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Original article

Epidemiologic characteristics and drug susceptibility profile associated with fungal diseases In Nasarawa State, Nigeria

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ABSTRACT

Background: Fungal infections have become a pressing issue in global health due to their persistence and the emergence of resistant strains. The study determined the epidemiology and drug susceptibility profile associated with fungal diseases in Nasarawa State, Nigeria. **Methods**: Samples of hair, nails, skin, and vaginal and cervical specimens were collected from patients, fungi isolated and identified and the antibiotic susceptibility pattern determined. **Results**: Fungal infections were highest among urban dwellers (61.8%) and students (69.5%) respectively. *Aspergillus* species among isolated genera *Candida*, *Epidermophyton*, *Trichophyton* and *Mucor* had the highest prevalence (50.8%). Hair samples had the highest number of fungi with 97 species, while sputum samples had the highest incidence of *Aspergillus* species 72(97.3%). Ketoconazole was the most effective antifungal with 70(52.6%) *Aspergillus* species, 32(62.7%) *Candida* species, and 10 (45.5%) *Trichophyton* species susceptible to the antibiotic, while itraconazole was the most resisted with 86(64.7%) *Aspergillus*, 16(72.7%) *Trichophyton* and 14(70.0%) *Mucor* species resisting the antibiotic. **Conclusion**: Fungal infections were prevalent among children and young adults in the study area with skin surface having higher fungal carriage compared with any other body parts. *Aspergillus* genera followed by *Candida* species are the two most implicated fungal species.

Introduction

Fungi are responsible for a substantial number of morbidity and death among humans globally, but unlike diseases caused by other pathogens, especially viruses and bacteria, adequate funding for research into fungal diagnostics, therapeutics and vaccines is not readily available [1]. Fungi are ubiquitous, and their spores when inhaled increase the infection rate among people with low immunity. The epidemiology of fungal disease has changed over the years due to challenges in diagnosis. Fungi such as Candida species, *Aspergillus* species, *Cryptococcus* species, *Pneumocystis jiravecii*, *Histoplasma capsulatum*, *Talaromyce marneffei* are among the leading cause of fungal diseases in humans [2]. Fungal infections and diseases pose a major public health challenge globally. It is promoted by poverty, poor diagnoses and climatic conditions that favour fungal proliferation in resource-limited settings, especially in the tropics [3].

According to Xu [4], over 1.5 billion individuals around the world endure superficial mycoses that target the skin and nails. In addition,

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women in their reproductive years are affected at a rate of 50-75% by vulvovaginal mycoses, with roughly 75 million women experiencing recurrent incidents annually. Mortality rates due to invasive mycoses are comparable to those of tuberculosis or malaria [5]. *Cryptococcus*, *Candida*, *Aspergillus*, or *Pneumocystis* cause more than 90% of lethal mycoses [6]. The incidence of immune-compromising diseases and the excessive use of broad-spectrum antibiotics are on the rise. As a result, infections caused by fungi, particularly resistant strains, are a cause for concern. This growing number of clinical issues necessitates improved surveillance and therapies [7].

The emergence of antifungal resistance poses a significant threat to global public health [3]. Attributable morbidity and mortality due to opportunistic fungal infections in Nigeria are on the increase [8, 9], and the absence of an effective vaccine, few classes of antifungal drugs to choose from, and antifungal drug resistance renders patients vulnerable. Despite the negative fall-out of antimicrobial resistance such as increased cost of treatment, longer stay at the hospital and in some cases mortality, it is projected that over 20 million people will become poorer and 10 million deaths recorded in the next 30 years [10]. Because antimicrobial resistance shows geographic variability, the absence of local data negatively impacts prescriptive and diagnostic efficiency and accuracy. Based on this background, this study was initiated to determine the fungal disease distribution and antifungal susceptibility pattern of pathogenic fungi in Nasarawa state, Nigeria.

Materials and methods

Study area

The research was undertaken at the two highest-level hospitals located in Nasarawa State - Dalhatu Araf Specialist Hospital (DASH) Lafia and Federal Medical Center, Keffi (FMC). Nasarawa State is situated in the north-central region of Nigeria and has an approximate population of 2.5 million individuals.

Study population

A cross-sectional analytical study was conducted on patients presenting with symptoms of fungal infections in the outpatient clinics of DASH and FMC who were recruited into the study. Four hundred and forty-six participants were sampled adopting the formula of Kish [11] a 95% confidence limit.

Ethical clearance and consideration

The Nasarawa State Ministry of Health in Lafia provided clearance for the ethical aspects of the research, as approved by the Research Ethics Committee (NAS/DASH/DCS/ADM/123/XXIX/1590). All patients who came to the hospital and were diagnosed with fungal infection by physicians and consented were included. Those who did not give their consent were excluded from the study.

Collection of sample and relevant information

All patients diagnosed with fungal or fungal-related infections at the various points of care in the hospital were recruited consecutively until the sample size was obtained. Research assistants administered the questionnaire to the patient immediately after obtaining signed consent. All samples were taken by trained health personnel and by established protocol. Samples of hair, skin, and nails were collected and properly kept. Vaginal and cervical specimens and sputum samples were collected using a sterile swab stick. Skin scraping of the affected part of the body was carefully taken using surgical blades.

Processing of collected samples

Direct microscopy was utilized to examine skin scrapings, nails, and hairs. To identify the fungal structures, a 10% potassium hydroxide (KOH) solution was employed with the 40X objective, allowing for visualization. Nails were grounded using laboratory mortar and pistol before the samples were cultured. All high vagina swabs and sputum samples taken were inoculated into Potato Dextrose Agar (PDA) and Sabouraud's Glucose Agar (Merck, Germany) supplemented with chloramphenicol (Sigma-Aldrich, USA), gentamicin (Sigma-Aldrich, USA) (SDA) and incubated at 30°C. *Candida* species were identified within 24 h on (CHROMagar Company, France) and germ tube test CLSI [12]. Other species of fungi were incubated between 3 - 5 days, depending on the growth of the fungi. Identification was done microscopically and by morphological comparison with the atlas.

Antifungal susceptibility test

Antibiotic drugs were employed to determine the susceptibility profile of the isolated fungi. Disks incorporated with fluconazole (25 µg; OxoidTM, India), itraconazole (1 µg; OxoidTM, India), nystatin (India), ketoconazole, and griseofulvin (Sigma-Aldrich) were used to evaluate the sensitivity of the fungi according to the disk diffusion test of yeasts outlined in the Clinical Laboratory Standards Institute (CLSI) M60 reference document. For dermatophytes, fresh colonies were picked from fresh culture into 5 mL sterile saline and vortexed for 15 min. An 11 µm diameter sterile filter paper filters the suspension to remove hyphae. With a sterile swab, the suspension was struck on PDA, and then the different antifungal disks were introduced on the plate after 5 min and incubated at 72oC for 24 -72 h. The zone of inhibition was measured according to the CLSI [12] protocol.

Results

Table 1 showed that patients from ages 1 – 40 totaling 207 (79.0%) had a higher incidence of fungal infections in the study compared to ages 41 years and above 55 (21.0%) reported cases. More participants from urban locations (162 (61.8%)) were infected as compared to 29 people (11.1%) from rural areas while the study lasted. Students with a population of 182 (69.5%) were most prone class to fungal infections among the occupation type sampled in the study.

Five genera belonging to the *Aspergillus, Candida, Epidermophyton, Trichophyton* and *Mucor* were isolated from the participating patients (Figure 1). *Aspergillus* has the highest species isolated (50.8%), while *Mucor* had the least with a 7.6% prevalence. Some isolated species were unsuccessfully identified (4.6%). Three species of *Aspergillus* were isolated with *Aspergillus niger* (*A. niger)* 74 (28.4%) being the most prevalent **(Table 2).** *Candida albicans* had a frequency of 43 (16.4%) as the second most isolated fungi in the study area. Other fungi isolated were *Trichophyton rubrum* and *T. interdigitale* with a 1 (0.6%) frequency each.

Samples collected from the skin surface had the highest number of fungal species (97) isolated **(Table 3),** while the least was from nail samples of the participants. Of the 262 isolates obtained in the study, *Aspergillus* species from sputum samples were the most isolated fungal species in the study while no other species were obtained from sputum. *Candida* species were the commonest species from vaginal and cervical (HVS) specimens collected.

Antibiotic susceptibility test in **table (4)** showed that ketoconazole was the most effective drug tested as 70 (52.6%) *Aspergillus* species, 32 (62.7%) *Candida* species, and 10 (45.5%) *Trichophyton* species were susceptible to the antibiotic drug. Nystatin gave the highest antifungal activity among the antibiotics with 10 (50.0%) susceptibility against *Mucor* species, while griseofulvin inhibited *Epidermophyton* species where it gave the best activity among the antibiotics. Itraconazole was the most resisted antibiotic as it was more resisted by *Aspergillus* species 86(64.7%), *Trichophyton* species 16(72.7%) and *Mucor* species 14(70.0%).

Aspergillus flavus, A. fumigatus and *A. niger* as shown in **table (5)** had high percentages of resistance against fluconazole, itraconazole and nystatin. Ketoconazole had the best activity against *A. flavus* (13(61.9%)) and *A. fumigatus* (23(60.5%)), while *A. flavus* were also more susceptible to griseofulvin 14(66.7%). A high number of the *Aspergillus* species were resistant to the tested antibiotics.

Table 1. Prevalence of the Socio-demographic characteristics of the participants.

Variable	**Population (N=262)**	
	N	%
Age (Years)		
1-20	97	37.0
21-40	110	42.0
41-60	49	18.7
61 and above	6	2.3
Sex		
Male	115	43.9
Female	147	56.1
Settlement		
Rural	29	11.1
Semi-urban	71	27.1
Urban	162	61.8
Occupation		
Civil Servant	53	20.2
Student	182	69.5
Self-employed	14	5.3
Unemployed	6	2.3
Others	2	0.8
Education		
No education	10	3.8
Primary	53	20.2
Secondary	46	17.6
First degree	80	30.5
Others	73	27.9

Table 2. Species of pathogenic fungi among patients in Nasarawa State.

Fungal species	**Frequency**	**%**
Aspergillus flavus	21	8.0
A. fumigatus	38	14.5
A. niger	74	28.4
Candida albican	43	16.4
C. glabrata	8	3.1
Epidermophyton floccosum	22	8.4
E. stockdaleae	2	1.2
Trichophyton flugenium	12	7.4
T. verrucosum	8	3.1
T. rubrum	1	0.6
T. interdigitale	1	0.6
Mucor	20	7.6
‘Unidentified fungi	12	4.6

Table 3. Fungal isolates and population in the sample sources.

Genera	Hair	HVS	Nail	Skin	Sputum	Total
	N (%)					
Aspergillus	3(14.3)	1 (2.0)	2(10.5)	55(56.7)	72(97.3)	133(50.8)
Candida	1(4.8)	49 (96.0)	0(0.0)	1(1.0)	0(0.0)	51(19.5)
Trichophyton	9(42.9)	0(0.0)	3(15.8)	10(10.3)	0(0.0)	22(8.4)
Epidermophyton	3(14.3)	0(0.0)	7(36.8)	14(14.4)	0(0.0)	24(9.2)
Mucor	5(23.8)	0(0.0)	1(5.3)	12(12.4)	2(2.7)	20(7.6)
Others	0(0.0)	1 (2.0)	6(31.6)	5(5.2)	0(0.0)	12(4.6)
Total	21(100)	51 (100)	19(100)	97(100)	74(100)	262(100)

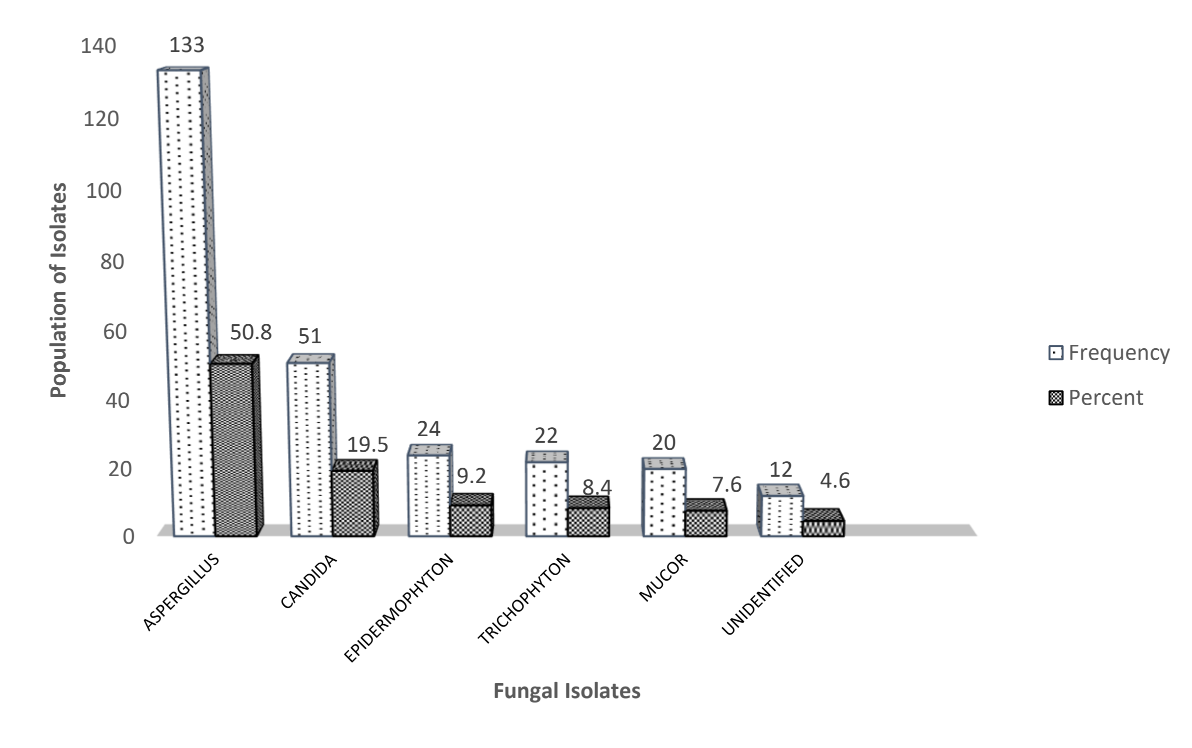
Table 4: Antibiotic Susceptibility of isolates to common antifungal drugs in the study area, Nasarawa State.

Isolated fungi			Fluconazole	Itraconazole	Nystatin	Ketoconazole	Griseofulvin
Aspergillus	(N=133) n (%)	**S**	54(40.6)	47(35.3)	51(38.3)	70(52.6	59(44.4)
		R	79(59.4)	86(64.7)	82(61.7)	63(47.4)	74(55.6)
Candida	(N=51) n (%)	**S**	16(31.4)	22(43.1)	19(37.3)	32(62.7)	22(43.1)
		R	35(68.6)	29(56.9)	32(62.7)	19(37.3)	29(56.9)
Trichophyton	(N=22) n (%)	**S**	9(40.9)	6(27.3)	7(31.8)	10(45.5)	7(31.8)
		R	13(59.1)	16(72.7)	15(68.2)	12(54.5)	15(68.2)
Epidermophyton	(N=24) n (%)	**S**	8(33.3)	10(41.7)	7(29.2)	9(37.5)	15(62.5)
		R	16(66.7)	14(58.3)	17(70.8)	15(62.5)	9(37.5)
Mucor	(N=20) n (%)	**S**	7(35.0)	6(30.0)	10(50.0)	8(40.0)	7(35.0)
		R	13(65.0)	14(70.0)	10(50.0)	12(60.0)	13(65.0)
Unidentified fungi	(N=12) n (%)	**S**	1(8.3)	3(25.0)	5(41.7)	7(58.3)	6(50.0)
		R	11(91.7)	9(75.1)	7(58.3)	5(41.7)	6(50.0)

Table 5. Antibiotic Susceptibility of isolated *Aspergillus* species to common antifungal drugs in Nasarawa State

Antibiotics	***Aspergillus flavus***		***Aspergillus fumigatus***		***Aspergillus niger***	
	(N=21) n (%)		(N=38) n (%)		(N=69) n (%)	
	S	**R**	**S**	**R**	**S**	**R**
Fluconazole	10(47.6)	11(52.4)	16(42.1)	22(57.9)	26(37.7)	43(62.3)
Itraconazole	8(38.1)	13(61.9)	10(26.3)	28(73.7)	27(39.1)	42(60.9)
Nystatin	7(33.3)	14(66.7)	14(36.8)	24(63.2)	30(43.5)	39(56.5)
Ketoconazole	13(61.9)	8(38.1)	23(60.5)	15(39.5)	31(44.9)	38(55.1)
Griseofulvin	14(66.7)	7(33.3)	13(34.2)	25(65.8)	29(42.0)	40(58.0)

Figure 1. Population of fungal isolates among the participants in Nasarawa State



Discussion

Estimating the disease burden of fungal infection is a challenge due to the poor attention it receives [13], therefore, it is difficult to galvanise policy and programmatic action comprising diagnosis, research and development priorities against it. The World Health Organization 2022 developed the Fungal Priority Pathology List (FPPL), which is aimed at responding to the rising threat of fungal infections combined with existing and emerging resistance [14]. The age group 21-40 years had the highest infection cases, similar to the report by **Aluyi et al.** [15]. The author reported that the highest proportion of patients presenting with pulmonary mycoses was among the age group 21-30. The age is associated with high sexual activity which predispose subjects to such disease as HIV/AIDS. Similarly, a high number of participants in the 21-40 age group were pregnant women attending the antenatal clinics. Pregnant women are reportedly associated with reduced immunity making them candidates for infection.

The result obtained in this study was different from that of **Joseph et al.** [16] in Akwa-Ibom state, South-South Nigeria, where the highest age group infected were less than 20 years old [16]. More fungal infections were recorded among female participants than males in the study population. The study observed that females attend hospitals more than men. The high concentration of oestrogen hormone and glycogen content in the vaginal mucosa provides an ample supply of sugar that promotes fungal growth during pregnancy [17]. The prevalence between males and females contrasts with findings in Ile-Ife, South-West Nigeria, which showed male preponderance [18]. The distribution of fungal disease varies due to many factors, such as age, sex, immune competency, occupation and socioeconomic status [19]. Males recorded a higher proportion of cases which agrees with the study by **Oke et al.** [18] in Ile-Ife South-West Nigeria.

The study discovered that fungal infections were more common among urban dwellers compared to rural and semi-urban dwellers. This might be because rural-urban migration is increasing in the country, with its attendant effect on overcrowding and transmission of infectious diseases [20]. Overcrowding has been reported in schools and in many other public spaces due to lack of or limited infrastructure. In India, the high prevalence in an urban setting was attributed to the inclusion of the outpatient departments of a large teaching hospital in the study [21], while in Kenya, a high frequency of hair barbing in public shops was implicated as the leading cause of high urban centres' prevalence of fungal infections [22].

Similarly, a higher prevalence of fungal infections in urban centres was reported in Rivers State [23] and Ebonyi State [24]. In contrast, studies in Osun by **Ayorinde et al.** [25] showed a low prevalence of fungal infections in urban communities. Students in the study recorded the highest prevalence of fungal infections in this study. This is in agreement with the study by **Oke et al.** [18]. Among the various occupational groups, a higher proportion of farmers were infected with fungal infections of the skin. This agrees with what was reported **by Jaishi et al.** [26] who adduced that the nature of work and repeated contact with soil and other farming tools are responsible for the results obtained.

The genus *Aspergillus* was the most prevalent pathogenic fungi isolated, followed by *Candida*. This is in agreement with a WHO [14] report that showed that Nigeria has the second largest burden of Chronic Pulmonary Aspergillosis in the world, second to only India, as reported by **Bongomin et al.** [13]. *Aspergillus* is gaining attention worldwide because it is implicated in most respiratory fungal diseases, and it has been classified under the first group priority list of WHO [14]. Sputum samples in this study yielded over 90% of *Aspergillus* species, which agrees with the work of **Yao et al.** [27], **Chowdhary et al.** [28] and WHO [14]. *Candida* species, particularly *C. albicans,* was the most predominant species causing vulvovaginal candidiasis in Nigeria [29]. In this study, *Epidermophyton floccosum* is mostly implicated in Skin and nail infections. This is in agreement with a study by **Kanna et al.** [19] which showed that *Epidermophyton* was the major cause of skin diseases in their study population.

Only a limited number of antifungal drugs are currently in medical practice [30]. The current antifungals in circulations are showing different patterns of resistance. Fungal resistance to commonly available antifungals is a global concern [31]. In this study, *Aspergillus* and *Candida* resisted all tested antifungals except ketoconazole. However, a study in Plateau and Niger States reported 100% susceptibility of *Candida albicans* and *Candida tropicalis* to nystatin and fluconazole [32], which is discordance with the findings of this current study. Fluconazole is one of the most prescribed and used antifungal drugs in our settings. The drug has become common, giving room for misuse and abuse by people. This misuse may be responsible for drug resistance experience in this current study.

Trichophytons had a sensitivity of less than 50% to all the commonly available antifungals. *Epidermophyton* had a susceptibility of 63% to griseofulvin and less than 50% to all other tested antifungals. Most school-age pupils come with an episode of dermatophyte infection due to the fungus, and the treatment option most times is to prescribe antifungal without doing antifungal susceptibility testing primarily because most fungal testing is not available at primary and even secondary health facilities. This diagnosis challenge has greatly impacted the effective management of fungal infection and antifungal stewardship. *Mucor* had a sensitivity of 50% to nystatin and less than 50% to all other tested antifungals. A study by **Ekundayo et al.** [33] in Ilorin reported that all four dermatophytes studied were resistant to griseofulvin, which agrees with the current study.

This implies that the resistance of commonly used antifungals is not limited to a particular region; therefore, antifungal agents should be used by relying on antifungal drug susceptibility testing. All other isolates were resistant to itraconazole and ketoconazole. Most resistance may be due to mutation, mainly at the Cyp51AP or CyP51A [34]. The resistance of Itraconazole is more prominent in Trichophyton, which agrees with **Monod et al.** [35]. The high prevalence of resistance may be due to the patient's attitude toward using antifungal drugs, which includes poor dosing, self-medication, and lack of conducting tests to know the right drugs to use.

Conclusion

The study concludes that the most predominant fungi causing diseases in the study group are *Aspergillus* species on skin and sputum, Epidermophyton on the nails, Candida species on vaginal and cervical secretions and Trichophyton on hair samples. The diseases are recorded in both gender and age groups. There is a high level of antifungal resistance to the most used fungal drugs in the study area. The study recommends improved diagnostic tests for fungal infections and improved methods of fungal antibiogram together with increased awareness of the need to stop self-medication.

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Conflicting interest

None declared.

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