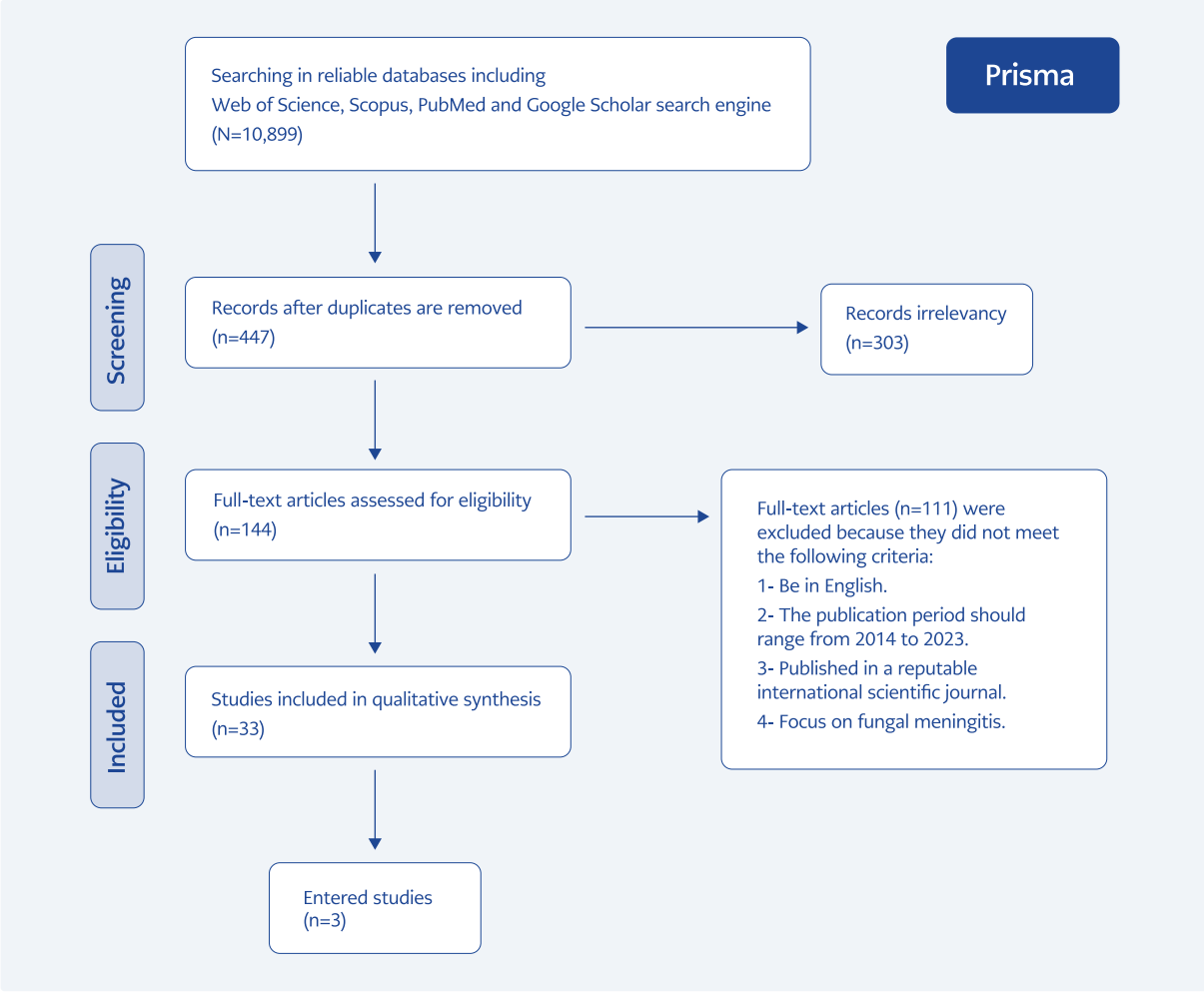

Figure 1. PRISMA flowchart showing the search strategy.

consuming, often leading to delays in treatment. Such delays can increase the risks associated with the disease. Furthermore, in cases with a low fungal burden, traditional diagnostic methods and cultures exhibit low sensitivity, making detection difficult (9, 10).

Although emerging diagnostic techniques—such as advanced molecular diagnostics and cerebrospinal fluid β-D-glucan tests—show promise, they remain largely inaccessible, particularly in resource-limited settings (9, 11). Additionally, immunocompromised patients, including those with HIV/AIDS or those undergoing immunosuppressive therapy, are at a higher risk for delayed diagnosis due to the atypical presentations of their infections (4).

The prognosis of fungal meningitis is influenced by several factors, including the causative agent, the patient's immune status, and the timing of diagnosis and treatment. For instance, when cryptococcus is the causative agent, which typically affects immunocompromised individuals, delays in initiating treatment can significantly increase morbidity and mortality rates (12). Early diagnosis and appropriate treatment generally lead to improved outcomes; however, studies indicate that neurological complications may persist even after early intervention. Despite advancements in treatment options, mortality rates continue to rise among these patients. Emerging therapies and enhanced diagnostic methods, such as molecular diagnostics, aim to improve these outcomes (13). The findings presented in this review can guide future research by identifying

gaps in understanding disease-causing factors and vulnerable populations.

MATERIALS AND METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). It is a systematic review of fungal meningitis that examines a collection of English articles.

We searched the databases Web of Science, Scopus, PubMed, and Google Scholar using the following English keywords: "meningitis and CNS fungal infections," "fungal meningitis," "fungal meningitides," "*Blastomyces*," "*Histoplasma*," "*Aspergillus*," "*Penicillium*," "*Sporothrix*," "*Pseudallescheria*," "*Candida*," and "*Coccidioides*.". Based on Medical Subjects Headings (MeSH) terms, the search period covered January 2014 through January 2023. We also performed combination searches using Boolean operators (AND, OR) to enhance the search strategy. Two authors manually reviewed the titles generated from the initial search to ensure all relevant sources were included.

In the next step, abstracts of all retrieved articles were reviewed, and studies unrelated to the topic were excluded based on predefined eligibility criteria (1): 1) articles must be written in English, 2) published between 2014 and 2023, 3) published in reputable scientific journals, 4) focused on fungal meningitis. Reasons for exclusion were documented to prevent bias and errors. Full texts of selected articles were retrieved, and studies without accessible full texts were excluded.

The full texts of the retained articles were reviewed and categorized by title, first author's name, year of publication, data collection methods, and key findings. The quality of each study was assessed using the Joanna Briggs Institute (JBI) tools. The findings were synthesized using the PRISMA framework to ensure a systematic, comprehensive, and unbiased review of the literature on fungal meningitis.

RESULTS

Following a systematic search of databases and other sources, 33 studies were retrieved and screened for eligibility. Figure 1 presents a summary of the study's PRISMA flowchart. All 33 studies were included in this descriptive review and used for the qualitative/narrative synthesis. The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) tool, with all studies scored between 6 and 9, indicating at least a moderate level of quality. The characteristics of the included studies are summarized in Table 1.

Most studies (60.5%) were published before 2018 (Figure 2). Among them, 16 studies focused on the general population, eight on hospitalized individuals, and nine on individuals diagnosed with AIDS. Sample sizes ranged widely, from 36 to 65,124,716 participants. The majority of the studies were conducted in the United States (5), Southern African countries (4), and Brazil (3) (Figure 3).

Gender data was reported in 42% of the studies. Among these, the majority of participants were male, with male representation ranging from 88% to 12% and female representation ranging from 12% to 87% —less than 1% of participants identified as transgender. In terms of age, 12% of the research specifically targeted individuals over the age of 18, while 42% included participants from all age groups.

The majority of studies (84.8%) documented cases of cryptococcal meningitis. In contrast, only one study reported cases of sporotrichosis meningitis, with a 100% prevalence among those with sporotrichosis. Candida meningitis was mentioned in 3% of the studies, with a prevalence of 18% among patients. Additionally, 27% of the studies reported fungal meningitis without specifying the species or genus of the causative agent (Table 2).

In 15% of the studies, *C. neoformans* was directly identified as the causative agent of meningitis, with prevalence among patients ranging from 56% to 100%. Overall, *Cryptococcus* spp. was reported as the cause of meningitis in 85% of the included studies. In 28 out of 33 studies, various physiological and pathological conditions were documented, with the most common being HIV (36.4%), immunosuppressed (9.1%), and organ transplantation (6%) (Table 3).

A total of 33% of the studies focused on individuals with AIDS, among whom fungal meningitis preva-

Table 1. Characteristics of included studies.

Authors (Reference)	Year	Country	Sample size
Adeyemi et al. (28)	2015	South Africa	127
Batac et al. (29)	2017	Philippines	1,852,137
Chayakulkeeree et al. (30)	2017	Thailand	65,124,716
Ellis et al. (31)	2019	Uganda	842
Dorratoltaj et al. (32)	2018	United States	807
Frola et al. (33)	2017	Argentina	123
Huang et al. (34)	2019	Taiwan	24,300,000
Hughes et al. (35)	2020	Newcastle	127
Lakoh et al. (36)	2020	Sierra Leone	170
Kumar et al. (37)	2014	India	10,226
Lagrou et al. (38)	2015	Belgium	11,099,544
George et al. (39)	2017	USA	42,634
Oliveira et al. (40)	2023	Northeastern Brazil	98
Tenforde et al. (41)	2019	Southern Africa	21,560
Strollo et al. (42)	2017	USA	138,433
Smith et al. (43)	2015	USA	391
Sawadogo et al. (27)	2016	Namibia	825
Sacarlal et al. (44)	2018	Mozambique	26,423,623
Rajasingham et al. (15)	2015	Uganda	188
Osmanov et al. (45)	2015	Ukraine	45,000,000
Ocansey et al. (46)	2019	Ghana	6275
Nunes et al. (47)	2018	Brazil	129
Lima et al. (48)	2022	Brazil	57
Britz et al. (49)	2016	South Africa	110,885
Okike et al. (50)	2014	England and Wales	7061
O'Hern et al. (51)	2023	Northern Australian	45
Taj-Aldeen et al. (24)	2015	Qatar	1,870,000
Li Y et al. (22)	2020	China	110
Nascimento et al. (17)	2021	Brazil	36
Terwin et al. (52)	2022	South Africa	236
McKenney et al. (18)	2014	USA	1872
Medina et al. (25)	2022	Guatemala	3457
Nyazika et al. (16)	2016	Zimbabwe	100

Table 2. Frequency of fungal meningitis type.

Types of meningitis	Studies n (%)	Frequency of cases
Cryptococcal meningitis	28 (84.8)	15.154
Candida meningitis	1 (3.0)	71
Meningeal sporotrichosis	1 (3.0)	17
Fungal meningitis (Including non-*Candida albicans*)	3 (9.1)	333
Total	33	-

Table 3. Diseases associated with fungal meningitis.

Diseases	Frequency	Percent	n(%)
Hepatitis and liver cirrhosis	1	3.0	13
Autoimmune disorders	1	3.0	12
Chronic kidney disease	1	3.0	7
Diabetes mellitus	2	6.1	13
Malignancy	2	6.1	7
Pregnancy	1	3.0	2
Transplant recipient	2	6.1	4
Alcoholism	1	3.0	6
HIV	12	36.4	43,334
Cancer	1	3.0	251
Immunosuppress	3	9.1	257
After surgery	1	3.0	69

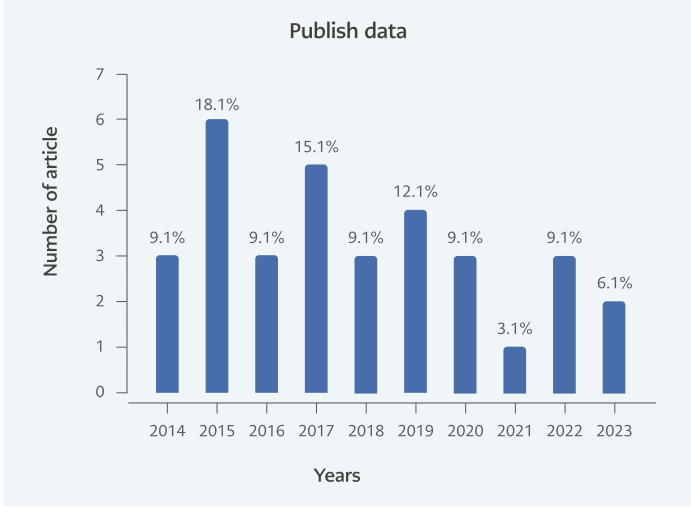

Figure 2. Number of articles published by year.

lence ranged from 4.5% to 100%. The association between meningitis and cancer was reported in 6% of the studies, with cancer patients representing less than 25% of all meningitis cases. Immunodeficiency was discussed in 9% of the studies, with the rate of affected patients ranging from 2% to 81%. Additionally, one study highlighted fungal meningitis as a postoperative complication.

DISCUSSION

This systematic review presents an overview of the global epidemiology and clinical characteristics of fungal meningitis, with a specific focus on cryptococcal meningitis. The findings highlight the significant burden of this disease, especially among immunocompromised individuals, such as those living with HIV/AIDS.

The majority of included studies (84.8%) reported cases of cryptococcal meningitis, which aligns with previous literature identifying *Cryptococcus* species as the leading cause of fungal meningitis worldwide (15). Cryptococcal meningitis was predominantly attributed to *C. neoformans* sensu stricto, consistent with reports indicating that *C. neoformans* is responsible for most HIV-associated cryptococcosis cases in sub-Saharan Africa (16). However, the study by Nascimento et al. (17) also found cases caused by the *C. gattii* species complex in non-HIV patients in Brazil, underscoring the importance of considering both species complexes.

The high prevalence of cryptococcal meningitis among HIV/AIDS patients (36.4%) is a concerning finding, corroborating the global burden estimates by Rajasingham et al. (4), emphasizing the need for improved prevention, early detection, and effective management strategies in this high-risk population. For example, McKenney et al. (18) reported a lower cryptococcal antigen (CrAg) positivity rate of 2.9% among HIV patients in the United States, potentially reflecting differences in access to antiretroviral therapy (ART) and healthcare resources. To address these challenges, implementing routine CrAg screening in HIV-positive individuals with low CD4 counts can facilitate early detection and preemptive antifungal therapy, thereby reducing the progression to meningitis and associated mortality (19). Enhancing access

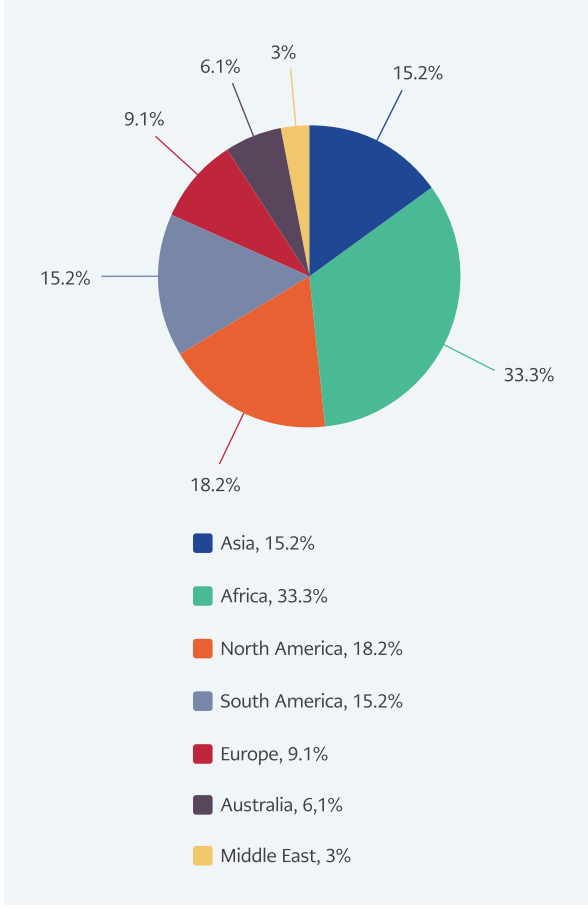

Figure 3. Distribution of published articles by continents.

to ART and ensuring adherence is crucial for restoring immune function and mitigating the incidence of opportunistic infections like cryptococcal meningitis (20). Additionally, education and awareness programs for both healthcare providers and patients can promote timely recognition and intervention, further improving patient outcomes (21).

Interestingly, a significant proportion of cases (9.1% immunosuppressed, 6.1% malignancy, 6.1% transplant recipients) occurred in non-HIV immunocompromised individuals, underscoring the importance of considering fungal meningitis in these vulnerable populations as well. Li et al. (22) found that 40% of cryptococcal meningitis cases in China occurred in individuals without underlying conditions, suggesting that immunocompetent individuals may also be at risk. For these populations, prophylactic antifungal therapies and stringent infection control practices in healthcare settings are essential to pre-

vent nosocomial transmission and manage existing vulnerabilities (23).

The geographical distribution of studies included in this review indicates a concentration of research in certain regions, such as the Americas, southern Africa, and Brazil. However, the study by Taj-Aldeen et al. (24) provides valuable insights into the burden of fungal infections in Qatar, highlighting the need for more regional data to inform public health policies and resource allocation.

While cryptococcal meningitis was the predominant focus, other forms of fungal meningitis, such as candidiasis and sporotrichosis, were also reported, albeit at lower frequencies. This diversity of causative agents underscores the importance of accurate diagnosis and tailored treatment approaches. The reported mortality rates for cryptococcal meningitis varied across studies, ranging from 30.8% in Guatemala (25) to 55.6% in Zimbabwe (16). These high mortality rates, particularly in resource-limited settings, emphasize the urgent need for improved access to diagnostic tools, antifungal therapies, and comprehensive care for affected individuals. The deployment of rapid diagnostic tests, such as lateral flow assays for CrAg, can facilitate early diagnosis and prompt initiation of treatment, thereby reducing mortality rates (26).

Several studies identified factors associated with poor outcomes, such as treatment delays, interruptions in induction therapy, and the presence of comorbidities like end-stage kidney disease (27). Additionally, the occurrence of immune reconstitution inflammatory syndrome (IRIS) in some cases (27) highlights the complexities of managing fungal meningitis in the context of immune system recovery.

The findings from this systematic review underscore the substantial global burden of fungal meningitis, particularly cryptococcal meningitis, among HIV/AIDS patients and other immunocompromised populations. Despite advances in understanding the epidemiology and clinical features of these infections, significant challenges remain in early diagnosis, treatment access, and management of complications. Continued research, enhanced surveillance, and improved access to healthcare resources are essential to mitigating the impact of this potentially life-threatening condition worldwide.

This review has several limitations. The exclusion of non-English studies may have omitted relevant research from non-English-speaking regions, potentially introducing language bias. Additionally, the variability in study designs and quality may affect the comparability of results. Publication bias is another concern, as studies with significant findings are more likely to be published. Furthermore, the heterogeneity among included studies in terms of population demographics, diagnostic criteria, and treatment protocols limits the ability to generalize the findings universally.

Future research should focus on expanding epidemiological studies to underrepresented regions, standardizing diagnostic criteria, and exploring the impact of emerging antifungal therapies. Enhanced surveillance and data sharing can facilitate a more accurate global understanding of fungal meningitis trends and inform targeted public health strategies. Additionally, research into developing novel antifungal agents and vaccines could provide long-term solutions for preventing fungal meningitis in high-risk populations.

CONCLUSION

Fungal meningitis, particularly cryptococcal meningitis, poses a substantial global health burden, especially among immunocompromised individuals. Addressing the challenges of early diagnosis, treatment accessibility, and comprehensive care is essential for reducing mortality and improving outcomes. Implementing targeted prevention strategies, such as routine antigen screening and prophylactic therapies, alongside standardized treatment protocols, can significantly mitigate the impact of this life-threatening condition. Continued research and international collaboration are vital to enhancing prevention, control, and management efforts worldwide.

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Informed Consent: N.A.

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