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Review

Aspergillus Contamination in Healthcare Facilities: An Ever-Present Issue—Prevention and Control Measures

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Abstract: *Aspergillus* spp. are ubiquitous fungi present in soil, organic debris, water, decaying vegetation and dust produced in renovation and/or building work. Several studies have shown the presence of aspergilli in various healthcare environments. Typically, thousands of fungal spores are inhaled every day, but if spore clearance fails (typically in immunocompromised patients), fungi can grow and invade lung tissue, causing invasive aspergillosis (IA) which is one of the most frequent infections in highly immunocompromised patients. *Aspergillus fumigatus* is the most common species involved; this species can be attributed to about 80% of the cases of aspergillosis. According to the WHO, *Aspergillus fumigatus* is one of four critical priority fungi. The first-line treatment of diseases caused by *Aspergillus*, in particular IA, is based on triazole antimycotics. Unfortunately, resistance to antimycotics is increasing, partly due to their widespread use in various areas, becoming a significant concern to clinicians who are charged with caring for patients at high risk of invasive mycoses. A recent WHO report emphasised the need for strategies to improve the response, and in particular strengthen laboratory capacity and surveillance, support investment in research and strengthen public health interventions for the prevention and control of fungal infections through a One Health approach.

Keywords: *Aspergillus*; healthcare infections; antifungal resistance

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1. Introduction

Fungi are eukaryotic, heterotrophic, mainly aerobic, commensal or environmental saprophytic microorganisms widely distributed in nature, and are mostly opportunistic pathogens capable of causing superficial and deep infections [1–3].

The occurrence of deep fungal infections is related to the widespread use of broad-spectrum antibacterial drugs (capable of subverting the residing flora in favour of fungi), immunosuppressive agents, organ transplantation, an increase in the number of patients with AIDS and malignant tumours and the elderly [3,4].

Patients with severe coronavirus disease (COVID-19) are at high risk of fungal infections as a result of use of corticosteroids, immunosuppressive agents and broad spectrum antibiotics, together with its association with lymphopenia, epithelial lung damage and dysfunction of the cellular immune response [5]. Compared to the pre-COVID-19 period, there is a significantly higher incidence of invasive fungal co-infections [6].

Fungal agents are responsible for at least 13 million infections and 1.5 million deaths per year globally, mainly in individuals with compromised immune function [7,8].

Various studies have described environmental contamination by fungi in healthcare settings and healthcare-associated infections [2,5,6,9–16].

Aspergillus spp. are among the fungi causing the greatest concern in healthcare settings worldwide.

The aim of this article is to review the problem of *Aspergillus* contamination in healthcare facilities, the prevention and control measures of healthcare-associated aspergillosis and the issue of the spread of antifungal-resistant strains.

2. Source

A literature search using the terms "*Aspergillus*", "healthcare facilities", "Aspergillosis", "prevention and control measures" and "antifungal resistance" was conducted. PubMed and Web of Science databases were searched. Additional reports were also identified through the references cited. The search was restricted to articles published in English. Meeting abstracts were excluded.

3. *Aspergillus* spp. Characteristics

Aspergillus is among the most common fungi, and has a structure characterised by conidiophore stalks, foot cells, vesicles, metulae, phialides and spores or conidia (Figure 1). Spores have a diameter of 3.0–5.4 µm and a rough-walled subglobose shape [17].

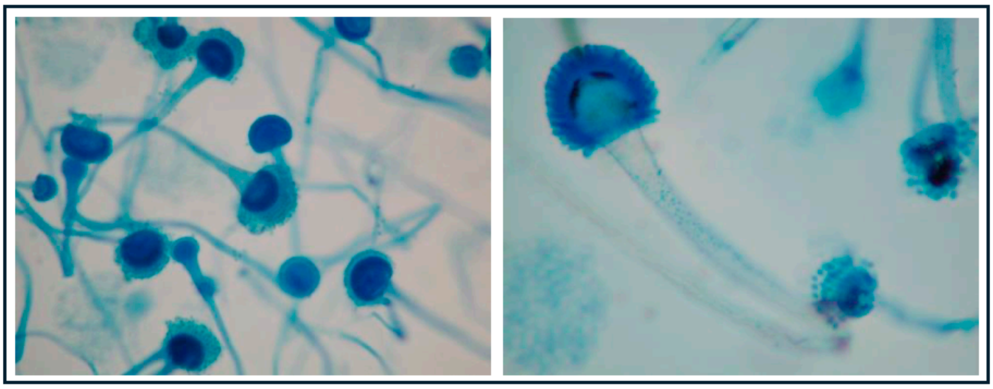

Figure 1. *Aspergillus* spp. (microscopic view of lactophenol cotton blue staining of isolates at 100×).

Aspergillus spp. are ubiquitous and present in soil, organic debris, water, decaying vegetation and dust produced in renovation work and/or building work [2,11,18,19].

Fungal spores from the various environmental reservoirs are released into the air and the processes of sedimentation and resuspension can be repeated. Air plays a crucial role in the spread of *Aspergillus* spores in the environment, constituting the main transmission route. *Aspergillus* spores in air can be transported over great distances by normal atmospheric conditions, such as convection currents and wind [19]. The slightest air flow can cause spores to disperse due to their high hydrophobicity; the degree varies from mildly to highly hydrophobic, which affects the efficiency of spore dispersion. The complex conidia of the species *A. fumigatus* are considerably more hydrophobic than those of many other aspergilli. Conidial hydrophobicity is confirmed by the presence of surface hydrophobin, encoded by the rodA gene [20].

Several studies have shown the presence of aspergilli in various healthcare environments [2,21,22]. In a study we conducted [9], airborne contamination by fungi was assessed in various rooms of 10 hospital facilities. Sampling was performed with portable surface air system (SAS) Super 100 impactors and counting plates containing fungus-selective medium (Sabouraud with chloramphenicol). This research showed that 35% of the inpatient wards monitored (ordinary, protected environment and intensive care wards) were contaminated with *Aspergillus* spp., with an average concentration of 1 ± 2.3 CFU/m^3. These wards were equipped with an aeraulic system with filters with an efficiency of 80–85%, guaranteeing a number of hourly changes of six air changes per hour (ACH) and a positive pressure of 1 Pa. Of the operating theatres equipped with a HEPA-filtered aeraulic system, with a number of hourly changes of 15 ACH and a positive pressure of 10 Pa, 7% tested positive for *Aspergillus* air contamination.

4. *Aspergillus* Infections and Risk Factors

Clinical syndromes and diseases associated with *Aspergillus* spp. can be cutaneous (primary skin and burn-wound infections, especially in neonates and children), hypersensitivity (asthma, allergic bronchopulmonary aspergillosis), chronic non-invasive or semi-invasive pulmonary aspergillosis and invasive aspergillosis [23–25].

The primary route of acquiring *Aspergillus* infections is through the inhalation of spores; the respiratory tract is therefore the most common portal of entry of *Aspergillus* spp. spores [26,27]. Airborne fungal spores can penetrate deep along the respiratory tree; indeed, the small diameter of the spores allows them to reach the pulmonary alveolar spaces where they may germinate to form hyphae [19]. In most healthy and immunocompetent individuals, inhaled *Aspergillus* spores are removed by innate defence mechanisms; immunocompromised patients, on the other hand, are extremely susceptible to the penetration of *Aspergillus* spores into the respiratory system. Typically, thousands of spores are inhaled every day, and if spore clearance fails (typically in immunocompromised patients), fungi can grow and invade lung tissue, causing invasive aspergillosis (IA) [26], which is one of the most frequent infections in highly immunocompromised patients [15,19].

Aspergillus fumigatus is the most common species involved; this species can be attributed to about 80% of the cases of aspergillosis [23]. The other species that can be involved to a lower level are *A. flavus*, *A. niger*, *A. nidulans*, *A. terreus* and cryptic species of *A. fumigatus* complex [28].

Patients at increased risk of aspergillosis are patients undergoing hematopoietic stem cell transplantation, patients with chronic obstructive pulmonary disease, patients undergoing chemotherapy, organ transplant recipients, patients with immune system deficits receiving care in a general intensive care unit (ICU), haemodialysis patients and preterm infants. Factors that may influence severity and outcome are the duration of the immune system deficiency [25,29–31].

Among the extrinsic risk factors, a high-risk element is environmental contamination, especially in hospital settings. The aerial concentration of fungal spores and the duration of exposure are important factors in the pathogenesis of IA [32,33]. To date, the lowest airborne concentration of *Aspergillus* spores sufficient to cause infection in immunocompromised patients is not yet known. According to some authors, airborne fungal spores at any concentration may represent a threat to severely immunocompromised patients [19].

According to a study by Sherertz et al. [34], no cases of IA have been observed in the presence of an airborne concentration of fungal spores of $\leq$0.009 CFU/m^3.

Rhame et al. [35] showed a higher risk of invasive aspergillosis (IA), at an average *A. fumigatus* concentration of 0.9 CFU/m^3.

Using a regression model, Alberti et al. [36] found a significant relationship between the incidence of IA and the concentration of *Aspergillus* spores in the air and on surfaces; in particular, the authors showed that peak airborne concentrations of *Aspergillus* at values of $\geq$2 CFU/m^3 play a decisive role in the relationship between environmental contamination and the incidence of IA.

5. The Emergence of Antifungal-Resistant Aspergillus

The first-line treatment of diseases caused by *Aspergillus*, in particular AI, is based on triazole antimycotics such as voriconazole which target the ergosterol biosynthesis pathway [23,37]. Despite the efficacy of triazoles, there have been adverse events associated with their chronic use [19]. Even though voriconazole is still the treatment of choice, isavuconazole and posaconazole have similar efficacy with less toxicity. Combination therapy is used in cases of severe immunosuppression and extensive infection [38].

Unfortunately, resistance to antimycotics is increasing, partly due to their widespread use in various areas. Indeed, in addition to their use in medicine, azole antifungals are largely used in veterinary treatment, material preservation and agriculture (e.g., prothioconazole, difenoconazole and tebuconazole).

The threat of climatic change to food security has contributed to adaptive agricultural practices (including increased chemical treatments and fungicides) [39]. Extensive use of azole fungicides in agriculture to prevent crop losses is contributing to increasing rates of azole-resistant *Aspergillus fumigatus* infections, with azole resistance rates of 15–20% reported in parts of Europe and over 80% in environmental samples in Asia [40,41].

Resistance to triazoles can severely limit treatment options and is associated with a worse prognosis for the patient [42]. Variants of *A. fumigatus* resistant to voriconazole often show cross-resistance to other agents, such as itraconazole, isavuconazole and posaconazole.

An international study showed a 3.2% prevalence of azole-resistant *A. fumigatus* in 3788 *Aspergillus* isolates from 22 centres in 19 countries. Resistance was found in 11 countries (57.9%), including Italy, UK, Austria, Belgium, Denmark and France [23,43].

Azole-resistant isolates of *A. fumigatus* have been shown to have, for the most part, a resistance mechanism mediated by the cyp51A gene. Most resistant strains exhibit a tandem repeat in the promoter region of the cyp51A gene, together with point mutations that lead to amino acid changes in cyp51A [44]. Depending on the specific mutation, azole-resistant isolates of *A. fumigatus* may show resistance to one azole or to any azole. Recently, a mutation in the promoter of the cyp51A gene (TR120) has been described, which is probably more associated with prolonged exposure to azoles. Other mutations at various positions of the cyp51A gene have also been associated with resistance, of which the most common are the G54 and M220 mutations [42,43,45–47].

Echinocandins may be used alternatively in the case of azole resistance, although echinocandin-resistant strains have also been reported [37,48].

This has encouraged the search for new therapeutic alternatives; antifungal peptides have recently arisen as molecules with clinical potential as a result of their capacity to alter the structures of fungal cells, their low resistance response and broad spectrum [23].

6. Epidemiology

The prevalence of invasive fungal infections is increasing worldwide, particularly in intensive care units, where *Aspergillus* spp. is among the most important pathogens [49].

The document "WHO fungal priority pathogens list to guide research, development and public health action", published in October 2022 by the World Health Organisation (WHO) represents the first global effort to give "systematic priority" to the serious public health threat caused by pathogenic fungi [41,50].

The list of priority pathogens is divided into three categories: critical, high and medium priority, based on their impact on public health and/or the risk of resistance development. *Aspergillus fumigatus* is one of the four critical priority fungi (Table 1).

Invasive aspergillosis affects about 300,000 patients per year and more than 30 million patients are at risk [42]. This disease can be a major cause of death in immunocompromised patients. In these patients, the mortality rate of invasive aspergillosis can reach 80–90%; mortality rates approach 100% if diagnosis is delayed or missed and if severe neutropenia persists [20,30].

Table 1. WHO fungal priority pathogens list ([41], modified).

Priority Level	Pathogens List
Critical Priority	• *Cryptococcus neoformans* • *Candida auris* • ***Aspergillus fumigatus*** • *Candida albicans*
High Priority	• *Nakaseomyces glabrata (Candida glabrata)* • *Histoplasma* spp. • Eumycetoma causative agents • *Mucorales* • *Fusarium* spp. • *Candida tropicalis* • *Candida parapsilosis*
Medium Priority	• *Scedosporium* spp. • *Lomentospora prolificans* • *Coccidioides* spp. • *Pichia kudriavzeveii (Candida krusei)* • *Cryptococcus gattii* • *Talaromyces marneffei* • *Pneumocystis jirovecii* • *Paracoccidioides* spp.

A large prospective study found that the one-year survival rate for people with invasive aspergillosis was 59% among solid organ transplant recipients and 25% among stem cell transplant recipients. In a broad US healthcare network of intensive care unit autopsy studies, aspergillosis was one of the top four most common diagnoses that likely led to death [51].

AI is emerging as an important complication in patients with severe viral infections requiring intensive care, including influenza virus, and more recently SARS-CoV-2. Severe influenza-associated AI, which goes by the name of IAPA (influenza-associated pulmonary aspergillosis), has been documented in 16–23% of influenza patients admitted to the ICU, with a mortality rate of more than 50% [52–54].

In the COVID-19 pandemic period, an increasing number of cases of invasive aspergillosis associated with SARS-CoV-2 infection were documented, identifying this superinfection as an additional factor in mortality and with the name CAPA (COVID-associated pulmonary aspergillosis). CAPA has been documented in ICUs in 18–39% of COVID-19 patients, with a mortality rate of up to 64.7% [52,55,56]

Although most cases of aspergillosis are sporadic, outbreaks of invasive aspergillosis occasionally occur in hospitalised patients [57]. Numerous epidemic episodes of aspergillosis described in the scientific literature have developed in connection with a wide variety of construction activities, such as renovation, demolition, maintenance and excavation.

Some of these episodes, including the spread of spores following a fire in a building adjacent to a hospital, are reported in Table 2.

Therefore, invasive aspergillosis outbreaks are often found to be associated with hospital construction or renovation works in or near hospitals, which can increase the facilities' environmental dispersion of dust and debris and consequently the amount of airborne *Aspergillus*, resulting in respiratory infections in high-risk patients [51].

Table 2. Some cases of nosocomial outbreaks of *Aspergillus* spp. during construction work.

Hospital Unit	Associated Pathological Conditions or Reason for Admission	Number of Patients Involved in the Outbreak	Number of Dead Patients	Circumstances	*Aspergillus* Species Involved	References
Military medical center	Immunocompromised (lymphoreticular malignancy, high-dose corticosteroid therapy or disseminated carcinoma)	11	11	Hospital renovation of medical ICU and several hospital wards.	*A. flavus*, *A. fumigatus* *A. niger* *Aspergillus* sp.	[58]
Haematology department	Leukaemic patients in medullary aplasia	22	18	Hospital construction work was responsible for the spread of fungal spores from false ceilings, fibrous thermal and/or acoustic isolation materials and roller-blind casings.	*A. fumigatus*	[59]
Haematological ward	Acute leukaemia	10	4	Indoor building renovation, increased spores in ward locations with heavy traffic of patients and staff.	Unknown	[60]
University medical center special care unit	Neutropenic patients who underwent high dose chemotherapy	5	Unknown	Hospital construction, increase in fungi in the air occurred in the patient rooms and corridor adjacent to construction staging area, windows in the adjacent corridor as the most likely source of fungal contamination.	*A. fumigatus*, *A. flavus*	[61]
Hematology–oncology unit of a university tertiary-care center	Leukemia or bone marrow transplants	36	17	Antiquated ventilation system in hospital which could not filter the *Aspergillus* spores that were dispersed during construction activity.	*A. flavus* *A. fumigatus* *A. niger*	[62]
Leukemia and bone marrow transplant (BMT) unit	Leukemic or BMT patients	21	Unknown	During active construction, *Aspergillus* spores may have entered the oncology unit from the physically adjacent hospital because the pressure in the oncology unit was negative with respect to it.	*A. flavus*	[63]
Department of Hematology	Acute leukemia	25	6	Presence of building work near to hospital wards in which patients were cared for.	*A. fumigatus*, *A. terreus*, *A. flavus*	[64]
Children's medical center	Children with acute leukemia	50	10	Major renovation with excavation of the grounds for construction of a new tower connected to the existing buildings.	*Aspergillus* sp. and other fungi	[65]
Hematologic wards	Hematologic malignancies	29	8	Heavy hospital construction works with demolition and excavation	*A. fumigatus*, *A. flavus*, *A. niger*	[15]
ICU	COVID-19 Post-operative care Septic shock	7	2	Electricity maintenance on the corridor ceiling of the ICU.	*A. fumigatus* *A. flavus*	[66]

It has been estimated that about half of all healthcare-associated *Aspergillus* outbreaks are caused by construction or renovation activities in or around hospitals [20].

The first outbreak of invasive aspergillosis associated with construction and renovation work was described in 1976 by Aisner J. et al. [67]. Eight cases of invasive aspergillosis occurred in cancer patients after the transfer of a hospital ward to a newly built facility where fireproof material was identified as a source of dispersion of *Aspergillus* spores [20,58].

Since then, several other authors have described cases of infection and/or outbreaks of nosocomial invasive aspergillosis in high-risk wards (intensive care, organ transplantation, haematology, oncology and immunocompromised patient wards) associated with construction, demolition or renovation work in or near hospital facilities [14,15,62].

In a study conducted by Sarubbi et al. [68], an outbreak of aspergillosis by *A. flavus* was described in connection with construction work, caused by the contamination of the ventilation system's prefilters and improper positioning of the end filters, which resulted in air leakage. This resulted in the passage of unfiltered air contaminated by *Aspergillus* spores dispersing into the inpatient area.

Another important factor that is contributing to an increase in the spread of fungi and fungal infections is climate change. Indeed, climate change is causing profound long-term effects on fungal ecosystems and has been associated with an increase in the incidence and severity of devastating natural disasters, which in turn often cause outbreaks of fungal diseases [39]. After the tsunami following the Great Japan Earthquake in 2011, cases of severe infections with *Scedosporium* and *Aspergillus* spp. were reported [39,69]. The overloaded healthcare systems as a consequence of natural disasters contribute to fungal outbreaks, as shown by an outbreak of five cases of *A. fumigatus* meningitis linked to contaminated medical equipment in a tsunami-affected Sri Lankan hospital [39,70].

7. Difficulties in Invasive Aspergillosis Diagnosis

Despite advances in our understanding of the interaction between *Aspergillus* species and the human immune system response, invasive aspergillosis remains difficult to diagnose and treat early, so mortality rates associated with IA remain high [19].

Diagnosis usually involves culture investigations for fungi and histopathology of tissue samples; these include galactomannan antigen detection tests on serum and/or bronchoalveolar lavage fluid [71].

Since cultures are time-consuming and histopathological examination results can be falsely negative, most treatment decisions are based on strong presumptive clinical evidence.

The determination of soluble aspergillar antigens such as galactomannan can be specific, but in serum is often not sensitive enough to identify most cases in their early stages. In invasive pulmonary aspergillosis, the galactomannan test on bronchoalveolar lavage fluid is much more sensitive than that on serum and is often the only option for patients with thrombocytopenia, for whom biopsy is contraindicated [71].

Successfully targeting antifungal therapy requires correct species identification. Fungal species identification can be performed by amplification of specific sequences of DNA regions and by sequencing of internal transcript sequences, calmodulin, tubulin and other large partial subunits of rDNA regions [28,72,73].

Recently, next-generation metagenomic sequencing (mNGS) has been used as a modern approach to provide molecular-based fungal DNA evidence in the suspected diagnosis of pneumonia. Ideally, sequencing could reveal the species and also give information on possible drug resistance. Nevertheless, the application of BALF of mNGS on immunocompromised patient groups identified a greater number of viral pneumonias but had a much lower degree of diagnostic accuracy for fungal infections (99% vs. 77%) [28,74].

8. Management of Preventive Measures of Invasive Aspergillosis During Hospital Construction Activities

Since many fungal outbreaks have been described in healthcare settings during construction works, this indicates the importance of prevention, an indispensable measure when such activities are planned and performed in order to avoid consequences for hospitalised patients [20]. Several organisations and experts have approved and encouraged a multi-disciplinary team approach to coordinate the various phases of construction activities (e.g., project initiation, project implementation, final verification and completion) [30], in order to prevent the dispersion of *Aspergillus* spores (Table 1).

The control of airborne *Aspergillus* contamination in hospitals, especially in conjunction with construction work, requires a series of plant engineering measures, such as the filtration of the air supply by means of high-efficiency HEPA filters (with at least 99.97% efficacy in the removal of particles smaller than 0.3 μm in diameter), a high number of hourly changes, the adoption of positive pressure in the patient rooms together with their isolation from the surrounding environments, the direction of the air flow and adequate humidity values.

The CDC [30] has defined the characteristics that "PE rooms" (i.e., protected environments intended for the hospitalisation of high-risk and immunocompromised patients) must possess in order to contain *Aspergillus* air concentrations within a hospital. These requirements can be summarised as follows: presence of an absolute air filter system (HEPA); number of air changes per hour $\geq$12 ACH; positive pressure in the patient room relative to the corridor (2.5 Pa); well-sealed rooms.

Furthermore, during construction and/or renovation work, a number of additional preventive measures must be taken. Depending on the location and extent of the construction, it may be necessary to relocate patients to other areas of the facility not affected by construction dust. Such a transfer may be particularly prudent when construction takes place within units housing immunocompromised patients.

Outdoor construction and demolition activities require measures to keep dust and moisture out of the facility (e.g., sealing windows and vents and keeping doors closed or sealed). Containment of dust and moisture generated from construction inside a facility requires barrier structures (either prefabricated or built with stronger materials, as needed) and engineering controls to clean the air in and around the construction or repair site [30].

Table 3 shows further measures and precautions that should be taken in the presence of construction works and activities that increase the level of dust and thus the dispersion of spores.

Various studies have shown that, in the inpatient environments of at-risk patients equipped with HEPA filters, there was a significant reduction in both *Aspergillus* concentration and aspergillosis rates [32].

In a study we conducted [10], it was shown that the use of an air-conditioning system equipped with HEPA filters significantly reduced the environmental concentration of aspergilli.

Air samples were taken in three hospital facilities: the first had no aeraulic system (facility A), the second had an aeraulic system equipped with low-efficiency filters (MERV) (facility B) and the third had a continuously controlled aeraulic system equipped with absolute filters (HEPA) (facility C). Air samples obtained by active sampling were positive for fungi only in facilities A (mean concentration = 0.5 CFU/m^3) and B (mean concentration = 0.16 CFU/m^3). Samples obtained by passive sampling (settling fungal load) were positive only in facility A (mean concentration = 0.14 CFU/cm^2/h).

Table 3. Some precautions during renovation and construction work in healthcare facilities.

-	Completely enclose the renovation site with construction barriers that extend from the floor to the ceiling, exceeding the false ceiling if present.
-	Create a filter zone before entering the work area where workers wear a paper suit before entering, which is removed when they leave, or where they are subjected to dust extraction before leaving.
-	Place a mat in the anteroom, at the exit of the anteroom and in the patient care areas in order to trap the dust present under the workers' shoes.
-	Identify precise areas for the storage of used equipment.
-	All personnel entering the construction area should wear shoe covers, which must be removed on leaving.
-	Seal all air communications with the work site, close windows and cover air ducts.
-	Remove debris from the work site according to a predetermined route.
-	Immediately remove dust that has arrived outside the protective barrier.

Optimal air filtration, however, is not effective if the aeraulic system is not properly maintained. Ventilation and air conditioning systems for which appropriate maintenance and verification of technical requirements is not carried out have frequently been identified as a source of contamination. In fact, it has been shown that in particular environments with air conditioning systems, Aspergilli may be present in higher concentrations than those found in the outdoor environment [75].

Primary prophylaxis is recommended for patients known to be at high risk of IA; particularly patients with prolonged profound neutropenia or active graft versus host disease [20]. Combariza et al. [76] demonstrated that the addition of prophylaxis with posaconazole to environmental control measures resulted in a decrease in the incidence of invasive aspergillosis from 14.4% to 6.3% [20,76].

Le Clech et al. [77] showed that the incidence of IA decreased significantly during construction periods when prophylaxis with posaconazole was used (1.59 vs. 4.87 per 100 hospitalisation days, $p < 0.0001$), suggesting the importance of antifungal prophylaxis in addition to HEPA filtration in the prevention of IA during hospital construction.

9. Conclusions

Unlike bacteria and antibiotic resistance, fungal infections receive little attention and an insufficient investment in resources. Antifungal resistance is becoming a significant concern to clinicians who are charged with caring for patients at high risk of invasive mycoses.

To date, quality data on the epidemiology of antifungal resistance are scarce, making it difficult to estimate their exact burden and not favour effective response. Indeed, the WHO report emphasises the need for strategies to generate evidence and improve the response, and in particular strengthen laboratory capacity and surveillance, support investment in research and strengthen public health interventions for the prevention and control of fungal infections through a One Health approach.

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