Biotechnology and Bioprocess Engineering 24: 436-444 (2019)
DOI 10.1007/s12257-018-0477-0

pISSN 1226-8372
eISSN 1976-3816

REVIEW PAPER

Invasive Fungal Infections and Their Epidemiology: Measures in the Clinical Scenario

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Received: 10 December 2018 / Revised: 14 February 2019 / Accepted: 14 February 2019

Abstract Fungi are increasingly recognized as major clinical pathogens in critically ill patients. Emerging groups of fungal pathogens such as *Candida* and *Cryptococcus* spp. are most frequently isolated from clinical setup, including filamentous fungi. Assessment of risk factors of these infections such as hospital-acquired fungal infection and environmental factors, including changes in medical practices and epidemiology as well as fungal infection mediated immunomodulation have provided important therapeutic options in the diagnosis of the fungal infections for clinicians. This review aims to furnish information on the factors affecting invasive fungal infections in a clinical scenario, especially for immunocompromised patients. A review of the recently published literature via PubMed, Elsevier and Medline database was performed. Relevant invasive fungal diseases and their worldwide cases were reviewed. Data on the immune response to the fungal infections in terms of release of anti-fungal effectors have been provided. Information on the anti-fungal mechanistic action via upregulation of immunity through predominant cytokines has been summarized, as well as factors affecting disease scenario of invasive fungal infections in clinical practices. The epidemiology and clinical features of fungal infections have also been reviewed.

Keywords: Invasive fungal pathogens; infection; human diseases; diagnosis; immunomodulation

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1. Introduction

In recent times, the rise in fungal infections has undertaken an alarming rate [1]. Both the systematic and invasive fungal infections have exhibited an increase, which is becoming a public health concern and is setting a challenge to healthcare professionals. There are several reasons behind the increased prevalence of fungal infections such as the greater use of immunosuppressive and antineoplastic agents, prosthetic grafts and devices, broad-spectrum antibiotics, and surgery [1]. Fungal infections incurred in the hospitals and health care facilities are other reasons behind the rising trend. *Candida albicans*, the most prominent pathogenic species are observed in 17% of the patients treated in the intensive care unit (ICU), and these infections are greatly associated with mortality and morbidity [2,3]. Non-*albicans* species are also becoming common, specifically in neutropenic patients and those on azole therapy [3]. Changes in medical practices such as the use of immunosuppressive drugs and intensive chemotherapy have raised the population of immunocompromised individuals that are prone to fungal infections [4]. The other contributors to this problem are HIV and other diseases that cause immunosuppression. While some of the fungal infections may be fatal, others that are subcutaneous and superficial infections affecting the skin, mucous membranes, and keratinous tissues can substantially lower the quality of an individual's life [5]. In some circumstances, such infections can also be invasive and spread to other people. Diagnostic delays, low sensitivity, difficulty in the discrimination of colonization from invasive candidiasis, limitations in current diagnostic techniques are the present challenges in the treatment programs of fungal infections [6]. Occasionally, the causative agent is only confirmed at autopsy [7]. Therefore, there is a lot that needs to be done to improve this rising threat.

First, this review conducts thorough research on the reasons behind the increased emergence of fungal infections. Second, it outlines the changing epidemiology of these infections and presents an account of the bottlenecks in the diagnosis of the infections. Lastly, it underpins some necessary steps that need to be addressed to curb this problem at its earliest stage.

2. Reasons for the Rise of Fungal Infections

Fungal infections are becoming increasingly common. The expansion has numerous underlying reasons such as the rise in the number of immunocompromised patients, including transplant recipients in immunosuppressive therapy, cancer patients with chemotherapy-induced neutropenia, and patients affected by human immunodeficiency virus [8]. Moreover, cancer patients prone to fungal infections have increased over the past few decades [9]. The majority of the infected individuals are patients of bone marrow transplant or acute leukemia [10].

Improved antimicrobial therapies and enhanced control of various underlying diseases result in prolonged survival; thus, putting patients at a greater risk of acquiring the fungal infection. Broadly, the reasons behind the rise of fungal infections depend on a number of factors such as a rise in the number of susceptible hosts, in addition to laboratory expertise in the detection and identification of fungi, and so on.

It has been estimated that around one billion people are suffering from fungal infections related to skin, nail, or hair. Additionally, millions have mucosal candidiasis, and around 150 million plus are suffering with serious fungal infections. The recent estimate of fungal diseases globally is shown in Fig. 1.

3. Hospital Acquired Fungal Infections

An increasing trend of the incident is being observed for infections as a result of clinical manifestations. These include post-operative sites of infection, urinary tract infections, and oropharyngeal infections. Fungal infections can be acquired in hospitals with the greatest incidence of infection noticed in ICUs. In 2007, a study covering 1,265 ICUs in 75 countries concluded that 19% of the pathogens were fungi in the ICU patients [11] and most of these infections were caused by the *Candida* species [12]. It was ranked fourth among the hospital acquired infections by a national surveillance study in the USA [13]. It has been suggested that the length of the ICU stay is detrimental to the risk of fungal infections; nevertheless, serious infections can prolong a patient's stay in the hospital, making the length of the stay both a cause and a consequence of

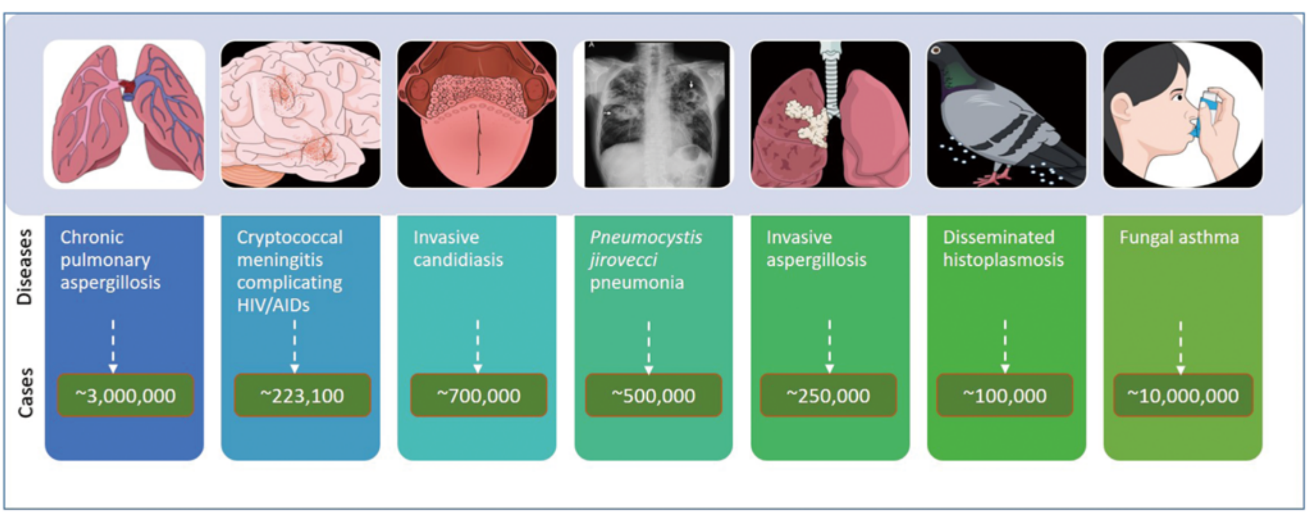

Fig. 1. Recent estimated global cases of fungal diseases.

infection [14]. Candida infections are also becoming an increasing problem in the neonatal ICUs [15]. These are particularly prevalent among low birth weight infants. Risk factors include the presence of a central line, prior to antibiotic exposure, fungal colonization, and endotracheal intubation [16].

4. Changes in the Medical Practices

Changes in the medical procedures account greatly for the increased incidence of fungal infections [17]. Typically, the first line of defense against the infections is the anatomical barriers. The mucosal and skin surfaces prevent micro-organisms from entering the body, whereby enzymes, acidic pH, mucus and other antimicrobial secretions, in turn, protect the anatomical barriers from infections [18]. During surgery and in times of the use of indwelling catheters, fungal cells seek entrance into the body [19]. Additionally, skin can also be damaged during chemotherapy, burns, radiotherapy, graft-versus-host diseases and by some viral infections. Some mucosal lesions also allow the fungi to reach the blood and tissues. The second line of defense is pronounced by the immune system in healthy individuals. When the system is suppressed or compromised, the risk of fungal infection increases and diseases such as HIV can weaken the entire immune system. Moreover, many cancers are also associated with immunodeficiency [20]. Some medications can also cause suppression of the immune system [21]. All these factors increase the chances of getting infected due to altered medical procedures.

5. Environmental Factors

Fungi are ubiquitous in the environment. Approximately 1.5 million different species of fungi exist on earth with about 300 known to cause sickness in humans [22]. Pathogenic fungi that infect the brain, blood, bones, heart, and other internal organs kill about 1.5 million people worldwide [23]. There are number of environmental sources of fungi that infect humans via animals directly or indirectly. Pets in the houses, miniature rodents, reptiles, and exotic animals like parrots are potential sources of fungal infections for people [24]. Other common environmental sources of fungi are soil and decaying vegetation; these are also found in ornamental plants, tobacco, building material, food, household dust, and water [25]. Conditions that enhance the dispersal of fungal molds are activities such as demolition and excavation, construction, defective or inadequate air handling, water leaks, dust accumulation, and moisture accumulation [26]. An estimated 5,000 deaths annually are due to construction-related infections in healthcare settings [27]. Moreover, construction and renovation in the hospital premises have been an ever-constant phenomenon that causes dust contamination and possible fungal spore dispersal [28].

6. Changing Climate as a Major Reason

Fungi are keeping pace with the increase in temperatures under global warming. The past two decades have witnessed growth in the number of virulent infectious diseases in managed landscapes and natural populations [29]. In both plants and animals, there has been a rapid increase in the fungal and fungi-like diseases, leads to severe die-offs and extinctions of wild species and have jeopardized food security [30]. Combustion of fossil fuels has led to the buildup of greenhouse gases in the atmosphere that have caused unprecedented changes in the earth's climate [31]. Resultantly, the incidence and distribution of fungal infections have changed. In the northern hemisphere, fungal pests are shifting poleward at a rate of 4.7 miles per year, suggesting that fungal threats for some of the world's important grain producers in North America and Europe would be high [32]. Fungal diseases could become more threatening as the climatic changes; temperature and moisture effects on pathogen sporulation and dispersal could favor certain pathogens and the changed circumstances may also introduce new potential vectors [33]. Global warming may also drive the evolution of heat-tolerant fungi that can survive at hot temperatures [34]. Such a change would have big implications on human health.

7. Changes in the Epidemiology of Fungal Infections

Although the invasive mycoses have been recognized as critical pathogens, specifically in the immunocompromised individuals, the frequency of opportunistic fungi is increasing as well and the invasive mycoses spectrum is changing [35]. *Candida* and *Aspergillus* species still cause the majority of invasive fungal infections; nevertheless, infections caused by non-*albicans* species are also becoming increasingly common [36]. In the case of systemic fungal infections, assessing the incident is difficult as the infections are mostly diagnosed only at autopsy. Incidences of the nosocomially acquired infections have increased in the past two decades, with fungal infections totaling to about 25% of all hospital-acquired infections [37]. In particular, *Candida* blood infections have rapidly increased since the 1980s and cause 8–15% of all blood infections [38]. The spectrum of causal organisms has also changed

Table 1. Invasive fungal diseases and their worldwide cases [42]

Invasive fungal disease	Main epicenters	Estimated cases per annum	Estimated mortality per annum
Cryptococcal meningitis	Sub-Saharan Africa, South East Asia	950,000	625,000
Pneumocystis pneumonia	Asia, Latin America, Sub-Saharan Africa	400,000	150,000
Disseminated histoplasmosis	North America, Sub-Saharan Africa	300,00	10,000
Disseminated penicilliosis	South East Asia	50,000	5,000

Table 2. Reported cases of human fungal diseases and infection in current years

Fungus	Site and mode of infection	Country	Reference
Rasamsonia aegroticola	Lung infection	USA	[69]
Candida albicans	Head & neck infection in cancer patients	India	[70]
Candida, *Aspergillus*, *Cryptococcus*, and *Zygomycetes* species	Due to the lack of diagnostic tools in the Hospital	Germany	[7]
Cryptococcus gattii	All immunocompromised and AIDS patients	USA	[71]
Pneumocystis jirovecii, *Histoplasma capsulatum*	HIV infected patients	USA	[72]
Alternaria tenuissima	Immunocompromised humans, Diabetic patients	USA	[73]
Candida species	Central nervous system	USA	[74]
Aspergillus, *Candida, Penicillium*, *Cryptococcus*, *Fusarium*, and *Rhizopus* species	Human population via water infection	USA	[75]
Pneumocystis jirovecii	Patients with idiopathic pulmonary fibrosis (IPF)	USA	[76]
Aspergillus flavus, *Aspergillus niger*, *Aspergillus terreus,* and other	Spine fungal infection	USA	[77]
and *Aspergillus* species	Bronchopulmonary infection	UK	[78]

lately. Surveys have revealed that greater than 75% of *Candida* infections in the 1980s were due to *C. albican*s; however, the proportion of it has now fallen to lower than 60% [39]. Moreover, *C. tropicalis* infections have jumped from 2% to 24% and *C. parapsilosis* infections have risen from 10% to 20% [40]. The recent rise in the number of *Aspergillus* infections has also been witnessed [41]. Infections by other fungal species are encountered less. Some of the fungal diseases and their estimated cases are recorded in Table 1 [42] and some of the major reported fungal diseases in recent years are shown in Table 2.

8. Emerging Yeasts

As mentioned, *C. albicans* is the most common agent of invasive yeast infections. With the introduction and use of fluconazole, the infections caused by *C. albicans* have decreased; nonetheless, the same has registered an increase in the infections caused by *C. glabrata* [43]. *C. glabrata* has become the second most common agent of candidemia in the USA since the early 1990s [44]. Furthermore, it is also progressively becoming associated with oropharyngeal candidiasis in patients getting radiotherapy for neck and head cancer [45]. One big problem with infection due to *C. glabrata* is its low susceptibility to fluconazole. With newer azoles, cross-resistance is also a matter of grave concern because the fundamental mechanism of resistance to the drug is the over-expression of multidrug efflux pumps [46]. Geographical differences of regions account for the complexity of fungi epidemiology; these include several factors such as practice patterns, host factors, and specialties of regional medical centers in supporting the emergence of varying *Candida* species as dominant pathogens.

9. Emerging Molds

The epidemiology of mold infections has altered substantially over the past ten years with a significant increase in the incidence of invasive aspergillosis [47]. There are also reports of an increase in mold causing infections that show resistance to typical antifungal agents and Zygomycetes [48]. Invasive aspergillosis is increasingly being diagnosed in patients with multiple myeloma, this could be due to double autologous transplantation or non-myeloablative allogeneic transplantation.

Another trend is the increase in the number of infections caused by mold species other than *Aspergillus fumigatus* (*A. fumigatus*) with the specific concern of *A. terreus* due to poor clinical treatment to amphotericin B [44]. Furthermore, zygomycosis has also increased in numbers in transplant recipients with most probable causes being the type and severity of immunosuppression [49]. Increase in the prevalence of non-*Aspergillus* mold infections has also been observed specifically in recipients of liver transplants [50].

10. Changing Patterns in Fungal Infections

The initial reports of antifungal resistance emerged in patients with mucocutaneous candidosis that was treated with ketoconazole. The problem has gained greater clinical relevance with the beginning of the AIDS epidemic [51]. The typical reason for the development of azole resistance is the repeated and prolonged use of fluconazole for the treatment of esophageal and oral candidiasis in AIDS patients. With the widespread use of this antifungal agent, reports of resistant strains grew more frequent. Simultaneously, patients getting fluconazole reported a shift from the highly susceptible to less susceptible *Candida* species. Epidemiological studies of the patients revealed that although the number of *C. albicans* had declined significantly, the frequency of *C. krusei* and *C. glabrata* increased greatly [52]. During the antifungal treatment, the development of candidaemia is another phenomenon that could be the result of the resistant strains emergence [53]. The past decade has seen extensive use of fluconazole in neutropenic patients, which has resulted in a marked decline in the infections caused by invasive candidosis and a rise in less susceptible *Candida* species, specifically *C. glabrata* that has surfaced as an important pathogen [52]. Additionally, resistance has also emerged towards susceptible *Candida* species; however, a much smaller magnitude.

11. Fungal Infection and Immunity

Fungal infection generally occurs through epithelial or endothelial cells, effective on both the mucosal and endothelial surfaces. During the invasion of fungal infection, innate and adaptive immune cells are activated which in turn initiate the release of a number of antifungal effectors. On first exposure to fungal infection, neutrophils, macrophages, and dendritic cells produce diverse types of cytokines predominantly IL-12, IL-10, and IL-18 [54]. Further, in response to the fungal invasion, adaptive immune cells secrete a plethora of cytokines: Th1 cells produce INF-γ and TNF-α; Th2 cells produce IL-4 and IL-5; Th17 produce IL-17 and IL-22 and T_{Reg} cells produce TGF-β and IL-10 [55].

In addition to the cytokines, B-cells secrete antibodies to mount a cellular response against a fungal breach. The host tissue damage caused by inflammation at the site of infection is tolerated by the production of anti-inflammatory cytokines, released by Th2 cells and regulatory T lymphocytes.

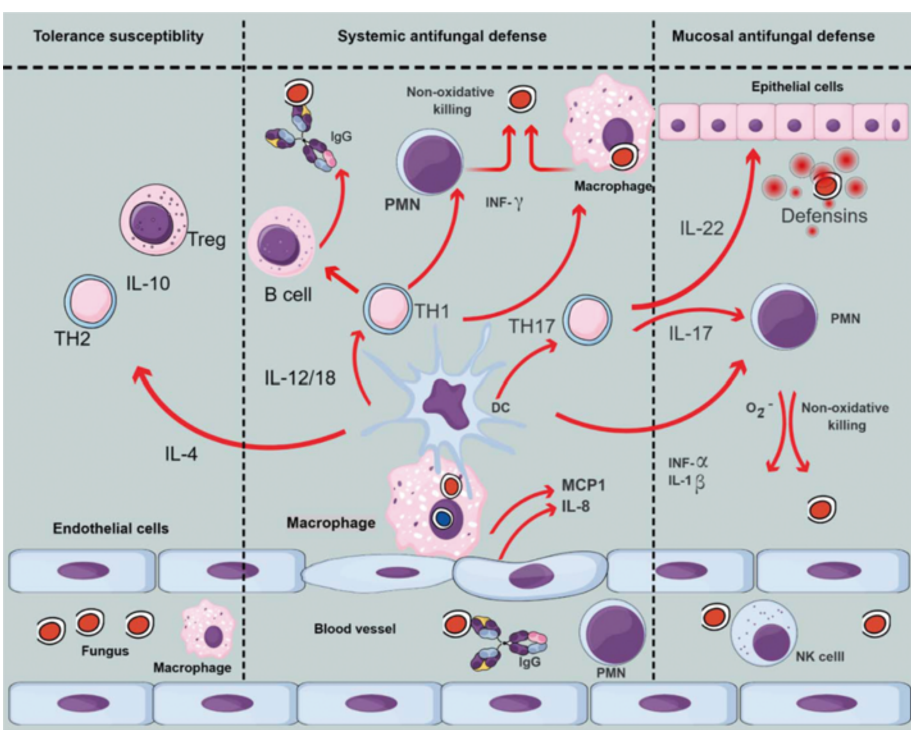

Fig. 2. Mechanism of immunity against fungal infections.

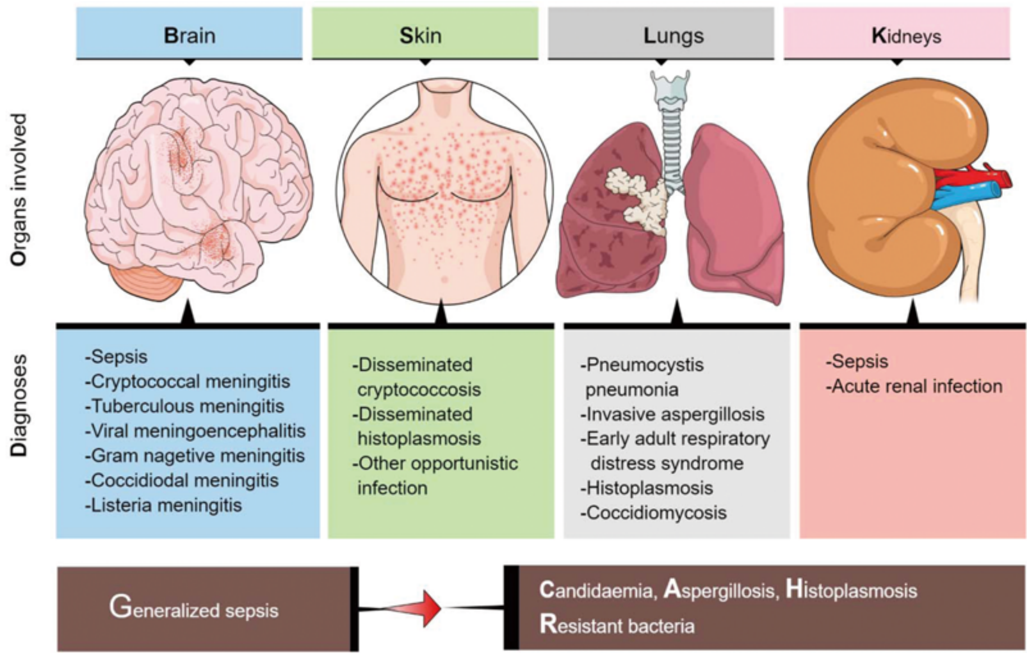

Fig. 3. Clinical scenario of fungal infections.

Failure in the regulation of anti-inflammatory response mounted by Th2 cells and regulatory T lymphocytes could result in down-regulation of anti-fungal immunity and therefore, could enhance susceptibility to fungal infection (Fig. 2).

12. Bottlenecks in the Diagnosis of Fungal Infections

One of the major challenges in the diagnosis of invasive fungal infections is the shortcoming of the current diagnostic techniques. Blood cultures are slow and insensitive, for instance, a blood culture has the sensitivity of about 50% in the case of invasive candidiasis and 0% for invasive aspergillosis [56]. In some of the infections, the identification is straightforward like the detection of cryptococcal antigens in the cerebrospinal fluid and blood with the use of a care dipstick test [57]. Nonetheless, for the most of the fungal infections, the available diagnostics (fungal antigen detection, X-ray CT scan, and radiography) lack sensitivity, specificity, or both and in some developing countries, are unaffordable [58].

Bottlenecks are also prevalent in the diagnosis of invasive aspergillosis, where serum testing for fungal galactomannan poses a sensitivity of 80% for detection of the disease in neutropenic patients that are not receiving itraconazole, posaconazole, and voriconazole under the therapeutic regimen of anti-mold prophylaxis but the sensitivity is only 20% if patients are not on these drugs [59]. This diagnostic technique is even less effective in solid organ transplant and intensive care patients [60]. On the other hand, chronic pulmonary aspergillosis is often confused with tuberculosis both clinically and radiologically [61]. These complications paired with clinical presentation often end in delayed diagnosis and compromise health care. Fig. 3 depicts the clinical scenario of fungal infection associated with different organs prone to fungal infection.

Another challenge is disappointing patient outcomes as a result of antifungal treatments. Fungi are pathogens that are evolutionarily closer to humans, which limits the drug development scope. The introduction of third generation triazoles and echinocandins has improved the therapeutic options for several fungal diseases [62]. Yet, antifungal drugs have mild success in reducing the high mortality rates that come with invasive diseases. The primary reasons behind the modest success are the delay in disease diagnosis and identification of fungi that, in turn, delays early antifungal therapy [63]. Overall, development of antifungal treatments with a broad range of efficacy has always been a great challenge. Yet, further, challenges include the development of drug resistance, toxicity, and undesirable drug interactions, making it more complicated.

13. Moving Forward

There is a lot that needs to be done to bring under control the rising incidence of fungal infections. Simple diagnostics along with better screening methodologies are the need of the hour. Despite the importance of medical mycology, the fungal infection study has lagged behind the study of other pathogens and lethal fungi continue to undo the achievements made in the intensive care patients, treatment of cancers, and severely immunocompromised individuals.[42] At the same time, there is a limited public health understanding concerning the impact of fungal diseases in the community and hospital both [64]. Therefore, critical to treatment, public awareness about the magnitude of the fungal problem is a key factor. In addition, certain preventative steps can be taken to control the spread of the fungi. Nevertheless, areas that need immediate attention are primarily the development of better and rapid diagnostics that allow quicker implementation of appropriate therapy and treatment [65]. Development of such tools of diagnosis may impact mortality rates and would facilitate the gathering of more accurate epidemiological data [66]. Furthermore, there is a need for safe and effective antifungal drugs. Additionally, there is a need to expand the knowledge of antifungal immunity to develop immunotherapeutic strategies for the treatment of immunocompromised people [67]. Finally, the development of antifungal vaccines may play an important role in curbing the fungal infections, in the long run; such vaccines may benefit both invasive as well as widespread superficial infections [68]. Fulfillment of all or any of these goals would drive a significant impact in reducing the negative impact of infections caused by the pathogenic fungi.

14. Conclusion

The rise in the incidence of fungal infections is due to multiple reasons, including climatic change, change in the medical practices, increased dispersal of fungal spores, and more. Although the use of certain fungal agents has helped in reducing the incidence of susceptible fungal species, it has encouraged the rise of unsusceptible fungal species that accounts for the changes in the fungal epidemiology. Widespread use of drugs has led to the emergence of resistant fungal strains and such drugs also pose shortcomings of toxicity and undesirable drug interactions in the body. Diagnostic techniques, in several cases of infections, particularly invasive fungal infections, are lagging behind and result in a delay in therapeutic treatment of the infection. Despite different antifungal therapies, still, nearly a billion people are estimated with fungal infections with a mortality rate > 1.6 million, which nearly the same as tuberculosis. Therefore, considering these factors, several measures need to be taken to tackle the menace of rising fungal infections.

Acknowledgments

This work was supported by the 2016 Yeungnam University Research Grant. Also, we acknowledge financial support from the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2014R1A5A1009799).

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