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ANTIFUNGAL RESISTANCE PATTERNS OF MOLDS: A SYSTEMATIC REVIEW

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Abstract

Introduction: Invasive fungal infections present a significant risk to public health and are often overlooked as a part of the growing issue of antimicrobial resistance, which is becoming a global crisis. With significant changes occurring in the global environment and an increasing number of vulnerable populations, pathogenic fungi that infect humans are developing resistance to all approved systemic antifungal medications. **Methods:** A comprehensive search was conducted using electronic databases, including Scopus and PubMed, to identify relevant studies on antifungal resistance in molds. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH) terms related to antifungal resistance and mold species. The inclusion criteria encompassed studies reporting on antifungal resistance patterns in clinical isolates of various mold species. The data extraction process involved evaluating the selected articles and extracting information on resistance rates, mechanisms of resistance, and the efficacy of commonly used antifungal agents. **Results:** A PubMed and google scholar search yielded 326 results. Of which several papers had to be rejected for the review due to our inclusion criteria (studies do not discuss the MIC distribution, antifungal resistance, Amphotericin B, Fluconazole, reviews, duplication, and commentaries) and finally, 20 papers were considered in our review. Findings indicated varying levels of resistance to different antifungal classes, including amphotericin B, and Fluconazole. Mechanisms of resistance observed in several mold species. Additionally, intrinsic resistance was noted in certain mold species. The review also highlighted emerging resistant strains in resistance rates, and the impact of antifungal resistance on treatment outcomes. **Conclusion:** This systematic review provides a comprehensive overview of antifungal resistance patterns among molds. The findings emphasize the need for vigilant surveillance and monitoring of antifungal resistance to guide appropriate treatment strategies. The identification of specific resistance mechanisms and the emergence of new resistant strains underscore the importance of developing novel antifungal agents and optimizing therapeutic approaches to combat mold infections effectively.

Keywords: Antifungal Resistance, Mold Species, Aspergillus, Fusarium, Azoles, Mechanisms of Resistance, Clinical Isolates

1. INTRODUCTION

Fungal diseases pose a significant global health challenge, affecting a large population worldwide and posing a threat to human health. The increase in invasive fungal infections can be attributed to various factors, including the use of immunosuppressive therapies, the widespread utilization of medical devices, and the extensive use of broad-spectrum antibiotics. Moreover, the recent COVID-19 pandemic has further complicated the situation, as viral respiratory illness renders patients more susceptible to life-threatening fungal infections, particularly in intensive care units (ICUs). Accurate

diagnosis and treatment of these fungal infections are challenging, given the overlapping respiratory symptoms with COVID-19 [1-4].

Candida, Aspergillus, Mucorales, and Cryptococcus are among the primary causative organisms responsible for most serious fungal diseases. Despite advances in medical care, healthcare-associated invasive fungal infections continue to have high mortality rates. However, the true burden of these infections is likely underestimated due to insufficient epidemiological data and misdiagnosis. In response to the clinical mortality and economic burden caused by invasive fungal infections, the widespread use of antifungal drugs has become a common practice [5].

Traditionally, antifungal treatment has relied on four main classes of antifungal drugs: polyenes, azoles, echinocandins, and the pyrimidine analogue 5-flucytosine [6]. However, fungi possess the ability to adapt and develop resistance to these drugs, leading to treatment failures. Several factors contribute to treatment failure, including underlying host immune deficiencies, properties of antifungal drugs (such as pharmacokinetics, pharmacodynamics, and drug interactions), and characteristics of the fungi themselves, such as diverse cell morphologies, antifungal tolerance, and inherent or acquired resistance [7].

Clinicians responsible for treating patients with invasive fungal infections are increasingly concerned about the emergence of antifungal resistance. Resistance to currently available antifungal medications can develop when patients are exposed to these drugs, leading to acquired mechanisms of resistance. Recent trends in antifungal resistance include higher resistance to azoles among non-Candida albicans isolates, azole resistance in Aspergillus fumigatus, and echinocandin resistance in Candida glabrata [8-10]. Additionally, certain fungal species exhibit inherent resistance to specific antifungal drugs, further limiting treatment options. Moreover, emerging fungal species such as Candida auris have the potential to demonstrate resistance to multiple classes of antifungal agents [11-14].

Although antifungal resistance is not as prevalent as bacterial resistance, the limited treatment options for resistant fungal infections pose a significant challenge, especially for patients with multiple comorbidities and weakened immune systems. This limitation further reduces the effectiveness of therapy, even in the absence of drug resistance. Therefore, there is an urgent need for new treatment strategies to address antifungal resistance, including the development of novel antifungal drugs that can overcome the limitations associated with current agents [14].

This systematic review aims to provide a comprehensive understanding of the prevalence and patterns of antifungal resistance in clinical isolates of molds. By synthesizing the available evidence, we can identify the current challenges posed by antifungal resistance and explore potential strategies to combat this growing problem. The findings from this review will contribute to improving clinical management and informing future research directions in the field of antifungal resistance.

2. MATERIAL AND METHODS

2.1. Source of Data and Eligibility

The search methodology for identifying relevant articles in this systematic review was developed by the author. Electronic databases, including Scopus and PubMed, were utilized to search for suitable papers. Additionally, online databases such as pubmed and Google Scholar were employed to identify any eligible papers.

The systematic review included the following criteria: a) peer reviewed journal articles, specifically investigating antifungal resistance in clinical isolates of various mold species b) In vitro studies assessing the activity of amphotericin B and fluconazole against fungal species. The review focused on articles written in the English language. The included articles were examined and evaluated independently, and relevant data was extracted from them.

2.2. Screening Strategy

In order to assess their relevance, the abstracts and titles of the research that were collected from the relevant electronic databases were examined. The terms used in the first search were divided into four groups, and these groups were then joined using the Boolean operators "AND" and "OR" throughout the search process using the previously indicated electronic databases (as shown in Table 1). The searched group of words included antifungal, resistance, minimum inhibition concentration, invitro activities, drug resistance, clinical isolates, and antifungal therapy.

All papers' full texts were obtained and reviewed cautiously. Inclusion in the research was restricted to those publications that made it through the first screening phase. In addition, we looked at the papers' reference lists to see if there were any other articles we might use. A well-known standard for reporting systematic reviews, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used in this work to appropriately portray the sequential screening technique [27].

Table 1: Searched group of words to screen the relevant papers in various electronical database

Anti-Fungal resistance	Drug	Type of method	Outputs
‘resistance’ OR ‘mold patterns’ OR ‘fungal susceptibility	‘Amphotericin B’ OR ‘Fluconazole’	‘CLSI’ OR ‘E-test’ OR ‘antifungal susceptibility test’ OR ‘broth microdilution’ OR ‘disc diffusion test’	‘MIC distribution’ OR ‘MIC cut-off value’ OR ‘Effect’ OR ‘Properties’

2.3. Data verification for consistency

To ensure internal quality control of the database, a Microsoft Excel spreadsheet (MS Office 2019, USA) was created to contain the relevant data. The information in the spreadsheet was reviewed for accuracy and consistency as part of the internal quality control process. Additionally, an external quality control process was implemented to verify the integrity of the data. In cases where inconsistencies or discrepancies were identified within the Excel sheets, the data were carefully reexamined to ensure accuracy and resolve any mismatches.

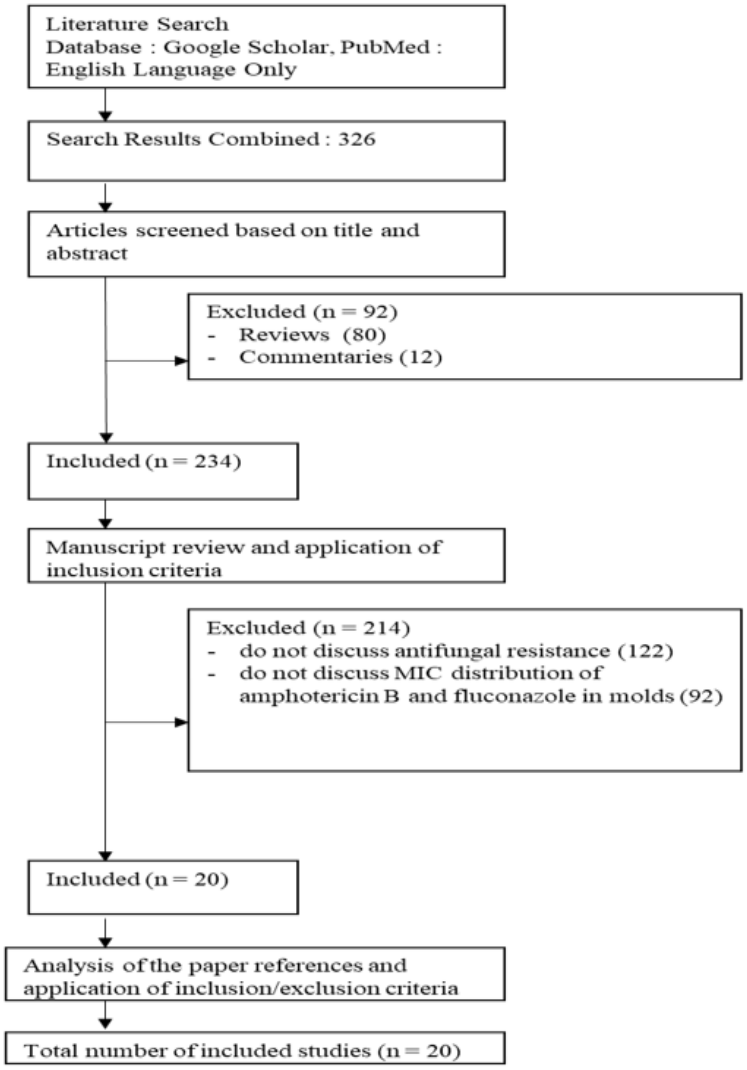

Fig. 1: PRISMA flowchart depicting the methodology for selecting suitable papers for review.

3. RESULTS

3.1. Literature search

The literature search yielded 326 records. There were two duplications detected. 304 studies were discarded because they meet the exclusion criteria, which were as follows: reviews (80), commentaries (12), topics other than antifungal resistance (122), topics other than MIC distribution of amphotericin B and fluconazole in molds (92). According to the selection procedure, a total of 18 studies were considered eligible.

Between 2015 and 2021, a total of 20 studies were published. In all this research, antifungal resistance was successfully recorded by MIC distribution. Most of the studies were carried out by foreign researchers.

3.2. Participant and setting characteristics

The studies included in the analysis have different sample sizes, with some involving a smaller range of 20 species up to larger studies that encompassed 4,010 species. This variation allows for more focused analysis in studies with smaller sample sizes,

while studies with larger sample sizes provide a broader perspective on susceptibility patterns.

The most commonly used method for susceptibility testing in the majority of the studies is broth microdilution. This technique involves exposing the microorganisms to different concentrations of antimicrobial agents in a liquid medium to determine the minimum inhibitory concentration (MIC). Some studies also employed additional methods such as disk diffusion, E-test, or EUCAST (European Committee on Antimicrobial Susceptibility Testing) for specific purposes.

Several studies focus on specific organisms. For example, Gupta et al. (2015) [19] and Li et al., (2018) [17] specifically examined Aspergillus spp., Khodavaisy et al. (2016) [18] studied Aspergillus flavus, and Vahedi et al. (2021) [31] focused on Aspergillus terreus. Other studies targeted Candida species, such as Castanheria et al., (2017), Tan et al. (2016) [22], Xiao et al. (2020) [23], Hou et al. (2017) [24], Borman et al. (2020) [32], and Borman et al. (2019) [33]. Maphanga et al. (2021) [28] examined Candida, while Mohammad et al. (2019) [34] focused on C. albicans and C. auris and Walther et al., (2021) [16] focused on fusarium species (Table 2).

Table 2: Summary of the studies evaluated for discussion

Author	No. of species	Species isolated	Method of suspectibility testing	Reference no.
Walther et al., 2021	257	Fusarium	Broth microdilution technique	15
Borman et al., 2017	4689	Alternaria, Aspergillus, Fusarium, Rhizopus, Rhizomucor, Lomentospora, Acremonium, Lichtheimia, Exophiala, Purpureocillium, Paecilomyces, Mucor	Broth microdilution	16
Li et al., 2018	25	Aspergillus	Broth microdilution	17
Khodavaisy et al., 2016	194	Aspergillus flavus	Broth microdilution	18
Gupta et al., 2015	44	Aspergillus spp.	Disk diffusion (DD) method and E-test	19
Espinel-ingroff et al., 2015	801	*Apophysomyces variabilis, Cunninghamella bertholletiae, Lichtheimia corymbifera, Mucor indicus, M. circinelloides, M. ramosissimus, Rhizopus arrhizus, R. microsporus, Rhizomucor pusillus, and Syncephalastrum racemosum*	Broth microdilution (CLSI)	20
Hou et al., 2016	31	Candida	Broth microdilution (CLSI)	21
Tan et al., 2016	861	Candida	Broth microdilution (CLSI)	22
Xiao et al., 2020	4010	Candida	Broth microdilution	23
Hou et al., 2017	411	Candida	Broth microdilution (CLSI)	24
Gago et al., 2016	28	Cyptococcus sp.	E-test and broth microdilution	25

Castanheria et al., 2017	3,557	Candida	Broth microdilution (CLSI)	26
Espinel-ingroff et al., 2021	16	Candida, Aspergillus spp.	E-test	27
Maphanga et al., 2017	50	E. africanus	E-test	28
Maphanga et al., 2022	394	Candida	E-test and broth microdilution (CLSI)	29
Singh et al., 2021	241	Penicillium/Talaromyces species, Trichophyton species, *A. fumigatus* and cryptic Aspergillus species, Scedosporium species, and *Alternaria alternata*	Broth microdilution (CLSI)	30
Vahedi et al., 2021	100	Aspergillus terreus	Broth microdilution (EUCAST)	31
Borman et al., 2020	35	Candida	Broth microdilution (CLSI)	32
Borman et al. 2019	82	Candida	Broth microdilution (CLSI)	33
Mohammad et al., 2019	85	C. albicans and C. auris	Broth microdilution (CLSI)	34

3.3. Minimum inhibitory concentration

When comparing the results from Table 3, we can observe variations in the MIC ranges and MIC cut-off values for Amphotericin B and Fluconazole among different studies. The MIC range for Amphotericin B varies across studies, ranging from 0.03 to 98.6. Walther et al., (2021), Borman et al., (2017), Mohammad et al., (2019), Hou et al., (2016) and Maphanga et al., (2017) report specific ranges, such as 0.5-16, 2->8, or 4-256, while Borman et al., 2020, Espinel-ingroff et al., (2015) provide a single value, such as 0.5 or a range that includes a wide spectrum of values like 0.06-16. The MIC cut-off values for Amphotericin B also differ between studies, with values like >8/>8, >8 to >256 µg/ml, or >64/>256 [15, 16, 34, 21, 28, 32, 27].

The MIC range for Fluconazole varies across studies, ranging from 0.12 to 7,226. Maphanga et al., (2017), Hou et al., (2017), Tan et al., (2016), Xiao et al., (2020), Vahedi et al., (2021) and Maphanga et al., (2022) report specific ranges, such as 0.12-1.0, 0.5->65, or 4–256, while Castanheria et al., (2017) provide a single value, such as 1 or a range that covers a broad spectrum like 0.008–2. The MIC cut-off values for Fluconazole also differ between studies, with values like <97.5%, <2 mg/L, >2 mg/mL, or 0.002 mg/mL [22, 31, 28, 29, 26] (table 3).

Table 3: MIC Range (resistance) of molds against Fluconazole and Amphotericn B

Author	MIC Range		MIC cut off value	Reference no
	Amphotericin B	Flucanazole		
Walther et al., 2021	0.5-16	-	>8/>8	15
Borman et al., 2017	0.03-16	-	<97.5%	16
Li et al., 2018	01-Apr	-	<2 mg/L	17
Khodavaisy et al., 2016	0.25—8	-	>2 mg/ml	18
Gupta et al., 2015	Jan-16	-	> 1 µg/ml	19
Espinel-ingroff et al., 2015	0.06–16	-	> 1 µg/ml	20
Hou et al., 2016	2 - >8	2 - >256	>8 to >256 µg/ml	21
Tan et al., 2016	-	0.12–1.0	≥ 64 mg/l	22
Xiao et al., 2020	0.5-98.6	0.5->65	>5 mg/ml	23
Hou et al., 2017	1–>256	≤0.12–2	> 0.5 µg/mL	24
Gago et al., 2016	0.06-0.25	>64/>256	>2 mg/ml	25
Castanheria et al., 2017	<0.12-0.25	1	99.8	26
Espinel-ingroff et al., 2021	-	3-7,226	>0.25 µg/mL	27
Maphanga et al., 2017	4-256	0.12-1	<0.008 µg/mL	28
Maphanga et al., 2022	0.008–2	4–256	0.002 mg/mL	29
Singh et al., 2021	0.25–16	-	2 mg/ml	30
Vahedi et al., 2021	1- >8	0.5 - 2	1 mg/L	31
Borman et al., 2020	0.5	-	>10	32
Borman et al. 2019	-	0.5-64	>64	33
Mohammad et al., 2019	0.5-2	0.5->64	1 mg/L	34

4. DISCUSSION

Clinicians are currently encountering various emerging challenges related to antifungal resistance. These challenges include rising rates of resistance to azole and echinocandins among non-Candida albicans species. Additionally, there is a concern regarding azole resistance in Aspergillus fumigatus, which can occur due to exposure to these antifungal agents in clinical or environmental settings. Furthermore, certain pathogenic fungi species exhibit reduced susceptibility or complete resistance to many existing antifungal drugs. To address these challenges, several new antifungal medications are currently being developed. These novel drugs hold the potential to be more effective in overcoming antifungal resistance while also minimizing the adverse effects and drug interactions associated with currently available agents [10, 13].

The findings of this systematic review demonstrate the complex and heterogeneous nature of fluconazole and amphotericin B resistance patterns in molds. The variability in MIC ranges and MIC cut-off values highlights the lack of standardized guidelines for mold susceptibility testing. This lack of uniformity in testing methodologies and interpretive criteria poses challenges in accurately determining the resistance status of molds. Furthermore, variations in clinical breakpoints and epidemiological cutoff values contribute to the observed differences in resistance patterns across studies [15-34].

Amphotericin B, an important antifungal agent, displays a wide range of MIC values across the studies. The MIC range spans from 0.03 to 98.6, indicating variations in the susceptibility of molds to this drug. Similarly, the MIC cut-off values for Amphotericin B vary, with values such as >8/>8, >8 to >256 µg/ml, or >64/>256 being reported [15-21]. These differences in MIC cut-off values suggest that the definition of resistance to Amphotericin B may vary depending on the study, making it challenging to establish a universally accepted cut-off value for this antifungal agent [23-26, 28-32,34].

Fluconazole, another commonly used antifungal drug, also demonstrates considerable variations in MIC ranges across the studies. The MIC range for Fluconazole varies from 0.12 to 7,226, indicating substantial differences in susceptibility profiles among the mold species. Similarly, the MIC cut-off values for Fluconazole differ, with values such as <97.5%, <2 mg/L, or >2 mg/mL reported. These variations in MIC cut-off values reflect the challenges in defining resistance to Fluconazole consistently among molds [22, 31, 28, 29, 26, 28, 33,34].

The identified mold species showed differential susceptibility to fluconazole and amphotericin B, emphasizing the need for tailored treatment strategies based on the specific mold species isolated. Geographical differences in resistance patterns suggest the influence of local epidemiology and the prevalence of specific resistant strains. Understanding these regional variations is crucial for guiding empirical antifungal therapy and formulating appropriate treatment guidelines [22, 25].

The differences in laboratory protocols and susceptibility testing methods used in the studies further contribute to the variations in reported resistance patterns. The studies employed various techniques, such as broth microdilution [15-17,20-26, 29-34], disk diffusion [19], or E-test [19, 27,28, 29], to determine susceptibility. These methodological variances can impact the MIC values obtained and subsequently affect the determination of resistance or susceptibility.

Furthermore, the discrepancies in MIC cut-off values can be attributed to variations in clinical breakpoints, epidemiological cutoff values, or expert consensus guidelines utilized by different authors. These cut-off values serve as reference points to classify strains as susceptible, intermediate, or resistant. The differences in cut-off values across studies may arise from different interpretations of these breakpoints or the absence of standardized guidelines for mold susceptibility testing.

It is important to consider the limitations of this discussion, including the lack of detailed information on specific mold species, patient populations, and clinical contexts in each study. Nonetheless, the data provided in Table 3 offer valuable insights into the antifungal resistance patterns of molds.

5. CONCLUSION

This systematic review highlights the variability and complexity of fluconazole and amphotericin B resistance patterns in molds. The observed differences in MIC ranges and MIC cut-off values emphasize the need for standardized susceptibility testing methodologies and interpretive criteria. Collaborative efforts among researchers, clinicians, and regulatory authorities are essential to establish uniform guidelines for mold susceptibility testing and to enhance our understanding of the mechanisms driving antifungal resistance. This knowledge will facilitate improved clinical management and the development of effective antifungal strategies to combat mold infections.

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