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Characterization and Antimicrobial Susceptibility of Candida Species Causing Urinary Tract Infection in Patients Attending Lagos State University Teaching Hospital, Nigeria

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Abstract

Urinary Tract Infection (UTI) is one of the most common microbial infections affecting all the age groups worldwide. Earlier studies have shown that apart from bacteria, many species of yeast in the genus Candida also cause urinary tract infection. However, modern diagnosis of Candida species and antifungal susceptibility testing in the laboratory have been undermined with no routine service available for antifungal susceptibility. This study was designed to characterize and determine the antimicrobial susceptibility pattern of Candida species causing infection of the urinary tract among patients attending Lagos State University Teaching Hospital, Ikeja Nigeria. A total of 250 participants whose provisional diagnosis was urinary tract infection were recruited for this study. Early morning midstream urine specimens were collected in sterile wide mouth universal containers. The samples were cultured aerobically on Sabouraud dextrose agar (SAB), Cystine-Lactose-Electrolyte Deficient (CLED) agar and Blood agar at 370C for 24 to 48 hours. The isolates were characterized to species level by employing microscopic, biochemical test, chromogenic media (Chrom agar Candida) and Analytical Profile Index (API) 32C examination analysis. The use of API and Chrom agar Candida as a routine diagnostic material for Candida species should be adopted. In addition, the Candida species were most susceptible to ketoconazole and Fluconazole. All the isolates were resistance to griseofulvin.

Keywords: Candida • Sabouraud dextrose agar • Analytical Profile Index • Antifungal agent • Lagos

Introduction

Urinary Tract Infections (UTIs) are consequences of microbial invasion and multiplication of pathogens in the urinary system with attendant signs of inflammation. The pathogens include fungi such as Candida spps, bacteria etc. Infection can take place at any part of the genitourinary tract such as urethra, bladder, ureter, renal pelvis, or renal parenchyma [1]. The urinary tract collects and stores urine thereby giving the urinary system tubes necessary to discharge it from the body. UTI can be asymptomatic or symptomatic with major symptoms such as strong urge to urinate frequently, even immediately after the bladder is emptied, painful burning sensation during urinating (Dysuria), discomfort, pressure, or bloating in the lower abdomen, pain in the pelvic area or back, cloudy or bloody urine (Haematuria) which gives strong odour, urination during the night (Nocturia) and frequent urination (Polyuria) among others.

Most Candida infections are opportunistic, occurring in debilitated persons and also in persons with prolonged broad-spectrum antibiotics therapy. Unfortunately the extensive use of these antimicrobial agents has invariably resulted in the development of antibiotic resistance, which has now become a major problem worldwide [2]. It was noted that even when the digestive flora remained balanced in otherwise healthy persons who lack beneficial bacteria in their gut (due to bad life style or bad feeding habits, probably on antibiotic, chemotherapy or on other strong chemicals); C. albicans was seen to over-proliferate and cause ill health. Different clinical forms of Candidiasis are known involving primarily the mucosal surfaces (thrush), GIT or urogenital tract, and deep-seated infections such as Candidaemia or Meningitis. These highly challenging risk factors cannot be over emphasized in establishing the pathogenicity of fungal (C. albicans) infection in the GIT in our teaming population and environment. These factors moreover have a worldwide recognition and view.

Opportunistic mycosis is a fungal or fungus-like disease which occurs in an animal or persons with a compromised immune system as opportunistic infections. Opportunistic organisms are normal

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resident flora that becomes pathogenic only when the host's immune defenses are altered, as in immunosuppressive therapy, in a chronic disease, such as diabetes mellitus, or during steroid or antibacterial therapy that upsets the balance of bacterial flora in the body. Fungi that may become opportunistic pathogens include species of Candida, Mucor, Aspergillus and Cryptococcus. When specimens from infected patients are cultured, Candida spp are considered as pathogens when isolated either in pure or mixed culture and counts ≤ 103, 104 and ≥ 105 cfu/ml are considered to be significant. Successful treatment of opportunistic mycoses depends on identification of the specific organism causing the infection without effective therapy a systemic infection of this type can be fatals.

Nevertheless UTIs occur in both men and women, studies suggest that the overall prevalence of UTI is higher in women due to their anatomy. Some factors that may contribute to urinary tract infections are structure of the female urinary tract, sexual intercourse, irregular urination, birth control methods, inadequate personal hygiene and history of previous UTIs, insufficient water intake, catheters or tubes placed in the bladder. Despite having up to 90 % of the patients with UTIs complain of urinary tract symptoms, one third or more of the patients with these symptoms do not have bacteriuria. The most common symptoms for which most patients seek treatment are dysuria and frequency. Dysuria and frequency together suggest the probability of UTI greater than 90%, effectively pointing in the diagnosis by history alone. The etiology of UTI is related to the great diversity of microbial invaders, such as opportunistic mycoses of fungi (Candida species), bacteria and viruses.

Successful treatment of opportunistic mycoses depends on identification of the specific organism causing the infection without effective therapy a systemic infection of this type can be fatal. Fungal studies are limited worldwide; however in Nigeria and Africa studies have shown that intestinal parasitosis in human immunodeficiency virus (HIV) infected adults with chronic diarrhoea as reported in Jos, Nigeria; which recorded 9.9% of Candida species out of the population studied. Immunocompromised (under aged, aged, HIV etc.) patients seem to be the most affected. Clinical reports have demonstrated that fungi are incriminated as causes of cutaneous, systemic, subcutaneous and opportunistic mycosis. The possibility of the UTI being infected may not be far-fetched in cases of immune depression, use of sedatives, contraceptives, chemotherapy, and prolonged usage of antibiotics or other forms of drugs. It is very important to determine the degree of pathogenicity of urinary tract fungal infection in the Nigeria environment. Therefore this study aimed to evaluate the causative organisms present in urine specimen with a view to characterize and determine the antimicrobial susceptibility pattern of Candida species causing infection of the urinary tract among patients attending Lagos State University Teaching Hospital, Ikeja, southwest Nigeria.

Materials and Methods

Lagos State is located in the South western part of Nigeria; Land Area - 3,474 km2. The Port of Lagos is Nigeria's leading port and one of the largest and busiest in Africa. It is a socio-cultural melting pot, attracting both Nigerians (from all over the country) and foreigners alike for all manner of businesses. The state has a population of over 21 million with a growth rate of 3.2%. Metropolitan Lagos, an area covering 37% of the land area of Lagos State is home to over 85% of the State population. Lagos State University Teaching Hospital (LASUTH) Ikeja, Lagos State is located in the northern part of metropolitan Lagos and draws its patients from all over the state and neighboring states.

A total of 250 consenting apparently healthy participants age ranged 1-60 years whose provisional diagnosis was urinary tract infection and the controls were recruited at random from both out-patient and in-patients clinics in Lagos State University Teaching Hospital (LASUTH) Ikeja for this study. The study was carried out from January to June, 2018. Subsequently, informed consent of the participants was duly obtained in writing where they are adults and informed assent of guardians in the case of minor.

Study procedure

Study data was collected on an individual participant level and as such, an additional front page was added to the consent form that included patient identifiable information (e.g. full name, gender, date of birth, hospital number and study ID number). This front page was only used at the time of data collection, to be able to trace back the appropriate participant and allow for data collection on an individual participant level. The study ID number only is entered into the database which serves as the only link to the identifiable information and was kept with the principal investigator.

Result

Urine samples were collected from150 participants, 82 (55%) of them were males and 68 (45%) were females. Age group (31-40 years) had the highest population of 29 (19%) and the least came from the age group 11-20 years with only 20 (13%) participants. Sixteen (10.7%) of the 150 participants' stool culture yielded Pathogenic Bacteria Isolates (PBI) in both female and male participants, whereas 50 (33.3%) yielded fungal growth, identified to be Candida species. Seventy six (56%) of the urine specimens yielded growth of normal flora; the stool cultures comprised mainly of mixed bacteria colonies and scanty colonies of fungi. The microscopic examination of these urine specimens had very scanty or no yeast cells. Out of the 50 participants whose urine samples where positive for Candida spp, 25 of them yielded pure isolates of C. albicans and the remaining 25 occurred as mixed candida isolates. Fifteen out of the 25 pure C. albicans isolates were found among the female participants and the remaining 10 were from male participants. Eighty-two (82) participants were males but only ten (10) were positive for fungal isolate (C. albicans) and 11 for pathogenic bacteria. Fifteen (15) female participants were positive for fungal isolate (C. albicans) and five (5) pathogenic bacteria were recorded among 68 female participants. A total of 84 (35 females and 49 males) participants had normal flora of the GIT in their stool cultures (Table 1).

Female						Male				
Age (years)	No. tested	C. albicans	Candida spp	PBI	GIT (NF)	No. tested	C. albicans	Candida spp	PBI	GIT (NF)
44470	7	2	2	-	3	17	1	3	6	7

4413 6	11	2	4	1	4	9	1	2	-	6
21-3 0	13	2	1	-	10	12	2	2	1	7
31-4 0	7	1	2	1	3	22	3	1	-	18
41-5 0	19	4	2	1	12	9	1	2	1	5
51-6 0	11	4	2	2	3	13	2	2	3	6
TOT AL	68	15	13	5	35	82	10	12	11	49

Table 1. Gender distribution of isolates among participants.

Twenty six of the participants were clinically diagnosed to have PUD, Six of their urine cultures yielded candida isolates, 2 in pure cultures and 4 in mixed cultures. No pathogenic bacterium was isolated in this group but 20 participants had isolates of normal urine flora. From the 40 participants with diarrhea, there were 4 cases with fungi isolates; one in pure culture and 3 in mixed culture. Samples from six participants in the group yielded pathogenic bacteria isolates, while samples from 30 participants yielded urine normal flora. Among participants with gastrointestinal bleeding, there were 12 cases of fungal isolates, 4 of these were pure isolates while 8 were mixed isolates. Samples from 2 and 6 participants in this group yielded pathogenic bacteria isolates and gastrointestinal normal flora respectively. Participants with immune suppression were 42. Samples from 14 of them yielded fungal isolates; 6 as pure isolates and 18 as mixed isolates. Culture of 8 participants' samples yielded pathogenic bacterial isolates, while the isolates from 20 participants were bacteria of the normal urinary flora. There were 21 HIV participants in the study. Thirteen of them had fungal isolates; 11 in pure culture and 2 in mixed culture. Samples from 8 participants yielded normal flora of the urinary tract. The sole participant on chemotherapy in this study had only fungal isolate in pure culture. Fifty of the 150 participants across all groups tested had fungal isolates in their cultures. Twenty five were in pure culture and another 25 in mixed culture. The microscopic examination of urine specimens yielding pure isolates revealed predominantly yeast cells with hyphae. While for those yielding mixed fungi isolates the microscopic examination revealed predominantly yeast cells only (Figure 1).

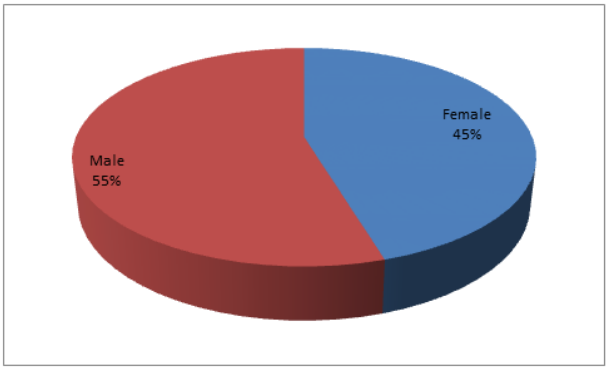

Figure 1. Sex distribution of participants.

Out of the 150 participants tested, 50 were positive for fungi culture but only 25 participants stool culture yielded pure *Candida* albicans isolates. The age group 51-60 years with 24 (11 females and 13 males) participants had pathogenic C. albicans infection in 25% of the participants in the group as the highest. The age group 1-2 years with 24 participants comprising 7 females and17 males, had the least rate (12.5%) of pure C. albicans infection. Among the age groups 11-20 years and 21-30 years, the C. albicans infection isolation rates were 15% and 16% respectively. For the age ranges 31-40 years and 41-50 years, the isolation rates were 13.8% and 17.9% respectively. The age group (31-40) years recorded the highest number of participants (twenty-nine) in this study with 4 participants being infected and a frequency of 3% of the total population (Figure 2).

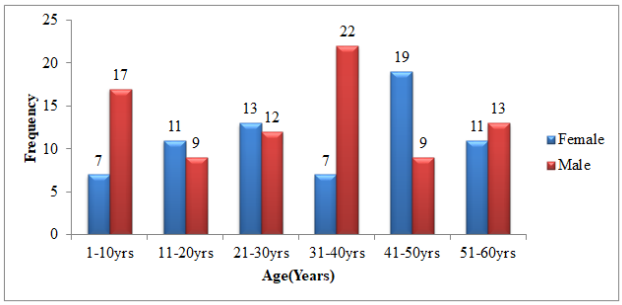

Figure 2. Age and sex distribution.

While the combination of C. albicans, C. tropicalis and C. parepsilosis was isolated in two participants: 1 with diarrhoeal disease and 1 with urinary tract bleeding. Three other combinations of 3 candida species were each obtained from one participant in the group with immune suppression. The same combination of four candida species was isolated from two participants with urinary tract bleeding. While a different combination of four mixed candida isolates was obtained from a participant with immune suppression. There was no mixed candida isolates obtained from the urine cultures of participants on chemotherapy. Candida albicans was part of the mixed isolates from 20 (80%) of the 25 participants. Candida tropicalis, C. dubliniensis and C. parapsilosis were present in the mixed isolates from 16 (64%), 13 (52%) and 5 (20%) of the participants. Candida lusitaniae, C. kruzei, C. membranaefaciens, C. galbrata, were also identified as parts of the mixed isolates in 4 (16%), 3 (12%), 2 (8%) and 2 (8%) respectively among the participants. Candida Kefyr was identified in only 1 (2%) of the 25 participants. The total number of control participants recruited for this study was eighty, thirty-six (45%) of them were females and forty-four (55%) were male participants. Their age distribution is described. All the urine samples collected from the participants in the control group yielded growth of normal flora (bacteria and fungi) of the urinary tract. Their stool microscopy revealed very scanty or no yeast cells (Table 2).

Age	Female	Male	Total no. age group (%)	Total positive cases	Total negative cases	Cumulative percentage
1-10 years	4	9	13 (16.3)	Nil	13	16.3
11-20 years	7	6	13 (16.3)	Nil	13	32.5
21-30 years	7	6	13 (16.3)	Nil	13	48.8

31-40 years	3	10	13 (16.3)	Nil	13	65
41-50 years	10	4	14 (17.5)	Nil	14	82.5
51-60 years	5	9	14 (17.5)	Nil	14	100
Total	36	44	80 (100)	Nil	80	

Table 2. Frequency table for control participants.

Discussion

Opportunistic fungal infections are increasing around the world with limited information on their prevalence in urinary tract infections (UGIT). The incidence of invasive opportunistic mycoses has increased because of the expanding population of immunosuppressed patients, including Solid-Organ Transplant (SOT) and Hematopoietic Stem Cell Transplant (HSCT) recipients, patients with cancer, patients with AIDS, premature neonates, elderly patients and patients recovering from major surgery [3]. A previous finding in Germany reported that *Candida albicans* was isolated from the stool specimens of about one-third of the study participants (34). That finding was highly associated with smoking habits of the participants as 45 (58%) of 78 smokers, but only 68 (28%) of the non-smokers participants' stool cultures yielded Candida species. The smoking habit may thus be responsible for the related prevalence of 32% and 24% of mixed and pure isolates recorded respectively amongst participants who may fall within the age group of those with such habit.

Fungal urinary tract infection has a relatively global distribution but few studies have been carried out in Africa, one in Cameroon and most probably none has been reported in scientific publications in Nigeria. Most studies in Nigeria only gave a significant parasitic representation in HIV/AIDS patients [4]. The study highlighted the need for investigating intestinal pathogens in HIV-infected patients

presenting with diarrhea, especially when their CD4+ counts are low since 56 (27.9%) patients harbored pathogens. The most frequent pathogens were Candida spp. (14.9%). The pathogenicity of fungal infection in this study was established in 17% of the studied population and C. albicans was confirmed to be the pathogenic fungus causing infection (gastroenteritis) in them. A sub group of participants with HIV infection in this study had a prevalence of 85% in pure culture and 15% in mixed culture respectively. The high prevalence in this sub group could be as a result of the limited number of participants with HIV in this study. Moreover, the immune system in HIV cases are suppressed hence the chances of C. albicans attaining pathogenic state were high.

In other disease conditions, the prevalence rates of C. albicans were significant, ranging from 25% in diarrhoea disease to 100% in the only participant with cancer and on chemotherapy included in this study. Co-existing infections is common when immunity is reduced and as a result, the prevalence obtained in the sub groups (HIV and Immune Supression) in this study were 85% and 43% respectively which were obtained for pure Candida albicans isolates. This was in line with the study obtained in Saudi Arabia with the overall prevalence of intestinal fungal infections of 58.7% in transplant recipients. The most prevalent fungus in that study was Candida spp., which was seen in 22% of the study patients and 24.4% of the control group. Co-existing infection with two or more fungi was seen in 14.8% and 3.4% in the case and control groups. Interestingly, there was no significant difference (p-value=0.05) in the prevalence of infection by a single organism between the two groups. However, co-existing infection with two or more species was more prevalent in transplant recipients. There was a significant difference in the prevalence between the case and control groups in this study and this was seen in all the disease conditions especially in cases of GIT bleeding and immune suppression. Stool samples from all the participants used as control, yielded growth of urinary tract flora in this study. This may be as a result of other host factors like irritable bowel syndrome etc. that must be present for Candida to exist as a pathogen.

High prevalence was also established in all the age groups studied. The age group 51- 60 years had the highest prevalence of 25% while those between the age group 1-10 years had the least prevalence of 13%. The probable reason for this is that those in the age group 1-10 years are less exposed than those in the age group 51-60 years. In a study at Isfahan, the prevalence of urinary parasites and fungi in hemodialysis patients were 23.9 and 36.1%, respectively. The highest rate of urinary tract parasites and fungi were reported in the age groups of 51-65 years (29.7 %) which is in line with the findings of this study with 25%, though only fungi infection was considered. The relationship of incidence of fungal infections and gender was significant (p=0.028) but not that of age (35). In this study as well, age did not have any significance but a prevalence of 22%was obtained in females as against 12% in males, this difference may be attributed to vaginal yeast infections and its overgrowth in the UTI which therefore calls for further investigation. Genrally, the prevalence in this study increased as the age increased except for those in the age group 31-40 years. The increase in prevalence may probably be attributed to the rate of exposure. The normal flora in the age group 1-10years is not the same as in the case of the higher age groups. Even in the case of depressed immune system, the chances that C. albicans will become pathogenic in the lower age group especially 1-10 years is less than in the higher age groups.

Contrary to the increase in prevalence in *Candida albicans* among the age groups,other Candida spp. isolated, did not show any order of prevalence in this study. The pair of C. albicans and C. dubliniensis was isolated in seven stool samples from participants with cases of Peptic Ulcer Disease (one), urinary tract bleeding (four) and Immune Suppression (two) in this study. This may be attributed to the closely related genetic materials shared by these species which may have helped to increase their level of invasiveness in strain related virulence factors, though further study may be required to establish this fact. Other stool samples also yielded pairs (five) but in combination of various species [5]. Ten stool samples occurred as mixed cultures of three different species and only three of the participant's stool reported a combination of four different species. In generally, fungal infection resulting in nephritis was found more in this study than bacteria nephritis which indicates a shift from the normal cases. The reason for this shift may be attributed to Candida overgrowth which was reported in previous findings and is in concordance with the results found in this study.

Conclusion

Of the total urine specimens examined macroscopically and microscopically, a preponderance of 17% that showed predominantly yeast cell and fungi hyphae and their culture results yielded pure isolates of *Candida albicans* and had a significant implication in gastrointestinal fungi infection which was statistically significant (p=0.012). Other Candida species in mixed culture were also found with a preponderance of 17% and their urine microscopic examination revealed only yeast cells. Therefore, it is plausible that the functions employed by C. albicans to spread from the human gut into systemic infections rely on the same regulatory circuit that evolved to enable growth in the host as a commensal organism. Consistent with this report, some disease conditions or impairment in the host immune system (Peptic ulcer disease, urinary tract bleeding, diarrhoea disease, immune suppression, HIV and Chemotherapy etc.) are typically required for C. albicans to fully cause an opportunistic infection.

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