

The Second International Collaborative Mycology Conference: evidence-informed fight against fungal diseases in Pakistan

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Introduction

The field of medical mycology is gaining global public health attention due to increasing number of at-risk populations, the emergence of new fungal pathogens, rising antifungal resistance resulting from overuse of antifungals, and paucity of new antifungal drugs.^{1,2} Considering the significant impact of fungal infections, the World Health Organization (WHO) published a fungal priority pathogen list (FPPL) in 2022, highlighting critical fungal pathogens.³ The aim of the WHO FPPL is to escalate efforts towards an increase in educational, research and policy activities towards better diagnostics, treatment, and prevention of fungal diseases globally.

Pakistan is a lower-middle-income country with a high burden of tuberculosis (TB), diabetes mellitus, and chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), all of which are important risk factors for fungal diseases. In 2017, the first estimate of the burden of serious fungal infections in Pakistan revealed that around 1.78% of the population is affected.⁴ This study highlighted a high burden of post-TB chronic pulmonary aspergillosis (CPA), mucormycosis as a complication of diabetes, and candidemia and invasive aspergillosis in various immunocompromising states as the most important fungal infections. These findings highlighted the need for continuing surveillance, improve fungal diagnostics, and take preventive measures to reduce the burden of these serious infections.

On 4–5 December 2017, the First International Collaborative Mycology Conference was held

in collaboration with the Global Action for Fungal Infections and Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP), with the aim of increasing awareness regarding fungal infection and highlighting significant impact of fungi on public health in Pakistan. The book “Practical Guide and Atlas of the Diagnosis of Fungal Infections” was also launched at this conference.⁵ The main message of the conference was capacity building of health care workers across the country to improve fungal disease outcomes.⁶ Since then, coronavirus disease-2019 (COVID-19) pandemic brought forth a new risk group for aspergillosis, candidiasis and mucormycosis with high mortality, diagnostic challenges and inequities in access to antifungals complicated with poor stewardship.⁷ It became imperative to reorganize the infectious diseases, microbiology and other clinical experts to disseminate knowledge of the changing local and global epidemiology and increased complexities of fungal infection diagnosis and management. This need led to the organization of the Second International Collaborative Mycology Conference. Through this article we are sharing the deliberations, key findings and recommendations to combat fungal infections in Pakistan.

Methods

On 25th May 2024, the Aga Khan University in collaboration with MMIDSP conducted the Second International Collaborative Mycology Conference in Karachi with the following objectives:

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- (1) To highlight the role of human-environment interface with fungal diseases of public health importance
- (2) To improve knowledge and skills of health professionals regarding fungal infections
- (3) To increase awareness of optimal use of fungal diagnostics and antifungals
- (4) To provide a platform for developing multidisciplinary inter-sectoral links towards reducing fungal disease burden in Pakistan

The meeting and pre-conference workshops were attended by more than 300 participants from all major cities of Pakistan. The pre-conference workshops focused on providing hands-on training in fungal bioinformatics, diagnostics including histopathological features, fungal identification and antifungal susceptibility testing, disease management, and prevention through ensuring a safe hospital environment. The full-day conference had three keynote presentations, eight plenary talks and two case-based multidisciplinary plenary sessions.

Qualitative synthesis

Thematic synthesis involved a systematic analysis of review of the conference proceedings, workshops, presentation slides, and participant feedback by the conference organizing committee. The data was categorized based on the specific objectives of the pre-conference workshops and the main conference. Thematic analysis included familiarization with the data, generating initial codes, searching for and reviewing themes, and defining and naming these themes. The findings were synthesized into a comprehensive report with recommendations for future conferences and collaborative initiatives, and the main themes are presented below.

Results

The following themes emerged from the presentations.

*Genomic surveillance of *Candida auris* and emerging fungal diseases in Pakistan*

Pakistan was one of the first countries to report emergence of *C. auris* in health care settings.⁸ After the initial emergence, *C. auris* remained a significant issue with sporadic outbreaks in

different hospitals across the country. The results of ongoing laboratory-based surveillance of *C. auris* strains isolated from clinical specimens received at the Aga Khan University Laboratory, Karachi, Pakistan from major cities and towns across Pakistan were shared in the meeting. The findings suggested ongoing transmission and detection of this pathogen from Karachi and many other cities of Pakistan. Whole genome sequencing (WGS) of most of the *C. auris* strains revealed very little genetic variation. Sequencing of fungal strains also helped in identification of emerging fungi that are misidentified using conventional diagnostic techniques. One such incidence was increasing fungemia cases by a particular yeast among children treated at health-care facilities in Pakistan. Initially identified as *C. lusitaniae* by phenotypic methods, WGS identified the isolates as *Scheffersomyces spartinae*. These findings underscore the importance of epidemiological monitoring for clusters of unusual infections and genomic or other molecular surveillance for positive identification of rare or novel potential pathogens.

Climate crisis and emerging fungal diseases were highlighted as a major theme in the conference. Global warming can potentially increase the thermotolerance of pathogenic fungi leading to new niches and improved adaptation and ability to transmit and survive in humans. Climate crisis has also been linked to increased natural disasters and leading to a higher risk of fungal infections.² These disasters affect communities that are underprivileged and hit by extreme weather events. Natural disasters have been linked to wider spread of fungi, most importantly for endemic mycoses such as *C. immitis* spread after earthquake-related landsliding and sandstorms leading to infection in non-endemic areas. Pakistan also has been experiencing impact of climate change with extreme flooding events in recent years leading to displacements and increased at-risk population for fungal infections.⁹

Antifungal resistance in Pakistan

Emergence of fluconazole resistance amongst *Candida* species has been reported in previous studies from Pakistan.¹⁰ Antifungal resistance surveillance data from both Aga Khan University (AKU) laboratory and the public sector evaluating strains collected from across the country were shared in the conference. AKU reported an

alarming increase in rate of fluconazole resistance in *Candida* species over 2015–2023 was reported. The increase in fluconazole resistance was due to increase in rates of isolation of *Candida* species that are generally resistant to fluconazole such as *C. auris*. There is an increasing proportion of candidemia due to uncommon *Candida* species which are often misidentified using conventional laboratory protocols. There was also an emergence of resistance in fluconazole susceptible species such as *C. parapsilosis*, *C. tropicalis*, and *C. albicans*. Fluconazole resistance was particularly high in *C. parapsilosis*. Based on the current resistance situation, empirical treatment with fluconazole does not seem to be an option in the country. Due to limited availability and high cost of caspofungin, the only available echinocandin in Pakistan, amphotericin deoxycholate is used as a first-line treatment option. Capacity-building efforts have been conducted by the National Institute of Health (NIH), Pakistan for yeast identification and susceptibility testing. This initiative has led to improved capacity of detection of cases of *C. auris* in 12 laboratories across Pakistan and assisted in institution of infection control and prevention measures. This surveillance initiative from NIH is in collaboration with the Centers of Disease Control, United States of America.

The proportion of azole resistance in *A. fumigatus* and *A. flavus* in clinical and environmental isolates, was reported to be low however creeping minimum inhibitory concentration (MICs) over the years were alarming. Susceptibility testing of Mucorales showed non-wild type MICs to both posaconazole and isavuconazole in one third of the tested strains. Most worrying is the detection of resistance in dermatophytes not only to terbinafine but also to itraconazole. Increased antifungal resistance signified the need of improving the capacity for fungal diagnosis and detection of antifungal resistance amongst diagnostic laboratories in Pakistan. Additionally, continuous surveillance to detect emerging resistance using both phenotypic and genotypic approaches is pertinent. Widespread and improved access to newer antifungals was also highlighted.

Chronic pulmonary aspergillosis:

Pakistan has a high burden of CPA mostly in patients with previously treated pulmonary tuberculosis (PTB).¹¹ Increasing awareness amongst clinicians and introduction of *Aspergillus* IgG

testing in recent past may have led to improved detection of CPA cases in the country.¹² However, accurate data is not available, and CPA remains underdiagnosed due to its nonspecific clinical presentation and clinical and radiological similarity with PTB. Most cases of PTB and CPA co-infection as well as CPA occurring as an early complication of TB are missed. It was highlighted that the diagnostic guidelines need to be modified to better diagnose PTB and CPA co-infection. It was emphasized that the current evidence supports a longer duration of treatment (12 months vs 6 months) with lower odds of relapse.¹³

Invasive aspergillosis:

Patient population at risk of invasive aspergillosis has now been expanded and includes patients with COPD, on high-dose steroids, with prolonged ICU stay, severe viral infections and liver cirrhosis. Pakistan has a high burden of COPD patients who require hospitalization and ICU stay.¹⁴ Invasive aspergillosis should be suspected in such patients if they have persistent fever, worsening respiratory distress and increased ventilatory requirements despite appropriate antibiotic treatment. Discussion on recent guidelines on invasive fungal diseases in adults in ICU (FUNDICU) was conducted and optimum diagnostic approaches in both ICU and non-ICU patients were presented.¹⁵ Current first treatment options for invasive aspergillosis; voriconazole and isavuconazole are available in the country. However, the high cost of isavuconazole limits its use in most clinical settings.

Mucormycosis is a devastating condition and although information on the actual burden of this infection in the country is not available, it is estimated to be high.⁴ COVID-19 infection led to an increase in incidence of mucormycosis in many countries including Pakistan. This infection is particularly difficult to diagnose due to challenges of tissue sampling for diagnostic testing. In Pakistan, apart from rhinocerebral mucormycosis, pulmonary mucormycosis has been reported in COVID and non-COVID patients.¹⁶ Mortality of pulmonary mucormycosis is higher than rhinocerebral in the country and significantly higher mortality is present in intubated patients.¹⁷ Limited availability of liposomal amphotericin has made treatment of these cases difficult, and clinicians often have to rely on amphotericin B deoxycholate.

The role of radiology in fungal diseases diagnosis

The crucial role of radiology in invasive fungal infection diagnosis was highlighted. The ability of CT scans and MRI in detection and differentiation of neurological lesions like brain abscesses, granulomas, leptomeningitis, and pachymeningitis can greatly aid clinicians in initiation of appropriate treatment. Sinus and pulmonary infections may have pathognomonic features including halo sign, air-crescent sign with invasive aspergillosis and reverse halo sign in mucormycosis. In the background of known risk factors, these features may be typical enough to differentiate and help in diagnosis.

Paediatric fungal infections

Candidemia and aspergillosis were highlighted as significant pathogens in paediatric population. Complicated fungal infections are, extremely difficult to treat in children. *Candida ventriculitis* and central venous line-related candidemia require antifungal therapy with agents that can penetrate biofilms. These infections are difficult to eradicate without source removal which may not always be possible. Patients with severe neutropenia are susceptible to aspergillosis and in this population infections with uncommon strains of aspergillus may be devastating.

Neglected fungal diseases in the community

A case-based discussion was conducted where challenging cases of fungal infections in community were shared. All these cases highlighted the need for close collaboration between physicians, surgeons, microbiologists and histopathologists for proper diagnosis and treatment. Discussion on histoplasmosis, blastomycosis, phaeohyphomycosis, chromoblastomycosis and mycetoma was initiated and it was highlighted that although these infections are uncommon, they can be extremely challenging as index of suspicion is frequently low among clinicians and laboratory personnel. Another challenge is increased use of aesthetics and cosmetic surgeries in community leading to chemical inflammation that may mimic fungal or mycobacterial infections.

Dermatophytosis and terbinafine resistance

A major discussion point of the conference was increasing treatment failure in patients with

dermatophyte infections who are treated with terbinafine. This issue is compounded by inability of local laboratories to perform culture or antifungal susceptibility testing. Most dermatologists are now using itraconazole to treat patients, however, the drug quality and erratic oral bioavailability of itraconazole is an ongoing issue. Considering this scenario, performing culture and susceptibility testing at least in patients with treatment failure and recurrent dermatophytosis was recommended. A detailed discussion was conducted on the misuse of steroids in treatment failure cases. Steroids are being prescribed in oral and intramuscular form leading to iatrogenic Cushing syndrome and adrenal suppression. An urgent need to educate both clinicians and public was emphasized to stop misuse of steroids.

The role of multidisciplinary team simulated by panel discussions and complex cases

Development of multidisciplinary team (MDT) for patient care in the management of fungal infections has been reported to enhance medical care. The MDT teams include health care professionals across disciplines that collaborate and discuss complex cases and provide effective and comprehensive patient care.¹⁸ The major disciplines that should collaborate are infectious diseases physicians and microbiologists because of their expertise in diagnosis and treatment, pharmacists as they can guide optimal antifungal treatment, haem-oncology specialists, pulmonologists, surgeons, radiologists and histopathologists. The conference included MDT-based discussions on complex cases where a panel of experts reviewed the cases and with consensus and collaboration provided recommendations. It was recommended that MDTs should be developed in centres dealing with serious fungal infections to optimize fungal diagnosis, treatment, ensure adherence to clinical pathways, and antifungal stewardship at each centre.

Recommendations

To effectively address fungal diseases in Pakistan, the following action points were raised to be implemented in the next 10 years (Figure 1). These recommendations pertained to relevant stakeholders including health care providers, diagnosticians, public health experts, researchers, pharmaceutical companies, governmental bodies and policymakers.



Figure 1. Top 10 action points to address fungal diseases in Pakistan.

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- (1) Establishing a robust national surveillance system for the accurate tracking of the incidence and prevalence of most common serious fungal infections in the country. Health care providers should be trained to identify cases using available diagnostic criteria and report to a centralized body using a standardized form. This surveillance will facilitate understanding of the epidemiology of fungal diseases in the country.
- (2) Investing in advanced diagnostic laboratories and training of laboratory workforce across the country to enhance the ability to detect fungal infections accurately.
- (3) Advocate for the availability and accessibility of essential, quality-assured systemic antifungal agents for major invasive fungal diseases, including liposomal amphotericin B, flucytosine, and later generations of triazoles such as posaconazole and isavuconazole. Ensuring nationwide access to these medications and improving drug supply chains through partnerships with pharmaceutical companies and international organizations is crucial to address treatment gaps.
- (4) Strengthening antifungal stewardship programmes to prevent the development of resistance. Promoting the rational use of antifungal medications through the development of national fungal diagnosis and treatment guidelines.
- (5) Increasing awareness among the public and healthcare professionals about fungal infections and their risk factors through public health campaigns and continuous medical education.
- (6) Investing in research and development as being critical for advancing the understanding and treatment of fungal infections. There are unmet needs for studies on the epidemiology, pathogenesis, and treatment of these diseases across the country. Research on the impact of climate change on the emergence and spread of fungal diseases is recommended to anticipate and mitigate future challenges.

- (7) Enhancing infection control practices in healthcare settings to reduce hospital-acquired fungal infections, particularly in high-risk settings such as the intensive care unit.
- (8) Developing multidisciplinary approaches to fungal disease management to foster collaboration between different healthcare sectors, including microbiologists, infectious diseases physicians, pharmacists, epidemiologists, clinicians, and public health officials. Utilizing MDT approaches for complex cases will enhance treatment outcomes and facilitate comprehensive care.
- (9) Focusing on vulnerable populations to address the specific needs of high-risk groups such as immunocompromised patients, individuals with chronic diseases, and children. Tailored interventions, education, and resources for these populations to help mitigate risks and improve health outcomes.
- (10) Advocating for policy and regulatory changes that prioritize fungal disease management within national health agendas.

Conclusion

The Second International Collaborative Mycology Conference reviewed emerging evidence on the burden of fungal diseases in Pakistan and outlined major action points for the next decade, emphasizing the importance of a comprehensive strategy encompassing diagnostic improvement, surveillance enhancement, anti-fungal stewardship, awareness campaigns, research investment, infection control measures, medication accessibility, multidisciplinary collaboration, targeted interventions for vulnerable groups, and policy advocacy. By implementing these comprehensive measures, Pakistan can substantially alleviate the burden of fungal diseases and enhance public health outcomes.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Author contributions

Joveria Farooqi: Writing – original draft; Writing – review & editing.

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Competing interests

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