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REVIEW

A Review of Healthcare-Associated Fungal Outbreaks in Children

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Abstract

Purpose of Review The aim of this review is to examine healthcare-associated fungal outbreaks (HAFO) in children. Our primary objective is to dissect epidemiology and etiology aspects to contribute to the investigation, prevention, and control of HAFO in pediatric settings.

Recent Findings Latest studies have highlighted an increase in fungal infections among hospitalized children. These studies have revealed the involvement of environmental sources and cross-transmission through healthcare workers in the development of outbreaks. The diagnosis of fungal infections poses challenges, as does outbreak control due to non-routine surveillance and resistance of fungi to disinfectants and therapeutic drugs.

Summary Recognition of risk factors, etiologic agents, diagnostic methods, and types of transmission that facilitate fungal infections in children is crucial to understand the importance of prompt outbreak investigation and control. Addressing research gaps in disinfection technologies and exploring the potential application of artificial intelligence on outbreak anticipation could aid in mitigating the impact of HAFO on pediatric populations.

Keywords Fungal infections · Healthcare-associated infections · Outbreaks · Prevention and control

Introduction

Healthcare-associated infections (HAIs) are a significant, and often preventable, complication of hospitalization, posing a threat to patient safety. HAIs can result from transmission of a wide range of pathogens, including bacteria, viruses, and fungi, contributing to increased morbidity, mortality, and healthcare costs. Among these, fungal infections in pediatric wards have gained growing attention due to the increasing number of susceptible patients [1••]. Numerous risk factors, such as immunocompromise, extreme prematurity, prolonged hospital stays, invasive procedures, broad-spectrum antibiotics, and antifungal use, contribute to fungal HAIs. The complex healthcare environment, with its blend of vulnerable patients, clinical interventions, and potential pathogens, provides fertile ground for HAIs to spread if patient care processes and infection control measures are disrupted, thus raising the risk of outbreaks.

The aim of these next few paragraphs is to review the several aspects needed for the development and management of a healthcare associated fungal outbreak (HAFO) in pediatric facilities.

Epidemiology of Healthcare-Associated Fungal Outbreaks in Children

Growing global rates of healthcare-associated fungal infections result partly from the extended lifespans of patients with chronic illnesses. These conditions often render them susceptible to invasive fungal infections (IFI) due to amplified use of medical treatments such as chemotherapy, transplantation, and immunomodulatory drugs [2–4]. Additionally, the increased use of invasive medical devices such as central venous catheters (CVCs) has increased the incidence of central line-associated bloodstream infections (CLABSIs) caused by yeasts, primarily *Candida* spp. such as *C. albicans*

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and, emerging as a concern, *C. auris,* particularly within the setting of hospital outbreaks [5].

Recent outbreaks, such as fungal meningitis and other infections associated with contaminated anesthetics and steroids, are increasing and have gained significant public attention. The Mycotic Diseases Branch of the Centers for Disease Control and Prevention (CDC) annually investigates 3 to 6 outbreaks caused by uncommon fungi associated with greater diagnostic and therapeutic challenges. In the past, during the 1990s, only one or two outbreaks were investigated and were found to be caused by identifiable common-source yeasts with lower resistance to classical antifungals [6].

Candida spp. are linked to severe HAIs, particularly in intensive care unit (ICU) patients, and are rising as an etiologic agent of hospital acquired bloodstream infections [4, 5]. In the United States, approximately 25,000 cases of invasive candidiasis (IC) are diagnosed every year [7]. However, the true incidence of candidemia is probably higher due to the 50% sensitivity of blood cultures for identifying *Candida* spp. Newer and faster nonculture-based testing has improved the diagnostic yield for candidemia [4]. Among yeasts, *Candida auris* has emerged as a multidrug-resistant species and is a diagnostic and therapeutic challenge, linked globally to HAFO [7, 8]. The mortality attributed to IC imposes excess healthcare costs that range from $35,000 to $68,000 per candidemia episode [4, 9]. Concerning invasive aspergillosis (IA), its incidence rate per million individuals has risen from 33 in 2000 to 46 in 2013, particularly in high-risk populations such as solid organ transplant (SOT) recipients. Aspergillosis represents almost 60% of all IFI and has a 6-week mortality rate of 22% in the severely immunocompromised [1••].

HAFO are linked to cross-transmission via the hands of healthcare workers (HCW), suboptimal environments in healthcare facilities, contaminated medical devices, and other exceptional situations such as the transplantation of infected organs. These outbreaks also encompass incidents involving medications contaminated with fungal pathogens. The escalating reports of pharmaceutical contamination with diverse fungal species over the past decade have resulted in complex outbreaks, shedding light on regulatory gaps within the pharmaceutical industry [10].

Risk Factors and Vulnerable Populations

Numerous studies have elucidated the risk factors that predispose patients to the development of IFI; these are summarized in Fig. 1 [2, 11, 12]. The impact of these factors is considerable, with high-risk patients experiencing a more than 50-fold increase in the incidence of IFI compared to those with no known risk factors [13].

Aspergillus spp., mucorales, and various molds are ubiquitous in both outdoor and indoor environments, including healthcare facilities. Numerous outbreaks of aspergillosis and mucormycosis have been documented in healthcare settings, with factors such as hospital construction, indoor water-system damage, and inadequate air filtration identified as contributing to these occurrences. In certain instances, hospital acquired outbreaks of IFI involve the transmission of yeasts through contaminated surfaces and the hands of HCW.

While most filamentous fungi HAFO outbreaks are typically caused by *Aspergillus* spp., there is a clear increase in mucormycosis outbreaks among hospitalized patients in the USA [14]. The shift from *Aspergillus* spp. to mucorales as the causative organism in outbreaks might be attributed to the growing utilization of voriconazole prophylaxis in immunocompromised patients [10].

New construction is identified as the predominant source of fungi, followed by renovation, demolition, and excavation; all these activities facilitate the aerosolization and dispersion of fungal spores throughout hospital areas. Within construction-related settings, various environmental sources can result in a HAFO; among these, the flow of contaminated and unfiltered air, air conditioning duct systems, and dust above false ceilings are only a few examples of potential fungal reservoirs [14].

The main in-hospital source of *Aspergillus* spp. infection is inhalation of contaminated air, with most outbreaks related to construction activities in about 50% of cases [1••]. However, *Aspergillus* spp. can also be found in the water and plumbing system of healthcare facilities. Studies have shown that the highest counts of airborne *Aspergillus* spp. spores were found in patient bathrooms due to aerosolization of spores from water streams from showers and faucets [3, 15].

Etiology of Healthcare-associated Fungal Outbreaks in Children

Yeasts

Candida spp. IC occur in immunocompromised patients, especially patients with chemotherapy induced neutropenia, where candidemia originates from the gastrointestinal tract. In the pediatric population, outbreaks caused by *Candida* spp. have been reported worldwide in several clinical areas, especially in the neonatal intensive care unit (NICU). In critically ill patients, usually the source of candidemia is a CVC colonized by *Candida* spp. from the patient's microbiome or from inanimate surfaces in hospital settings [1••]. *C. albicans* is the most frequent yeast to cause IC, yet in recent years, other non-albicans species such as *C. parapsilosis*, *C. glabrata*, and *C*

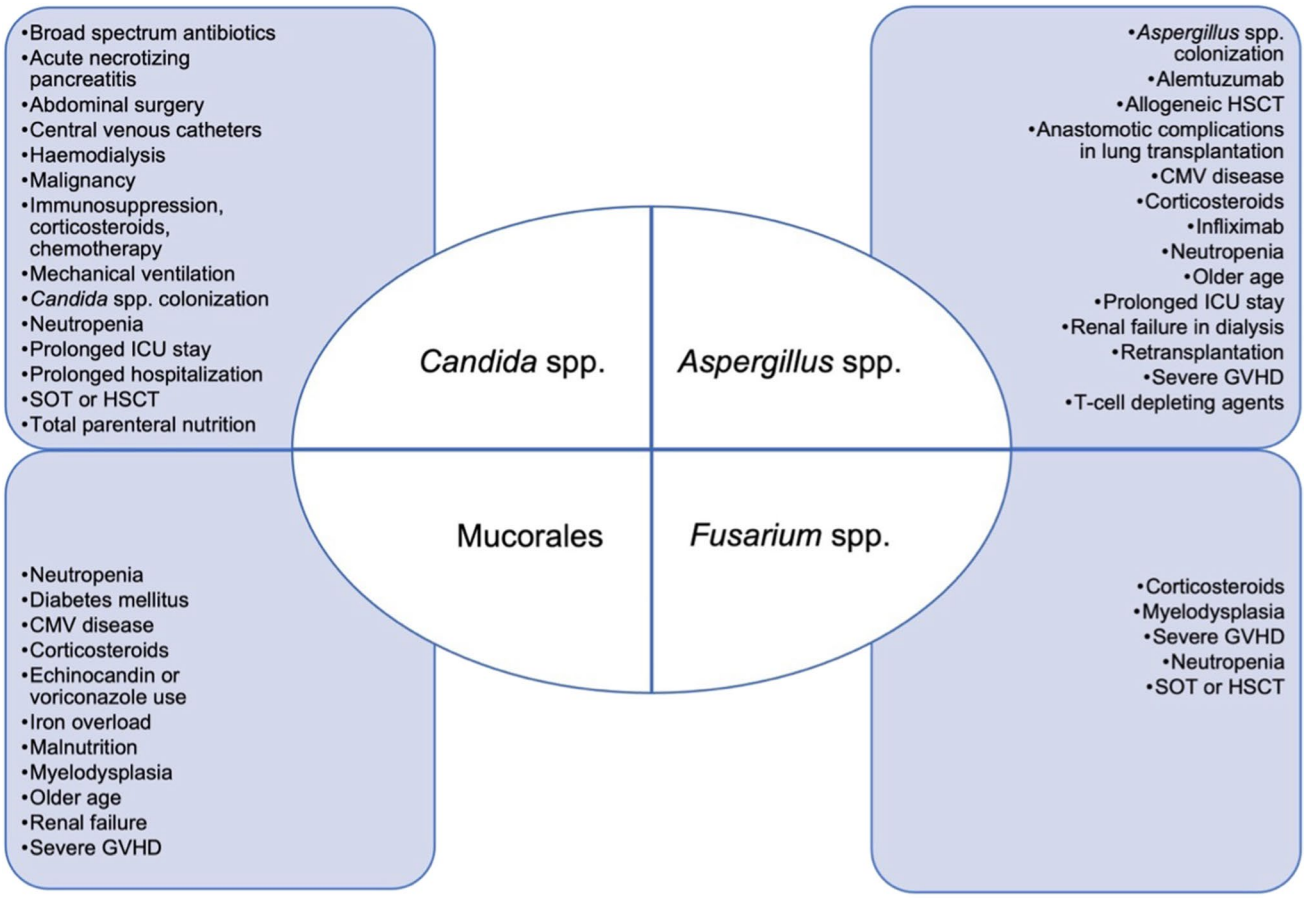

Fig. 1 Host-related risk factors for invasive fungal infections

tropicalis are rising. Widespread fluconazole use drives the selection of azole-resistant species, promoting the rise of non-albicans strains [16]. Of great concern is the emergence of *C. auris*, isolated in 2009 in Japan from a patient's external ear canal [17]. This multidrug resistant species has spread throughout all continents excluding Antarctica and caused multiple outbreaks [16]. Mortality is as high as 28–41% [19]. Most of *C. auris* infections are healthcare-associated due to its ability to contaminate the patient's surrounding environment and equipment, facilitating cross-transmission [20, 21]. *C. auris* can survive on humid or dry surfaces for as long as seven days or longer on plastic materials (up to 14 days) [22, 23]. Although carriage can be intermittent in the setting of an outbreak, it also represents an important reservoir of *C. auris* [24]. Diagnosis is challenging and the species is frequently misidentified as *C. haemulonii* or other non-albicans species [25, 26].

Other yeasts

Trichosporon spp. fungemia has been reported in children with hematologic malignancies and organ recipients, either hematopoietic stem-cell or solid organs. Mortality ranges from 42 to 83% [27, 28]. *Malassezia* spp. fungemia outbreaks have been reported in special populations such as preterm newborns and immunocompromised hosts. Prolonged use of CVCs and total parenteral nutrition (TPN) are important associated risk factors [29].

Some of the most relevant yeast outbreak reports in the pediatric population are summarized on Table 1 [19, 30–36].

Filamentous fungi or molds

Aspergillus spp. account for most of the healthcare-associated filamentous fungi outbreaks. Other molds have also

Table 1 Healthcare associated fungal outbreaks caused by yeasts in children

Microorganism	Country	No. of patients	Mortality	Age range	Hospital area	Source	Clinical syndrome	Reference
C. albicans	India	7	Not reported	< 28 days	NICU	TPN	Candidemia	Guducuoglu 2016 [30]
C. parapsilosis	China	16	6.25%	2–38 days	NICU	Several positive environmental sites (wiping cloths, sinks, faucets) but none confirmed as source	Candidemia	Qi 2018 [31]
C. krusei	South Africa	48	15%	7–17 days	NICU	Not identified	Candidemia	van Schalkwyk 2018 [32]
C. auris	Colombia	34	41%	0–10 years	-	Not identified	Candidemia	Berrio 2021 [19]
C. auris	Venezuela	18 (13 pediatric patients)	28%	0–18 years	NICU and ICU	Not identified	Sepsis	Calvo 2016 [33]
C. auris	India	22	41%	6 neonates 16 non-neonates	NICU and ICU	Not identified	Candidemia	Chakrabarti 2020 [34]
T. asahii	India	8	75%	6–21 days	NICU	Not identified	Sepsis	Vashishtha 2012 [35]
M. pachydermatis	USA	5	Not reported	5–61 days	NICU	Not identified	Fungemia peritonitis	Chow 2020 [36]

ICU intensive care unit, *NICU* neonatal intensive care unit, *TPN* total parenteral nutrition

been implicated such as mucorales, *Fusarium* spp., and *Scedosporium* spp.

A. fumigatus is the most frequent species associated with invasive disease in humans, although other species such as *A. flavus*, *A. niger*, and *A. terreus* have also been isolated. The ubiquitous distribution of *Aspergillus* spp. in the community and healthcare environment, especially near decaying matter as well as the uncertain incubation period of this mold, complicates defining healthcare-associated IA. Generally, IA is labeled as such when it presents after one week of hospitalization [1••]. However, due to their primary disease, patients with risk factors for IA usually have a history of recurrent hospitalizations or frequent healthcare facility visits either for diagnostic or therapeutic procedures, further hampering the possibility to establish IA as community-acquired or healthcare related. Among 53 *Aspergillus* spp. outbreaks that involved more than 450 patients, 65% occurred in HSCT or oncologic patients, 10% in SOT, and almost 10% in patients with no severe immunosuppression. The most frequent infection site was pulmonary, and mortality was higher than 50% in hemato-oncologic patients [37].

Mucorales, like *Aspergillus* spp. are ubiquitous molds in soil and decaying organic matter. HAFO due to mucormycosis are increasing. Mortality is high, but highest in newborns. The most common genus involved in HAFO is *Rhizopus* spp. Identified sources in different HAFO have been adhesive tapes, wooden tongue depressors, ostomy bags, hospital linen, ventilation systems, and construction sites [38].

Fusarium spp. is present in soil, air, and water in tropical and temperate regions. Only 12 species affect humans, the most common being *F. solani* (50%) and *F. oxysporum* (20%) [39]. Infection most frequently occurs after inhalation of conidia which are subsequently hematogenously disseminated. Hospital outbreaks have been described due to contamination of ventilation and water systems that result in dispersal of airborne conidia [1••]. CVCs have been associated with fungemia in outbreaks as well [39]. A major outbreak occurred in a Brazilian pediatric oncology unit, involving ten cases of invasive fusariosis with a 70% mortality rate. The primary source was traced back to contaminated water [40].

Some important outbreaks caused by non-*Aspergillus* filamentous fungi are summarized in Table 2 [39–44].

How to Investigate a Healthcare-Associated Fungal Outbreak?

Investigation of outbreaks caused by fungi must be an organized process to be successful. Following the principles of epidemiology, when a HAFO is suspected, the next steps

Table 2 Healthcare associated fungal outbreaks caused by filamentous fungi in children

Microorganism	Country	No. of patients	Mortality	Age range	Hospital area	Source	Clinical syndrome	Reference
Fusarium spp. *F. oxysporum F. solani*	Brazil	10	70%	10 months–17 years	Oncology unit	Water in patients' rooms	Invasive fusariosis	Litvinov 2014 [39]
F. oxysporum	Brazil	7	0%	0–8 years	Oncology unit	Central line catheters	Fungemia	Carlesse 2017 [40]
Rhizopus microsporus	UK	4	75%	< 28 days	NICU	Wooden tongue depressors	Cutaneous mucormycosis	Mitchell 1996 [41]
R. pusillus	UK	2	0%	5–15 years	Oncology unit	Water damage in linen storeroom and shower/air contamination	Rhinocerebral mucormycosis	Garner and Matchin 2008 [42]
R. delemar	USA	5	100%	0–13 years	Not specified	Hospital linens	Cutaneous mucormycosis	Duffy 2014 [43]
Rhizomucor	Egypt	5	60%	1–12 years	Oncology unit	Not identified	Rhinocerebral and pulmonary mucormycosis	El-Mahallawy 2015 [44]

must be completed. They are presented sequentially; however, it is important to keep in mind that many steps are tackled simultaneously [45]:

1- Confirm the outbreak by comparing the number of current cases to the usual frequency of cases in a similar period of time.
2- Verify the diagnosis: Review that there are no laboratory inconsistencies with the clinical findings. Ask yourself if there is an increase in microbiological identification because a newer fungal culture technology was introduced to your healthcare facility's laboratory and not because more patients are contracting the disease.
3- Construct a working case definition that can include clinical, laboratory/imaging and/or epidemiological data to define the "rule" by which other cases will become suspicious of being part of the outbreak. For example, in an outbreak of candidemia in the NICU, part of the definition might be "patients in the neonatal age-group."
4- Find cases systematically and record information. This is achieved through active (i.e., visiting different wards to look for patients that match the working case definition) and stimulated passive surveillance (i.e., clinicians are informed of a potential outbreak and instructed to report cases that fit the definition).
5- Describe the outbreak: Who is affected? When did the cases began to increase? Where are the cases increasing?
6- Develop hypotheses regarding the source: They must be logical with the type of pathogen identified or suspected. For example, in the case of a bloodstream infection outbreak caused by *Candida haemulonii,* it would not seem logical to culture air, as these yeasts are not transmitted by airborne particles.
7- Evaluate hypotheses epidemiologically: If the relation of the HAFO is not straight-forward towards a possible source (e.g., in a *Candida auris* outbreak where a colonized patient is identified and thus, is defined as the source), an effort should be made to conduct either a cohort study or a case–control study to find relationships between that could guide into finding the source.
8- If needed, reconsider, refine, and re-evaluate hypotheses: If no source is identified through the first investigation, it would be time to pause and retake the possible causes of the outbreak.
9- Implement control and prevention measures, and maintain surveillance: This is the purpose of the outbreak investigation and must be started as soon as the outbreak is suspected.
10- Communicate findings: In an orderly manner following the scientific method, with an aim to prevent panic, inform the involved authorities, and present the strategies implemented to control the outbreak.

Diagnosis

Early detection of HAFOs is essential for prompt and effective implementation of prevention and control measures. Microbiological diagnosis is key to finding and managing pathogen sources to break the chain of transmission. Despite advances with new methodologies over the past years, diagnosis of invasive fungal infections is challenging.

Diagnosis as proven, probable, or possible IFI depends on host risk factors, clinical signs and symptoms, and results from a variety of mycological tests [46]. The tools available for establishing the diagnosis of a fungal infection are summarized in the following paragraphs.

Fungal Cultures

The gold standard methodology for diagnosis. Main advantages are that it provides proven diagnosis and antifungal susceptibility tests can be made. Overall sensitivity for yeasts is low (50%) and even lower for molds (1–5%) [47]. Yeast blood cultures' positive turnaround time is 14–72 h. Candidemia is associated with candiduria in around 40–70% of cases, so if suspected, urine cultures must be considered [48]. Molds are rarely isolated on sterile fluids, except for *Fusarium* spp. which is easily identified in blood cultures during disseminated infection. Thus, in the case of suspected IA, detection in bronchoalveolar lavage (BAL) increases detection from 1.6% to 47.4% [49]. The long growth time delays appropriate treatment and consequently leads to higher mortality [50•]. Chromogenic media allows species-level differentiation for *Candida* spp. by using chromogenic enzymes. Results are relatively fast-delivered and cost-efficient, although there are some difficulties in distinguishing non-albicans species including the emerging *C. auris* [51].

A special mention must be made to air cultures for HAFO investigation as this is one of the few indications to sample air. Different techniques exist for air culturing [52]:

- Solid media impaction: Through vacuuming, air is driven to a selective solid agar plate such as Sabouraud medium.
- Filtration: Following the principle of impaction, air is driven to a selective medium but is filtered before reaching the agar plate to select only particles smaller than 0.2 µm.
- Liquid impregnation: Air is aspirated through a small tube and directed against a liquid culture medium.
- Sedimentation: The easiest, yet most easily contaminated method consists of placing agar plates open to the environmental air for a certain period (usually 1–2 h) to recover microorganisms that slowly fall on the plate by gravitational forces and naturally generated airflow.

Direct Microscopy and Histopathology

Direct microscopy and histopathology help distinguish fungal morphological structures that help differentiate septate molds (*Aspergillus* spp.), non-septate molds (Mucorales), and yeasts (*Candida* spp.). Accurate identification requires trained personnel [50•].

Biochemical Phenotypic Semi-automatized Identification Systems

Their diagnostic yield is better for common species (76–95%) than for uncommon species (58–78%) [53]. Most recent databases include *C. auris*; however, misdiagnosis with closely related species such as *C. haemulonii* is possible [25].

Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF)

This is based on the comparison of nucleoproteins' mass with a database for species identification of yeasts and molds. Commercially available systems are highly sensitive for yeast identification (96.8–98.7%) and have good performance for *C. auris* diagnosis. Advantages include accurate and fast identification at genus and species level [54].

Polymerase Chain Reaction (PCR) Methods

Several commercially available platforms are available for fungi diagnosis. Most recent blood culture panels allow identification of 7 yeasts including *C. auris* with a sensitivity > 98%. These methods are rapid and accurate [55].

Nuclear Magnetic Resonance (NMR)

The target organism is identified by beads that bind to the complementary sequences to the pathogen's DNA which is observed by NMR. T2Candida® allows identification of five *Candida* species with a sensitivity of 91.1% and specificity of 99.4% [59].

Serology

ß-(1,3)-D-Glucan Assay

A polysaccharide of fungal cell walls in several species. This antigen can indicate infection with *Candida* spp.,

Aspergillus spp., and *P. jirovecii* pneumonia. False positives are as high as 75% [56].

Mannan Antigen

This is a principal component of *Candida* spp. cell wall with a sensitivity of 50–85% and specificity of 87–98%. Interpretation must be cautious as *Candida* spp. are part of the normal human microbiome [57].

Galactomannan Assay

Cell wall antigen of *Aspergillus* spp. also presents in other fungi such as *Fusarium* spp. and *Histoplasma* spp. It can be detected on blood and bronchoalveolar fluid. Sensitivity ranges from 45 to 100% and specificity from 78 to 100% [58].

Clinical Imaging

X-rays, computed tomography, magnetic resonance, and positron emission tomography can all be used to support IFI diagnosis in thoracic or abdominal compartments as well as central nervous system disease [60].

Prevention and Infection Control Measures

Prevention and control of HAFO are based in interrupting the chain of transmission of pathogens to susceptible hosts. Different strategies can be set to prevent and control an outbreak caused by a fungal pathogen. These can be classified in the following strategies [61•]:

Horizontal Strategies: Directed Towards Control of Multiple Pathogens

These include ensuring strict adherence to hand hygiene, which remains the most cost-effective means to prevent HAIs, and in the context of fungi, to prevent cross-transmission among patients via HCWs hands [62].

Cleaning and disinfection practices are an essential component of horizontal preventive measures; emphasis on high-contact surfaces is crucial to stop cross-transmission in yeast outbreak settings. Daily cleaning and terminal disinfection after patient discharge are crucial during outbreaks. It is important to remember that there cannot be an effective disinfection process without a previous meticulous cleaning. Monitoring cleaning practices can involve visual inspection or more objective methods such as ATP measuring and fluorescence technologies. Fungicidal agents as 70% alcohol, iodophors, phenolics, and quaternary ammoniums are effective against fungi but not spores. Achieving sporicidal capacity requires using sodium hypochlorite or high-concentration hydrogen peroxide [63].

High-level disinfection devices such as UV-C irradiation and vaporized hydrogen peroxide, known as "no-touch" devices, are a useful complement to cleaning and disinfection routine practices as they diminish environmental microorganism burden and help in outbreak control. However, research is still ongoing to establish the best time and distance of exposure for effective disinfection of some fungi such as *C. auris* [64].

Portable ventilators and fans, commonly used in settings without air-conditioning, alter air flows and contribute to the propagation and aerosolization of fungal spores that are either suspended in the air or deposited on surfaces. While no specific guidelines exist for their use, we recommend avoiding portable ventilators, especially during outbreaks. Guaranteeing "safe air" is crucial to prevent HAFO; thus, repairing or installing ventilation systems that ensure temperature, humidity, and air exchanges is beneficial for healthcare settings. When not possible, physical ventilation methods like safe window openings are preferable to no ventilation at all [65].

Vertical: Directed Towards Control of a Single Pathogen

Contact precautions consist in the use of a gown and gloves for patient manipulation. During outbreak investigations, *C. auris* has been isolated from medical equipment, most probably contaminated through patient's skin shedding; thus, the use of individual patient equipment is recommended, and avoid sharing with other patients until it has been cleaned and disinfected (i.e., a thermometer, stethoscope). Although transmission-based precautions for the prevention of fungal spread are described specifically for containment of *C. auris*, based on the use of precautions for other multidrug resistant microorganisms, such as carbapenem-resistant *Enterobacterales* or methicillin-resistant *Staphylococcus aureus*, it seems cautious to use contact precautions for patients with isolation of any multidrug resistant *Candida* spp., particularly in the context of outbreaks. Single-patient rooms are ideal, but limited infrastructure, especially in middle and low-income countries, often makes this impractical and cohorting patients becomes an alternative. As a last resort, closing the unit might be necessary [66].

Concerning the risk of outbreaks by molds, controlling construction conditions in healthcare facilities is of utmost importance. Systematic processes to plan constructions in healthcare facilities must be established and consider the areas to be worked on as well as the characteristics of patients that will be potentially exposed. The Infection Control Risk Assessment is a tool to prevent outbreaks linked to construction, including those by *Aspergillus* spp. It can be

summarized into a checklist answered in a three-step process consisting of identifying the population at risk, the type of construction, and finally deciding and putting up different actions to set before, during, and after the construction [67].

Screening patients and contacts for colonization is a strategy that has been adapted from MRSA to recent *C. auris* outbreaks. CDC recommends screening patients and HCW in close contact with patients recently diagnosed as infected or colonized by *C. auris*. Screening is done by swab cultures of the axilla and inguinal region. Due to the difficulties in *C. auris* identification, coordination with a state laboratory may be required in case the diagnostic tools are not locally available [68].

Antibacterial and Antifungal Stewardship

While not directly tied to outbreak control, it is crucial to highlight the significance of stewardship in using antibacterial and antifungal agents. Overusing antibiotics raises the risk of fungal diseases, while the use of antifungal agents contributes to selective pressure, fostering resistant fungi that cause opportunistic and breakthrough infections. If disseminated, these infections could lead to HAFO.

Lastly, it is also important to keep trained personnel in charge of areas with ongoing outbreaks as this will limit errors in hand hygiene, donning and doffing of personal protective equipment, correct cleaning and disinfection techniques, and disease awareness.

Challenges for HAFO Control

Finding fungal reservoirs can be challenging due to the ubiquitous location of many molds. As to yeasts, their ability to survive on surfaces makes them difficult to control. Also, as fungal structures such as conidia and spores can resist environmentally defiant conditions such as heat and disinfection, special attention may be needed to destroy reservoirs. Resistance to antifungals is also a challenge since the difficulty to treat a patient signifies persistent shedding that prolongs the possibility of cross transmission to other susceptible hosts.

When investigating an outbreak, whether fungal or of other etiologies, the first step is to detect that the outbreak is happening. Particularly in the case of fungi, detection of mold outbreaks faces the challenge of variable incubation periods depending on the immune state of patients. Furthermore, surveillance of fungal infections is usually sporadic or research-focused instead of a part of routinary activities as it is human-resource costly and demands access to a laboratory with the technology that permits working with filamentous and dimorphic fungi. Therefore, many outbreaks that involve fungi are detected less promptly than are most bacterial and viral outbreaks.

Future Directions and Research Needs

Artificial intelligence (AI) and the concept of electronic surveillance are the most encouraging next step into fungal outbreak early identification and, thus, prompt source investigation and control. In fact, Baggio et al. have developed a model for screening chest computed tomographies through machine learning, with a promising outcome in the detection of probable IFI [69].

The COVID-19 pandemic, despite its devastating consequences, was a portal to explore the utility of AI for epidemic surveillance. In particular, concerning viral diseases, AI can be applied to simulate public policy interventions and to approximate mathematical models for which analytic transmission equations are not known. Effective outbreak preparedness relies on the ability to anticipate viral mutations that will be capable of evading host immune responses to help in vaccine and treatment design. As an example, the tool named EVEscape, developed by Thadani et al., estimates the viral escape potential of mutations and is available before other surveillance techniques such as sequencing or three-dimensional structures of antibody complexes. Investing in these AI-based epidemiologic resources would enable early identification of outbreaks, a sooner intervention, and earlier control [70].

Conclusions

Fungi pose a growing threat in pediatric healthcare settings, leading to increasing outbreaks. Identifying risk factors early demands access to radiologic and microbiologic tools. Active surveillance of risk factors and microbiological results are vital in these settings to prevent outbreaks. Measures for containing an occurring outbreak include horizontal and vertical actions as well as antibiotic and antifungal stewardship to prevent selective pressure and adding an antimicrobial resistance problem. A multidisciplinary team is crucial for preventing, identifying, studying, and controlling a healthcare-associated fungal outbreak in pediatric facilities. The infection control, clinical, microbiology, and engineering teams are all essential. Although not widespread as of today, the potential of artificial intelligence in boosting outbreak prevention and control is promising, not to leave behind the case of healthcare associated fungal outbreaks in in children.

Author Contributions All authors contributed to the study conception and design. Aarón Espinosa-Atri and Ana Cecilia Carbajal-César performed the literature search, and wrote the first draft of the work,

including preparation of Fig. 1 and Table 1–2. Cyntia Ibanes-Gutiérrez contributed to the literature search and critically revised the work. All authors read and approved the final manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval Given the nature of literature reviews, the necessity for Ethics Committee approval was waived as no procedures were performed nor clinical data was obtained.

Informed consent Not applicable.

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights This article does not contain any studies with human participants or animals performed by any of the authors.

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- • Of importance
- •• Of major importance

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