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Research Article

THE FRUGAL INVESTIGATION OF FUNGAL CANDIDIASIS

Raghavendra Rao M.V[1], Dilip Mathai[1], Vijay Kumar C[3] ,SP.Pallavi[1], Khizer Hussain Junaidy[2], Yahiya Hussain Junaidy[4], Badam Aruna Kumari[5], Mohammed Ismail Nizami[7] and Jithender Kumar Naik S[6]

[1]Department of Medicine, Apollo Institute of Medical Sciences and Research Institute, Jubilee Hills, Hyderabad, Telangana, India
[2]Department of Pharmacology, Gandhi Medical College, Secunderabad. Telangana, India
[3]Department of Pulmonology, Apollo Hospitals, Jubilee Hills, Hyderabad, Telangana, India
[4]Department of Medicine, Medvarsity, Park View Enclave, Jubilee Hills, Hyderabad, Telangana
[5]Department of Respiratory Medicine, Apollo Institute of Medical sciences and Research, Hyderabad, TS, India
[6]Department of Zoology, University College of Science, Osmania University, Hyderabad, TS, India
[7]Department of Emergency Medicine NIMS, Punjagutta, Hyderabad, TS, India

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A B S T R A C T

Candida is the most common fungal pathogen of worldwide. It is the fourth leading cause of nosocomial infection. Significant mortality and morbidity in low birth weight infants. It affects 75% of women. It is classified as STD by CDC. *Candida albicans* is normally present on the skin and mucous membranes such as skin, vagina, mouth, rectum and digestive tract. The fungus also can travel through the bloodstream in immunocompromised individuals. *Candida* can enter newborn infants during or shortly after birth.

Candida is an opportunistic pathogen. Antibiotics kill the good bacteria allowing *Candida* to grow freely. *Candida* is known to impair immune function by directly and negatively impacting the helper depressor ratio of T-lymphocytes.

The common cause of *Candida albicans* fungus is the overuse of antibiotics or oral contraceptives, steroid hormone medication, high sugar, and starch diet. Candidiasis in localized and disseminated forms. Localized disease is seen as erythema and white plaques in moist skin folds (diaper rash) or on mucosal surfaces (oral thrush).It may also cause the itching and thick white discharge of vulvovaginitis. Deep tissue disseminated disease is limited almost exclusively to the immunocompromised.

Diffuse pneumonia and urinary tract involvement are especially common.

INTRODUCTION

Several researchers have reported that early initiation of appropriate antifungal therapy is a key determinant of survival among patients with candidemia (1,2)

It invades the bloodstream and disseminates to internal organs. Poor outcomes, in part from the poor sensitivity of blood cultures, which is the current diagnostic gold standard. Blood cultures are negative in more than 50% of proven and probable cases of disseminated candidiasis and median time to positivity in 2-3 days after sample collection (3,4)

Candida species are among the most common causes of nosocomial blood stream infections. (5, 6)

Corresponding author:* **Raghavendra Rao M.V
Department of Medicine, Apollo Institute of Medical Sciences and Research Institute, Jubilee Hills, Hyderabad, Telangana, India

Infections caused by *Candida* species represent the main cause of opportunistic fungal infections worldwide, leading to significant morbidity and mortality, and *Candida albicans* remains the most common etiological agent of candidiasis (7)

In the subgroup of patients in whom co morbid conditions prevent surgery, a lifelong azole "maintenance "therapy is often preferred and has been associated, in some reports and a meta analysis with patients survival (8,9)

Endocarditic episodes are located in the right side of the heart, only 3% occur in patients without intracardiac devices or a history of intravenous drug use. Additionally, its clinical presentation, treatment, and outcome differ from the corresponding aspects of left-sided endocarditic condition.(10)

Vulvovaginal candidiasis is one of the most common infections of the female genital tract.

Most (80%–85%) cases are caused by *Candida albicans* (11)

Where as the non-*albicans* species of Candida account for a mere 5%–20% of the cases. Most of these infections with non-albicans species of *Candida* are due to *Candida glabrata* (5%–10% of cases) or *Candida tropicalis* (<5% of cases) (12)

Mortality rates for candidemia are approximately 40% despite anti fungal therapy (13)

Liposomal amphoterecin B has emerged as the most widely used agent of the licensed lipid formulations and AmB for the treatment of invasive fungal infections (14, 15)

Prosthetic valve endocarditic caused by Candida species is a rare but devastating disease (16,17)

Infectious disease society of America and Europian society of clinical microbiology and infectious disease guidelines Candida should be treated by anti fungals associated with early surgery.If surgery is not possible azole therapy should be administered to prevent recurrences (18, 19)

Treatment is the same as that for women; topical creams and oral capsules containing an azoles' are usually recommended for uncomplicated, acute thrush (20)

HISTORY

Descriptions of what sounds like oral thrush go back to the time of Hippocrates circa 460–370 BCE (21)

Vulvo vaginal candidiasis was first described in 1849 by Wilkinson. (22)

With the advent of antibiotics following World War II, the rates of candidiasis increased. The rates then decreased in the 1950s following the development of nystatin (23)

The colloquial term "thrush" refers to the resemblance of the white flecks.(24)

The current classification of Candida authorized for use by the International Botanical Congress (IBC) (25)

The genus *Candida* includes about 150 different species; however, only a few are known to cause human infections. *C. albicans* is the most significant pathogenic species. Other species pathogenic in humans include *C. auris, C. tropicalis, C. glabrata, C. krusei, C. parapsilosis, C. dubliniensis, and C. lusitaniae.*

The name Candida was proposed by Berkhout.The specific epithet *C.albicans* also come from Latin, albicare meaning "to whiten". These names refer to the generally white appearance of *Candida* species when cultured.(26)

Candida comes from the Latin term "candidus" which has the meaning of "glowing white" and also refers to as smooth and glistering (27)

Phenotypic, chemotaxonomic and phylogenetic analyses established *C. auris* as a new strain of the genus *Candida* (28)

The first case of disease-causing *C. auris* were reported from South Korea in 2011 (29)

The Indian researchers wrote in 2013 that C. auris was much more prevalent than published reports indicate since most diagnostic laboratories do not use sequence-based methods for strain identification (30)

The fungus spread to other continents and eventually, a multi-drug-resistant strain was discovered in Southeast Asian countries in early 2016 (31)

In April 2017, CDC director Anne Schuchat named it a "catastrophic threat" (32)

As of May 2017 the CDC had reported 77 cases in the United States. Of these, 69 were from samples collected in New York and New Jersey (33)

As of April 2019, the CDC has documented cases of C. auris from the following countries: Australia, Austria, Belgium, Canada, China, Colombia, France, Germany, India, Iran, Israel, Japan, Kenya, Kuwait, Malaysia, the Netherlands, Norway, Oman, Pakistan, Panama, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Switzerland, Taiwan, Thailand, the United Arab Emirates, the United Kingdom, the United States, and Venezuela (34)

Candida albican is readily phagocytosed and killed when opsonized by antibody and complement.In the absence of a specific antibody, the process is less efficient, but naturally, occurring IgG is able to activate the classical complement pathway and facilitate the alternate pathway.

As with other fungi, cytokine activation of macrophages enhances their ability to kill Candida albicans.A favorable outcome appears to require the proper balance between TH1 and TH2 mediated cytokine responses.

The cytokines associated with TH1 interleukin-2 (IL-2),IL-12, interferon-gamma, Tumor necrosis factor-alpha are correlated with enhanced resistance against infection in which TH-2 responses (IL-4),(IL-6), and (IL-10) are associated with chronic disease.(35)

Literature gap and future research

Is defined as a topic or area for which missing or insufficient information limits the ability to reach a conclusion for a question. Candidiasis most commonly caused by yeast *C.albicans.* Common in oropharynx and genetalia. Occur in oesophagus and tracheobranchial tree in immunocompromised people. Cutaneous Candidiasis occur in antibiotic therapy, very young and very old significant immunocompromised. In this Candida can erode mucosa with resultant Candidimia. Chronic mucocutaneous candidiasis characterized by persistant or recurrent candida infections of oro pharynx, skin and nail apparatus. Genital candidiasis occur non keratinized genital mucosa eg-vulva, vagina. Usually represents over grouth of endogenous colonizing Candida rashes than from exogenous source (Sexual partner)(36)

Where the researches go next?

Candida species are the most common causes of infection. Approximately 90% of the infections are caused by *C.albicans, C.glabrata, C.tropicalis, C.parapsilosis. Candida albicans* remains the most commonly isolated but is decreasing relative to the other species. The increasing incidence of *C.glabrata* is related to its reduced susceptibility to azoles drugs. Genome analysis suggests that virulence is associated with expansion of gene families particularly of cell wall genes. Similar independent process took place in *C.glabrata* species groups.(37)

New approaches in the Discovery of Novel Candidacies

Superficial candidiasis is caused by *Candida* species mainly *Candida albicans* Manifestations include oropharyngeal and vaginal candidiasis, chronic paronychia. Superficial candidiasis often follows antibiotic therapy.

Intertrigo is characterized by inflammation in skin folds with surrounding "satellite lesions". Chronic paronychia is

associated with frequent wetting of hands. Superficial candidacies is treated mainly with typical azoles, oral azole being reserved to refractory or recurrent diseases, several oropharyngeal and oesophageal candidacies is a consequence of CD4 -T lymphocytes depletion/dysfunction, as in HIV infection.

Recurrent vaginal or penial candidacies may be a manifestation of diabetes mellitus. Rare manifestation in the autoimmune regulator gene (AIRE) or signal transducer and activator of transcription 1(STAT1), cause a syndrome of chronic mucocutaneous candidacies.

This is characterized by infection of skin, mucosa, and nails, with hyperkeratosis nails and erythematous periungual skin, patients have cell-mediated immune defects against Candida and may have polyendocrinopathy and autoimmune features.(38)

Strictly from a clinical point of view to combat candidacies, the current options are limited to three classes of antifungal agents: polyenes, azoles, and echinocandins (39)

Candida albicans used to represent the predominant pathogen among the *Candida* species; however, today this species accounts for only half the isolates detected. A shift towards an increasing prevalence of *Candida glabrata* and *Candidaparapsilosis* species has been recently documented, especially among critically ill patients, probably due to an increase in oncology–haematological patients previously exposed to antifungal therapy. In addition, inappropriate antifungal use has contributed to the global increase in antifungal resistance to both triazole and echinocandin antifungal drugs, and merits continued vigilance.

Future genomics in Candida

Improvements in genome sequencing have been parallel by improvements in genome annotation particularly for *C.albicans* and other species. Use of RNA sequence and high resolution tiling arrays has led to the correction of many open reading frames (ORFs) and the identification of hundreds of novel transcriptionally active regions that may represent structural or regulatory RNAs.(40)

Strand specific RNA sequencing has revealed that the 5^1 end of transcripts that are differentially expressed between white and opaque cells are particularly long (41)

In *Candida parapsiolosis* several hundred new genes were identified and approximately 900 gene models were corrected.(42)

The developments of over expression library and constitutively activated transcription factors are also exciting (43)

Biotechnology for Molecular Diagnosis of Candidacies

Early diagnosis of fungal infection is critical to effective treatment. There are many impediments to diagnosis such as diminishing number of clinical mycologists, cost, time to result and requirements for sensitivity and specificity. In addition, fungal diagnostics must meet the contrasting needs presented by the increasing diversity of fungi found in association with the use of immunosuppressive agents in countries with high levels of medical care and need for diagnostics in resource-limited countries, where large numbers of opportunistic infections occur in patients with AIDs. Traditional approaches to diagnosis include direct microscopic examination of clinical samples, histopathology, culture and serology. Emerging technologies include molecular diagnostics antigen detection in clinical samples, innovative new technologies that use molecular and Immuno assay platforms have the potential to meet the needs of both resource-rich and resource limited clinical environments.(44)

Positive cultures from normally sterile sites support the diagnosis, but cultures must be interpreted with caution to rule out contamination with endogenous flora. The detection of *candida* in patients with bladder catheters in place most likely represents colonization. In patients without foreign bodies in the urinary tract, however, significant candiduria may be a marker of obstruction, DM or other serious conditions.

Isolation of Candida albicans from sputum and other respiratory specimens is common but rarely associated with pulmonary infection. In CNS infection, isolation of *Candida* from CSF is diagnostic, but the concentration of the organisms may be very low, so repeat testing and submission of a large volume of CSF per sample may be needed to establish the diagnosis.

When associated with signs of tissue damage or inflammation, this may provide reliable detection of infection. Diagnosis of oropharyngeal, esophageal, or vulvovaginal Candidacies may be made on the basis of clinical appearance and risk factors. Conformation may be established by the wet mount of gram stain examination or scrapings from the affected sites.

Histopathology shows yeast cells and mycelial forms, epithelial disruption with organisms invading through mucosal cells, and submucosal inflammation and mucosal candidiasis. deep tissue candidiasis shows organisms invading and disrupting infected tissue. Antibody detection has played a limited role in diagnosis

Researchers struggle to develop a new treatment for Candidacies

Antifungal drugs less toxic than Amphotericin B are available antifungal treatment for candidemia with or without deep organ involvement. For cutaneous Candidial infection preferred treatment is topical azole and alternative is topical nystatin. For vulvovaginal candidiasis infection oral fluconazole (150 mg) or azole cream or suppository.and alternative treatment is Nystatin.

For oral thrush Clotrimazole tablets, 100-200 mg/dl itraconazole solution (200 mg)/d Alternatives are Caspofungin, micafungin or amphotericin B.

Amphotericin B is the treatment of choice for invasive and life-threatening fungal infections. It is indicated for the treatment of fungal endocarditis,, intra abdominal infections, meningitis, septicemia, and urinary tract infections. Intravenous Amphotericin B has also been used for empiric therapy in febrile neutropenic patients.

Both Itraconazole and Fluconazole are available as oral and 1V preparation. The advantage of fluconazole is its long half-life, satisfactory penetration in most body tissues and minimal toxicity. The disadvantage of Itraconazole is the varying blood levels among patients taking the oral form of the drug.

Fluconazole is highly effective for the treatment of superficial and invasive Candida infections including in neutropenic patients, however, in an unstable patients and those who were receiving azoles for prophylaxis, Amphotericin B is the therapy of choice.(45)

Voriconazole 400 mg (6 mg/kg) twice daily for 2 doses, then 200 mg (3 mg/kg) twice daily is effective for candidemia, but offers little advantage over fluconazole as initial therapy. Voriconazole is recommended as step-down oral therapy for selected cases of candidemia due to C. krusei.

Transition from an echinocandin to fluconazole is usually recommended within 5–7 days for patients who are clinically stable and have isolates that are susceptible to fluconazole (eg, C. albicans)

Candidiasis drug discovery and development:

New approaches targeting virulence for discovering and identifying new drugs

The successful development of new antifungal will necessitate a concerted effort and the establishment of partnerships between basic researchers and clinicians, funding and governmental agencies, biotechnology and pharmaceutical companies.

Vaccination

Candidemia is a bloodstream fungal infection caused by *Candida* species and is most commonly observed in hospitalized patients. Even with proper antifungal drug treatment, mortality rates remain high at 40–50%. Therefore, prophylactic or preemptive antifungal medications are currently recommended in order to prevent infections in high-risk patients. Moreover, the majority of women experience at least one episode of vulvovaginal candidiasis (VVC) throughout their lifetime and many of them suffer from recurrent VVC (RVVC) with frequent relapses for the rest of their lives. While there currently exists no definitive cure, the only available treatment for RVVC is again represented by antifungal drug therapy. However, due to the limited number of existing antifungal drugs, their associated side effects and the increasing occurrence of drug resistance, other approaches are greatly needed. An obvious prevention measure for candidemia or RVVC relapse would be to immunize at-risk patients with a vaccine effective against *Candida* infections. Frontiers | The Elusive Anti-Candida Vaccine: Lessons From the Past and Opportunities for the Future | Immunology. In spite of the advanced and proven techniques successfully applied to the development of antibacterial or antiviral vaccines, however, no antifungal vaccine is still available on the market.(46)

Dectin-1-mediated pain is critical for the resolution of fungal inflammation

Candidiasis is a painful infection that affects a large number of individuals, occasionally causing severe pain that is solely controlled by resolution of infection. Here, Dectin-1 inhibition was found to block pain during fungal infection. Researchers found that clodronate, a drug that is currently used for osteoporosis treatment, could suppress severe pain in fungal infection, and that the Dectin-1 pathway could be an important new target for treatment of pain.

Current Relevance, Challenges and way forward

Nearly half of all nursing homes do not have adequately trained infection prevention staff and their efforts to combat the over prescription of antibiotics are suffering as a result, according to a new study in the American Journal of Infection Control, the journal of the Association for Professionals in Infection Control and Epidemiology, published by Elsevier

Bacterial pathogens are the leading causative agents in nosocomial infection, *Candida spp.* clearly range among the most common micro-organisms isolated in patients with sepsis. According to a large survey on bloodstream infections comprising a total of 24000 cases in US hospitals,(47)

New antigen- or DNA-based methods for early diagnosis still await clinical validation. Their routine use is hampered by methodological issues.(48)

Fatal fungal infections occur primarily in patients whose defenses are impaired because of diseases such as HIV/AIDS, rare genetic predispositions like granulomatous disease, medical interventions such as cancer chemotherapy, implanted devices (Eg heart valves, artificial joints, catheters) and organ transplantation or developmental immaturity as a consequence of premature birth.

Early Recognition and Management of Candidacies

To reduce the incidence rate of yeast infections include wearing cotton undergarments and loose-fitting clothing to avoid persistent and excessive moisture in the genital area. Also, women should not wear wet bathing suits or exercise clothing for a long period of time.

Women who may be prone to recurrent infections are recommended to soak in a salt bath, using a non-soap cleanser aqueous cream for washing or applying. Hydrocortisone cream to reduce itching.

Prescription oral medications may be taken regularly based on recommendations of the health care provider. Interestingly there are also a number of treatments that should not be used, such as treating sexual partners, switching to low-sugar, low-yeast or high -yogurt diet, putting yogurt in the vagina and trying natural remedies. (49)

CONCLUSION

In the context of the increasing number of immunocompromised patients, combined with advances in medical technology, fungi have emerged as a major cause of infectious diseases, with *Candida albicans* being the major pathogen. Candid species are known to form biofilms upon contact with various surfaces.

Additionally, the few antimycotics that are active against microbial biofilms rapidly results in the only fractional killing of the biofilm cells, leaving a subpopulation of the biofilm cells alive so-called per sisters. Advanced research based on these bioactive compounds can lead to a formation of novel antifungal agents/for combating these pathogens.

A new drug for the treatment of Candidiasis, Cryptococcal Meningitis, and other persons with weakened immune systems such as AIDS patients has recently been approved by the FDA. The drug diflucan (fluconazole) has been found effective against these types of infections in persons with weakened immune systems.

The drug amphotericin B lipid complex (Abelcet) has received an orphan drug designation for the treatment of Candidiasis. More studies are needed to determine the long-term safety and effectiveness of this drug for the treatment of Candidiasis.

Thus there is a necessity to search for novel effective anti-infective agents especially from plants for the treatment of infectious and non-infectious diseases.(50)

CDC Call for Candidacies

The Centers for Disease Control and Prevention (CDC) is warning US healthcare facilities about the emergence of a multidrug-resistant type of yeast.

The yeast, *Candida auris,* has most commonly caused healthcare-associated invasive infections such as bloodstream infections, wound infections, and otitis, and it has typically occurred several weeks into a patient's hospital stay, according to a CDC news release The CDC says it's aware of one isolate of C auris that was detected in the United States in 2013, but it's unclear if that isolate came from a patient.(51)

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