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Candida species associated with urinary tract infections

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Abstract

Around the world, candidemia is becoming more common. In the past thirty years, a number of factors, including the AIDS epidemic, an increase in the number of patients receiving immune-suppressive therapy for transplantation, and an increase in the use of antibiotics in hospital settings and even in the community, have changed the epidemiology of invasive fungal infections in general and candidemia in particular. Usage of broad-spectrum antibiotics, cancer treatment, Candida species colonization of mucosal surfaces and broad-spectrum use antifungal. Five species of the Candida genus are in charge of causing Urinary Tract Infections (UTIs): *Candida albicans, C. glabrata, C. parapsilosis, C. tropicalis, and C. krusei*. The key to managing candidemia episodes is early diagnosis and appropriate therapy.

Keywords: Candida species; Urinary Tract Infections; Candiduria; Candidemia

1. Introduction

The yeasts in the genus Candida, in particular, are possible harmful organisms. A majority typical fungus separated from patients who are humans is yeast. Candida isolates are pathogenic opportunistic fungus that can infect the mucous membranes of humans. (Odds, 1994). The infectious process may start if a host has a Candida species (commensal) living in their mouth, vagina, or digestive tract. (Diaz-Guerra et al., 1997).

With the development of corticosteroids with an immunosuppressive effect, broad spectrum antibiotics, and anticancer medicines additionally a rise in AIDS patients during the numerous decades since, their occurrence has significantly increased. (Pfaller and Diekema, 2004). The National Nosocomial Infection Surveillance System shows that In the intensive care unit, *C. albicans* is the secondary cause of nosocomial urinary tract infections. (Viale, 2009). Due to the high death rate and morbidity of Candida infections, it is crucial to look into the origin of the Candida isolates that cause nosocomial infections. (Fridkin and Jarvis, 1996; Qaddoori, et al., 2022).

The prevalence of nosocomial urinary tract infections (UTIs) brought on by Candida strains is rising. (NCCLS, 2002), According to reports, Candida may be the cause of up to 30% of nosocomial urinary tract infections (NUTIs). (Bryan and Reynolds, 1984). Candidaturia, on the other hand, is the presence of Candida species in urine. It is a finding that hospitalized patients are making more frequently. The discovery of candiduria may be a benign procedure connected to catheter use or antibiotic treatment. The fact that Candida species in urine can either be small (due to contamination or asymptomatic colonization) or they might be a sign of extremely dangerous disseminated disease makes candiduria one of the most difficult candidial infections to treat. There are other clinical possibilities between the two that can call for a particular treatment. (Kauffman et al., 2000). Candida growth in urine has been linked to a number of risk factors, including the use of urinary devices, diabetes mellitus, the use of antibiotics, immunosuppressive medication, prolonged hospitalization, extreme ages, and female gender. (Sobel, 2002). However, this clinical specimen has frequently

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contained species other than *C. albicans*, include: (*C. tropicalis* and *C. glabrata*). The most frequent yeast found in urine cultures is still *C. albicans*. (Nucci, 2000).

In addition, several pathologic diseases, including superficial lower urinary tract infections, invasive renal parenchymal disease, fungal balls and obstructed ureters, and urinary tract infections. Candidaturia is most prevalent in intensive care units (ICUs) in hospitals. Candida colonization is linked to urinary catheterization, however it is very challenging to differentiate between infection due to colonization (Candiuria without symptoms) of the urinary tract. For illustration, the majority of critically sick patients who are catheterized in ICUs do not feel any particular symptoms, such as urgency, frequency or dysuria. Additionally, catheterized patients do not benefit from the diagnostic value of quantifiable counts of fungi in the urine or the presence of hyphae as a fungal morphology. As a result, there are currently no valid criteria for differentiating between colonization and infection, or, when infection is evident, between infection restricted to the lower urinary tract and infection associated with systemic involvement. (Kauffman et al., 2000).

Numerous factors affect how Candida species develop their pathogenicity. The synthesis of proteolytic enzymes, in particular aspartyl proteinase, which aids tissue penetration and invasion, and the ability to bind to host tissue are some of these variables. The reversible change from filamentous to unicellular yeast forms is another component of pathogenicity. Most Candida species are present in humans and other warm-blooded animals as commensals. However, when these yeasts produce hyphal outgrowths, they can occasionally turn pathogenic. (Sullivan et al., 2005).

Looking for analogous traits in other less harmful or non-pathogenic yeasts, including Saccharomyces cerevisiae, may help determine the the importance of these several potentially pathogenic *C. albicans* virulence factors. (Monod and Zepelin, 2002). Although it appears that a variety of virulence traits play a role in the infectious process, no one factor fully explains Candida virulence, and not all expressed virulence traits may be required at every stage of infection (Odds, 1994).

Numerous phenotype screening tests have been used to differentiate between those organisms, but no single phenotype test has emerged as particularly potent, necessitating the use of genotypic assays for certain identification. There is a want for clinical laboratories to possess phenotypic testing that are as trustworthy as the carbohydrate assimilation profiles due to the fact that molecular approaches are comparatively time-consuming and expensive. (Alves et al., 2001).

Understanding the infections' causative agents and their patterns of susceptibility is essential for choosing the right antifungal treatment. It is frequently important to test particular yeast pathogens against the proper antifungal agents because the susceptibility of yeasts to antifungal medicines cannot always be predicted. In vitro tests for antifungal susceptibility guarantee that the drug chosen will be effective against the infecting organism and hence have a positive therapeutic effect on the patient being treated (Rex and Pfaller, 2002).

The state of the art for assessing yeasts' susceptibility to antibiotics is similar to that of bacteria in many aspects. Antifungal susceptibility testing is now easily accessible to many clinical microbiology laboratories thanks to the introduction uniform susceptibility testing protocols, quality assurance strains, user-friendly substitutes for the standard procedure. (Pfaller et al., 1997). Therefore, the need for expanded use of in vitro antifungal susceptibility testing due to the discovery of new antifungal medications, an increase in infections caused by yeasts other than *Candida albicans*, and reports of antifungal treatment resistance. (Nyilasi et al., 2010).

2. Literature Review

2.1. Yeasts

In the kingdom of fungus, yeasts are eukaryotic microorganisms that now have 1,500 recognized species. A few species reproduce binary fissionally, but the majority reproduce asexually through budding. Although most molds have pseudohyphae, or fake hyphae, which are a string of connected budding cells, some species with yeast forms can develop into multicellular organisms (Kurtzman and Fell, 2006). Although most yeasts are 3–4 mm in diameter, some can grow to be over 40 mm in diameter, depending on the species. (Walker et al., 2002).

2.2. Taxonomic classification of yeasts

Yeasts are eukaryotic microscopic creatures that belong to the kingdom Fungi. There is no distinct taxonomic or phylogenetic classification for yeasts. Only 1% of all yeast species are thought to have been described as of yet (Kurtzman and Piskur, 2006).

2.3. Nutrition and growth requirements of yeasts

Because they utilise organic substances as a source of energy, yeasts are chemoorganotrophs. Hexose carbohydrates like fructose and glucose or disaccharides like sucrose and maltose are the primary sources of carbon. Pentose sugars like ribose can be metabolized by some animals (Barnett, 1975). As obligate aerobes, all yeast species depend on oxygen for cellular respiration. However, certain yeasts are facultatively anaerobic and can get energy through fermentation, such as when glucose is converted to ethanol. Between 10 to 37 degrees Celsius, somewhat acidic conditions are excellent for yeast growth, with 30 to 37 degrees Celsius being the ideal range (Kavanagh, 2005).

2.4. Pathogenic yeasts and Spectrum of their infections

Yeast infections are a broad term for a variety of infections that affect people. These infections are divided into two categories: systemic and superficial. The human body's various organs, including the skin, mouth, digestive system, nails, vagina, and oesophagus, are all susceptible to acute superficial yeast infections (Thevissen, 2005).

The Candida species are the most prevalent yeasts to infect people. Over half of all cases of candidal infections worldwide are caused by *C. albicans*, which continues to be the most common species of the candida genus. Other parts of the world have documented a rise in the prevalence of yeast infections brought on by Candida spp. not *C. albicans*, such as: (*C. glabrata*, *C. krusei*, *C. tropicalis*, and *C. parapsilosis*) (Pfaller and Diekema, 2007).

Candidasis refers to the infection brought on by a species of Candida. Non-invasive candidiasis and invasive candidiasis are the two main kinds of Candida infections. (Fauci et al., 2008).

2.5. Predisposing and virulence factors of Candida infections

Many people carry Candida species unknowingly, especially on the epithelial surfaces of the mouth, gastro-intestinal tract (GIT), vagina, and skin. The majority of them can create pseudohyphae, which are filamentous cells, whereas *C. albicans* and *C. dubliniensis* can form true mycelium and chlamydospores, which are refractile spore-like structures. They normally grow as ovoid blastospores. In healthy people, these species are harmless, but when the host's immune system is weakened in any way, these organisms have the ability to proliferate and create serious issues. Immunosuppression (caused, for example, by HIV infection, anticancer therapy, and treatment with immunosuppressive drugs used in organ transplantation), catheterization (which permits direct inoculation of the yeast cells into tissue and blood vessels), premature birth (immature immune system), extreme old age (defective immune system), use of broad-spectrum antibiotics (disturbance of the normal bacterial microflora), use of corticosteroids, and catheterization are risk factors for (direct inoculation of yeast cells into the blood stream) (Sullivan et al., 2005) .

Pathogenicity is the term for a microorganism's capacity to afflict disease upon a host. It is obvious that some bacteria are more likely to cause disease than others, and this is typically because they have certain characteristics that are related to their capacity to harm host tissue. These characteristics are sometimes referred to as pathogenicity factors collectively (Sullivan et al., 2005).

The development of successful colonization or infection mechanisms by all harmful microorganisms (Finlay and Falkow, 1989). In order to enable them penetrate human defenses, inhabit host tissues, and produce illness, the majority of infections, counting species of Candida a potent arsenal potential pathogenicity elements and unique methods. Depending on the type of infection, different Candida species, especially *C. albicans*, may express or require different virulence factors (systemic or mucosal) (Odds, 1994). The most extensively researched aspects of *C. albicans* pathogenicity in recent years have been hyphal development, surface recognition molecules, phenotypic switching, and hydrolytic enzyme synthesis (Calderone and Fonzi , 2001; Zainurin et al., 2022).

It is quite simple to pinpoint virulence factors in the case of some bacterial spp. (such as the toxins generated by *Vibrio cholerae* and *Clostridium botulinum*); yet, it is quite challenging to pinpoint which traits about Candida spp pathogenesis; participate in. Given that *C. albicans* continues to be the greatest significant yeast pathogen, more research has been done on its virulence mechanisms than that of any other species of Candida. These studies have shown several characteristics that *C. albicans* expresses that may be putative virulence factors (Sullivan et al., 2005).

For pathogenicity, the capacity to transition between yeast, hyphal, and pseudohyphal morphologies is frequently required. Pseudohyphae and hyphae are both invasive. It is hypothesized that this characteristic would facilitate tissue penetration in the initial phases of infection, whereas the yeast form might be better suited for bloodstream dispersion. The filamentous forms may be crucial for colonizing some organs, such the kidney (Gow et al., 2002) .

Any germ, whether they are harmful or commensal, must possess the capability to cling to host tissue, which is one of the most crucial criteria. The microbial cell must be able to identify and adhere extracellular matrix proteins and cell membrane elements are examples of hosts for ligands, in order to accomplish this. In doing so, the organisms are able to take root on the host's surface and are shielded from host secretions like perspiration or saliva. *C. albicans* has so far had a number of these proteins discovered in it (Sullivan et al., 2005).

Instead of existing as planktonic cells in their natural environment, many microorganisms are found to form biofilms (a sessile community that is derived from microbes that is characterized by cells that are permanently attached to a substrate, interface, or to one another, embedded in a matrix of extracellular polymeric materials that they have produced, and displaying a different growth phenotype and altered gene transcription) instead. It has been established that bacteria in biofilms differ from those in planktonic forms in ways such as greater opposition to antibiotics therapy and the capacity of biofilm cells to withstand host immune defenses. Given that biofilms are involved in 65% of all human microbial illnesses, microorganisms play a significant role in public healthcare (Donlan and Costerton, 2002; Ramage et al., 2006). Because the implanted medical device provides the surface necessary for bacteria to adhere and form a biofilm, biofilms can develop particularly on implanted medical devices. Therefore, because these biofilms are less susceptible to antimicrobial medicines, they significantly harm medical devices. Therefore, the best course of treatment is frequently to remove the contaminated medical gadget. Additionally, cells could separate from the biofilm and be discharged into the bloodstream, creating a long-lasting infection source. Additionally, the creation of biofilms may result in the failure of the medical equipment, which would be detrimental to the patients' health. For all of the aforementioned reasons, bacteria' production of biofilm has a big impact on public health. (Donlan, 2001a; Ramage et al., 2005). Numerous investigations shown that the development of biofilms is related to the majority of diseases caused by Candida species. (Ramage et al., 2005).

The adhesion, tissue injury, and invasion of host immune responses are caused by the secreted aspartic proteinases (Saps). Tissue invasion and its proteolytic activities have been linked (Hube and Naglik, 2005), the invasion of the host mucosal epithelia is thought to be aided by the release of extracellular phospholipases, which is a crucial characteristic. All cell membranes primarily consist of phospholipids, which are hydrolyzed by the phospholipases (Monod and Zepelin,2002).Another potential virulence component that may contribute to the pathophysiology of candida is hemolysin. In particular, hyphal invasion in disseminated candidiasis is facilitated by hemolysin secretion followed by iron acquisition (Malcok etal.,2009).

2.6. Candida spp. as the yeast responsible for urinary tract infections

It is unclear what candiduria's natural history is. Consideration should be given to urinary tract colonization because it occurs often in hospitalized patients and affects 6.5-20% of them (Abi-Said et al., 1997). Patients admitted to hospitals and long-term facilities are more frequently experiencing candiduria, which is a significant problem, especially in those with altered immunological mechanisms, such as those with diabetes mellitus or tumors, those who have permanent urinary catheters, and those who are routinely taking wide-ranging antibiotics or steroids (Kauffman et al., 2000).

Because women have a shorter urethra and frequently have vulvovestibular colonization with Candida (10%–65%), ascending infection—by far the most prevalent route for urinary tract infection—occurs more frequently in women than in males. When an infection rises from the bladder, it can also spread to the upper urinary system. This is especially true if there is vesicourethral reflux or obstruction of the urine flow. It can also cause acute pyelonephritis and, very rarely, follow-up candidemia. (Lundstrom and Sobel, 2001).

The most frequent way that kidney infection manifests itself is by hematogenous dissemination (i.e., renal candidiasis). One study found that 90% of individuals with disseminated candidiasis who passed away showed renal involvement at autopsy. Additionally, urinary tract candidiasis may present with a variety of clinical symptoms, including (Lundstrom and Sobel, 2001)

- Patients with indwelling catheters who are hospitalized frequently experience asymptomatic candiduria. Typically, these patients don't exhibit any of the UTI-related symptoms or indications.
- The a list of bladder discomfort symptoms, such as hematuria, suprapubic hematuria, frequency, and dysuria discomfort, may accompany symptomatic lower UTIs. Given the prevalence of candiduria in catheterized patients, the fact that symptomatic Candida cystitis is highly uncommon suggests that the bladder is rather resistant to invasion by Candida species.
- Upper UTI: Patients with upper urinary tract infections exhibit fever, leukocytosis, and soreness at the costovertebral angle.

- Renal candidiasis: Patients may have a high temperature, hemodynamic instability, and varying renal failure due to hematogenous seeding of the kidneys by candidemia.

2.7. Identification of yeasts

Because of this, it is now more crucial than ever to identify the infecting organism down to the species level. First off, not only has the distribution of Candida spp. changed recently, but different Candida spp. have different susceptibilities to antifungal medications. Therefore, understanding the species that is infected is highly predictive of likely medication susceptibility and can serve as a therapeutic guide (Pappas et al., 2004). Second, species-specific identification is important for epidemiological reasons. For instance, repeatedly identifying a specific species in a hospital ward or other location may point to a point source outbreak, especially if the species is unusual or occurs at a higher rate than it has in the past (i.e., *C. lusitaniae*, *C. lipolytica*) (Denning et al., 2003). Third, the severity of clinical signs and the danger of developing profound organ involvement vary depending on the species that is infected (Denning et al., 2003).

Frequency, dysuria, suprapubic hematuria, and hematuria are commercially available in a variety of formats, are the most practical and well-liked techniques for identifying Candida species. These systems, which include the API 20C AUX, API Candida, Auxacolor, and Uni-Yeast-Tek kits, among others, are readily and simply inoculated with yeasts. These tests produce accurate findings for the more prevalent By raising turbidity, Candida species and yeast genera can be eliminated. (API 20C AUX) or producing color (Auxacolor, API Candida, and Uni-Yeast-Tek) (Verweij et al., 1999).

It was common practice to identify *C. albicans* isolates by the development of germ tubes and chlamydospores, which were thought to be typical of this species. However, it was discovered that certain isolates found using these traits varied from the known *C. albicans* strains genetically and in their carbohydrate absorption patterns. As a result, *C. dubliniensis* , a new species, was described. By Sullivan et al. (1995). According to two yeast culture collections' confirmation investigations, 1% to 2% of *C. dubliniensis* isolates were mistakenly classified as *C. albicans*. (Odds et al., 1998). Several phenotype-based tests are available to distinguish between these species due to the desire of clinical diagnostic laboratories for accurate, dependable, affordable, rapid identification approaches that can be applied to large quantities of samples. The most popular phenotypic assays involve analyzing colony form and color using differential media. (Ells et al., 2009).

C. dubliniensis was initially noted by Sullivan et al. in 1995. Despite being found in different human groups and at many body places, *C. dubliniensis* is most frequently found in patients with the Human Immunodeficiency Virus in their oral cavities (HIV). This novel yeast is widespread and shares characteristics with *C. albicans*, such as appearance and metabolism. It is classified as an opportunistic yeast pathogen but is also acknowledged as a minor component of the normal human oral microbial flora (Sullivan et al., 1997; Alves et al., 2001). *C. albicans* produces a single chlamydospore at the terminal of an extended suspensor cell, in contrast to *C. dubliniensis* , which typically generates pairs, triplets, or clusters of chlamydospores on the extremities of short-branched hyphae. But when attempting to distinguish between distinct species utilizing chlamydospore formation, caution should be exercised (Ellepola et al., 2003).

Due to the ambiguous clinical indications and the naturally commensal condition of these opportunistic infections, it is challenging to make an accurate and prompt diagnosis of invasive candidiasis. Non-culture approaches, such as the identification of different Candida cell wall and cytoplasmic antigens in blood and other sterile bodily fluids, have been developed to get around these problems. The Candigen enzyme-linked immunosorbent test (ELISA) antibody-capture kit is one such commercial kit that analyzes *C. albicans* specific antigen in serum (Elsayed et al., 2001). Therefore, the identification of infectious agent antigens in samples from hosts and the identification of the host's antibody response to these antigens are the two techniques used in serological diagnosis of human illnesses (Cloud et al., 2007).

Additionally, it has been proven that fungal DNA may be detected from clinical materials with great sensitivity and specificity. Technical issues include the possibility It may still be necessary to find a solution to the problem of contamination and the inability to distinguish between colonized cases and infected ones. For the addition of a molecular diagnostic technique to routine clinical laboratories, as well as the standardization and improved efficiency of DNA extraction and DNA detection procedures simpler (Fujita et al., 2006). Because of this, the majority of nucleic acid-based systems begin the identification procedure by amplifying fungal DNA using PCR techniques. Selecting the right DNA targets and PCR primers is necessary before PCR amplification can take place (Guiver et al., 2001; Salman et al., 2022). It is possible to generate a employing a single set of PCR primers and conditions that are optimal for that set of primers, PCR products from all Candida species can be produced., which is the fundamental benefit of employing amplification targets from DNA sections that are conserved across all Candida species (Coignard et al., 2004).

2.8. Antifungal drug development and therapy

The creation of antifungals is challenging due to the many parallels between fungal and mammalian cells. They both have eukaryotic organelles, DNA replication, and protein synthesis in common. Although there are a few metabolic distinctions between the host and the fungus, antifungal medicines must take advantage of these differences. The biggest distinction at the molecular level is that human cells lack cell walls while fungal cells do. Aside from mitotic spindles, intermediate metabolism, and DNA biosynthesis inhibitors are other antifungal targets. The fact that the sterol composition of mammalian and fungal cell membranes differs is the distinction that has received the most attention. Unlike fungus cells, which contain ergosterol, mammalian cells possess cholesterol (Caudle, 2010).

The number of antifungal medications now used in the treatment of invasive mycoses, like as echinocandins, azoles, and polyenes, is rather low. The polyene antibiotic (AMB) is still the benchmark for treating severe fungi, but its clinical application is constrained by its persistent and severe toxicity, including reduction in renal function. Due they are fungistatic and inhibitory effects on the crucial Lanosterol demethylase, a cytochrome P450 enzyme, which is involved in the manufacture of ergosterol, azoles are the most often used medications for treating Candida infections. For treating severe systemic mycoses, fluconazole and itraconazole are the two medications of choice (Liang et al., 2009).

3. Conclusion

According to a study of the literature, females are more likely than males to experience candiduria , indwelling urinary catheters, diabetes mellitus, and extended antibiotic usage are the main causes of candiduria. Although non-albicans species are now becoming more common, *C. albicans* is still the principal infective species.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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