Preventive Measures, Treatment Strategies and Antifungal Resistance of Candidiasis

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Abstract: Fungal infections from species such as Candida, Aspergillus, Cryptococcus, and Pneumocystis result in serious illness and mortality, particularly among immunocompromised individuals. However, these infections are often overlooked due to inadequate surveillance and diagnostic difficulties. Candida albicans, the main pathogen responsible for invasive candidiasis, employs mechanisms like biofilm formation and evasion of the immune response that complicate treatment and lead to recurrence. Meanwhile, the multidrug-resistant Candida auris represents a significant public health threat due to its rapid dissemination in healthcare environments. Diagnosis is challenging because of nonspecific symptoms and limited test sensitivity, making hygiene and risk reduction essential for prevention, along with antifungal treatments such as amphotericin B and fluconazole; but the increasing resistance makes it essential to use combination therapies and novel strategies. With the advent of nanotechnology, which includes metal nanoparticles (like silver, gold, and iron) and innovative carriers such as liposomes and dendrimers, there are improvements in the delivery, effectiveness, and safety of antifungal medications. These developments present promising options for addressing drug resistance. Together with enhanced diagnostics and genomic insights, these innovations are crucial for creating personalized approaches to managing and controlling candidiasis in the face of ongoing clinical challenges.

Keywords: Fungal species, Candida, Antifungal prophylaxis, Immunocompromised, Diagnosis, treatments, Antifungal Resistance

1. Introduction

Only about 300 of the more than 100,000 known fungal species are harmful to humans [1]. A protective thermal barrier against most species that thrive at room temperature may be provided by our body temperature [2]. The most prevalent pathogens that cause over 90% of recorded fungal disease deaths are Candida, Aspergillus, Cryptococcus, and Pneumocystis spp [3,4,5,6,7,8,9]. Fungal diseases are often overlooked on a global scale, despite the fact that the top ten fungal infections cause at least as many deaths as malaria or tuberculosis [10]. This is demonstrated by the World Health Organization's lack of initiatives and the dearth of national surveillance programs. Invasive fungal diseases (IFDs) are on the rise nationally, but their prevalence is probably underreported. IFDs have a high rate of morbidity and death. Their diagnosis can be difficult, and prompt treatment frequently requires a high degree of clinical

suspicion. The objective of this review is to provide a summary of the current status of the four most prevalent IFDs: Pneumocystis pneumonia, aspergillosis, cryptococcosis, and invasive candidiasis. Each year, an estimated two million people worldwide are infected by Aspergillus, Candida, Cryptococcus, and Pneumocystis [11]. Most are severely ill or immunocompromised. Among critically ill patients and those who have received abdominal organ transplants, Candida is the most prevalent fungal pathogen. On the other hand, the implementation of antifungal prophylaxis with fluconazole and later with Mould active posaconazole has resulted in a notable decrease in invasive candidiasis in high-risk haemato-oncological patients. The impact on invasive aspergillosis is probably going to be comparable. People with exacerbated chronic obstructive pulmonary disease on corticosteroids are more likely to have invasive aspergillosis, which is still the most common invasive fungal disease (IFD) among patients with hemato-oncology and solid organ transplant recipients. Pneumocystis pneumonia and cryptococcosis are now uncommon in HIV patients in the developed world due to antiretroviral therapy; they are primarily found in patients who have received solid organ transplants or who are immunocompromised [12]. Proper diagnosis is the primary obstacle in the developing world, where cryptococcosis is still a prevalent and extremely deadly illness that affects people with HIV who also have invasive candidiasis and invasive aspergillosis [13]. Both specificity and sensitivity are lacking in the current diagnostic tests, and the clinical presentation is nonspecific. Combining multiple tests increases sensitivity but not specificity. It may be possible to diagnose invasive aspergillosis and candidiasis more quickly and precisely with standardised polymerase chain reaction-based assays [3]. However, medical concern alone is frequently the basis for starting treatment. However, empirical therapy may miss its target in cases of resistance or result in overtreatment for patients without IFD. Even though antifungal prophylaxis has been successful in lowering the incidence of IFDs in patients with hemato-oncology, a significant number of breakthrough infections show both fungal resistance and the emergence of uncommon and frequently fatal fungal pathogens. Therefore, it is essential to understand the local epidemiology and antifungal resistance. There are significant gaps in the current trial-based guidelines for identifying the most vulnerable individuals who might benefit from prophylactic treatment. Continuous searches for genetic variations linked to disease may help create personalised risk profiles and focused preventative measures [14]. The past few years have seen the use of DNA sequence-based techniques to validate taxonomic relationships within the genus and to verify that both sexual and nonsexual species of Candida are ascomycetes [15]. According to molecular techniques, a large number of the medically significant species of Candida are members of the CTG clade, a phylogenetic subgroup of mostly commensal yeast species that translate CTG as serine rather than leucine. Up to 8% of women experience frequent recurrent infections from vulvovaginal candidiasis (VVC), which affects the majority of women at least once in their lives. Candida albicans is the primary cause of VVC, with Candida glabrate being the second most frequent cause [16]. An essential part of the normal oral flora in humans are Candida species, which have the potential to overgrow and result in oropharyngeal candidiasis (OPC). OPC in people with HIV has significantly decreased since the mid-1990s, when highly active antiretroviral therapy (HAART) was introduced[17,18].Approximately 30 to 50% of the general population, 50 to 65% of denture wearers, 65 to 88% of long-term care facility residents, 90 to 95% of HIV-positive individuals, and patients undergoing corticosteroid, chemotherapy, immunosuppressive, or radiation

treatment for head and neck cancers are estimated to harbour Candida albicans (C. albicans) isolated from the oral cavity [19,20,18,21,22,23,24]. Most isolates of Candida albicans are generally completely susceptible to all of the main classes of antifungal agents, such as polyenes, azoles, and echinocandins. One of the rarest species of Candida is parapsilosis, which is often isolated from physical surfaces in the hospital setting. Because the remaining Candida species linked to human disease are rarely found, not much is known about the epidemiology or aetiology of the diseases they cause [25]. Only under a microscope can one see microbes, which are minuscule living entities that are invisible to the naked eye. Since Candida is a form of yeast, it is a fungal infection that can affect the body [26]. Because the infectious agent is a yeast called Candida, candidiasis is known as the yeast contagion. Important pathogens, Candida albicans are found everywhere and primarily live with many bacteria in the vicinity of the mouth, gastrointestinal tract, and vagina. The first person to describe candidiasis was Wilkinson in 1849. It is called thrush, or oral candidiasis. Cutaneous candidiasis is an infection of the skin that develops in areas of the skin with very little ventilation and unusually high moisture content [27]. When fungi infiltrate the body, get into the bloodstream, and spread throughout the body, it's known as deep candidiasis. Each case has a different approach to treatment. To avoid contracting the illness, you must practise natural prevention [28]. The most common form of Candida, Candida albicans, is responsible for invasive candidiasis, a dangerous fungal disease associated with medical treatment. Nevertheless, the prevalence of these organisms differs significantly by geographical location. From candidemia with mild symptoms to fulminant sepsis, which has a death rate of over 70%, invasive candidiasis can cause anything [29]. Candida spp. are common commensal organisms in the gut microbiota and skin, and alterations in the gastrointestinal and cutaneous barriers (gastric perforation, for example) promote invasive illness. The primary pathogen is Candida albicans because of its high infection prevalence and phenotypic variability [30]. Fungal virulence factors that include the capacity to grow at 37 °C, morphological transition, secretion of hydrolytic enzymes, haemolytic activity, tissue adhesion and invasion, immune system evasion, filamentation ability, and biofilm formation all affect C. albicans colonisation and infection.

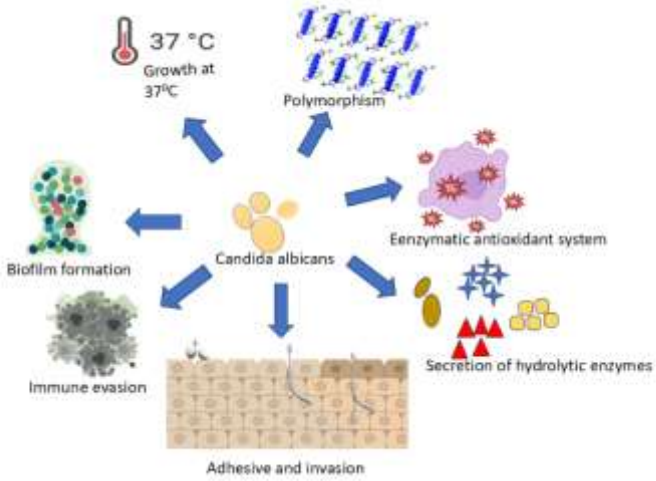


Figure 1: Thermostasis, polymorphism, biofilm formation, immune evasion, adhesion, invasion, and the release of hydrolytic enzymes (like lipase, phospholipase, and sap) and

antioxidant enzymes (like catalase and superoxide dismutase) are some of the main virulence factors of Candida albicans

C. albicans can grow biofilms on biotic and abiotic surfaces, such as host tissues, medical equipment, dentures, and catheters, in a variety of environmental settings. Encased in a self-secreted polymeric extracellular matrix, biofilms are communities of yeast, pseudohyphae, and hyphae. Biofilms of Candida albicans are intricate structures that shield cells from their surroundings and offer a high degree of resistance to both host immune system components and traditional antifungal medications. These biofilms make antifungal treatment difficult and contribute to recurrent candidiasis [31,32].

OUTBREAK OF CANDIDIASIS

The multidrug-resistant nature of Candida auris and its capacity to spread quickly in healthcare settings make this outbreak a serious public health concern. Numerous outbreaks worldwide, especially in critical care units and nursing homes, have been linked to C. auris since its initial discovery in 2009. Its ability to colonize environmental surfaces and patients makes it easier for it to spread throughout facilities.

Around 3,600 environmental samples and 540 patient isolates were analysed during the August 2016–2018 outbreak in New York. A preponderance of colonisation in the nares as opposed to other body sites was revealed by this investigation, which validated 413 clinical cases and 931 cases of colonisation in various healthcare settings. C. auris showed resistance to several antifungal agents, such as amphotericin B (61% resistance), voriconazole (81% resistance), and fluconazole (intrinsic resistance). The significance of ongoing research and public health initiatives is highlighted by these findings, which emphasise the urgent need for enhanced surveillance and control measures to stop the spread of this pathogen in healthcare settings [33].

SIGNS AND SYMPTOMS

A condition caused by yeast called candidiasis is brought on by an overabundance of the Candida fungus. The location of the infection has a significant impact on its symptoms. (Table no.1)

Type of Candidiasis	**Signs and Symptoms**
Vaginal Candidiasis (Yeast Infection)	- Itching or soreness in the vagina - Pain experienced during intercourse - Discomfort or pain during urination

	- Cottage cheese-like vaginal discharge that is abnormal [34]
Oral Thrush (Candidiasis of the Mouth and Throat)	The tongue, throat, and inner cheeks all have white spots. - Redness or discomfort in the oral cavity - A sensation similar to cotton in the mouth - Pain when swallowing or eating [34,35]
Candidiasis of the Esophagus	- Pain and trouble swallowing - The symptoms of oral thrush frequently overlap [34]
Invasive Candidiasis	- Colds and fever that do not go away when treated with antibiotics - signs that indicate organ involvement, like joint, brain, or heart pain if the infection spreads [34]
General Symptoms for All Types	- Pain, irritability, and swelling in the impacted areas - A yeast and bacterial imbalance is frequently the cause of symptoms.

1.1. Etiology

An accidental infection is candidiasis. In healthy individuals, Candida albicans colonises the mucosa of the gastrointestinal tract, oesophagus, and oropharynx. In these regions, where Candida albicans typically reside in an immunocompromised host, they can result in mucosal candidiasis. Patients who have leukaemia or lymphoma as a result of taking cytotoxic drugs or corticosteroids have weakened immune systems, which can result in candidal infections.

The use of antibiotics is frequently linked to candidiasis. Fungemia brought on by Candida albicans, which arise from fungal translocation through weakened mucosal barriers, can be brought on by cancer cytotoxic chemotherapy. Changes in the host's conditions and the size or makeup of the endogenous microbial population can cause fungal commensals in the upper and lower GI tract to become opportunistic pathogens.[36] Pregnancy, oral contraceptive use, and diabetes mellitus all increase vaginal colonisation. HIV patients are closely linked to oral candidiasis. Over 90% of HIV patients have candidiasis when they first arrive.

TB, myxoedema, hypoparathyroidism, Addison's disease, nutritional deficiencies (vitamins A, B6, and iron), smoking, poorly maintained dentures, IV tubes, catheters, heart valves, old age, infancy, and pregnancy are additional risk factors for candidiasis. Because xerostomia lacks the protective antifungal proteins histatin and calprotectin, it is also a risk factor [37].

1.2. EPIDERMIOLOGY OF CANDIDIASIS

Reported that there has been a notable rise in Candida infections during the last ten years. This is especially true for hospitalised patients, where the prevalence of blood-stream infections caused by Candida species has nearly 500% increased during the 1980s. This increase is accompanied by a significant excess mortality and a longer hospital stay duration. This pattern persisted into the 1990s, when Candida species accounted for 8% of all hospital-acquired bloodstream infections and were still the fourth most prevalent bloodstream pathogen in the US [37]. The fact that species other than Candida albicans are responsible for over one-third of bloodstream infections caused by candida is noteworthy. Although endogenous colonisation is the primary cause of most of these infections, the identification of antifungal agent resistance and the reporting of nosocomial transmission, or "cross-infection," present novel and serious issues. According to recent studies, 15–54% of healthcare workers in intensive care units may have hands that have been isolated from Candida, and patients with infection may share the type of Candida that these hands carry [38].

1.3. Pathophysiology

Thrush is caused by Candida albicans when the host's normal immunity is compromised. On the oral mucosa, the organism may overgrow, resulting in keratin, bacteria, and necrotic tissue buildup as well as desquamation of epithelial cells. A pseudo-membrane formed by this debris sticks firmly to the mucosa. Rarely, this layer of tissue may have large patches of underlying mucosal oedema, ulceration, and necrosis. During passage through the affected vagina, C. albicans typically colonises neonates with thrush; the likelihood of a neonate developing thrush increases if there is an active vaginal yeast infection.

Candida enters the bloodstream through three main routes: the mucosal barrier of the digestive system is the most common, followed by an intravascular catheter and a localised infection. Both patients in the intensive care unit and those who are neutropenic can have Candida enter their bloodstream. They are also a component of the normal gut microbiota, and bloodstream candidiasis can result from any illness that compromises an individual's immune system. Candida can grow on indwelling catheters, particularly central lines, at the hub or the implantation site, which can result in a subsequent Candida infection. A localised infection rarely causes bloodstream invasion, but an ascending Candida urinary tract infection linked to either intrinsic obstruction or extrinsic compression frequently does.

Local or systemic antimicrobial therapy may cause vulvovaginal candidiasis, which can also lead to recurrent episodes of the disease. It is still unclear how precisely antibiotics cause candidal vulvovaginitis. The reduction or alteration of normal vaginal flora, as well as

inhibitions of yeast colonisation and proliferation, could theoretically be the cause of vulvovaginitis [39].

1.4. CLINICAL ASPECTS

The opportunistic infection known as candidiasis is brought on by yeasts belonging to the genus Candida. Over 80% of yeast infections are caused by them, and in the past few years, their incidence has skyrocketed.[40] Candidiasis can be systemic or superficial, based on where it is infected [41].

Table no.2: the ecology of Candida species frequently identified in medical laboratories [41]

Most frequent species	Ecology
C. albicans	More than 75% of the yeasts isolated in humans are commensal yeasts found in the mucosa of the respiratory, genital, and digestive tracts.
C. glabrata	urinary tract and digestive mucosa
C. parapsilosis	Skin
C. tropicalis	Water, soil, respiratory, urinary, and digestive systems
C. krusei	Food (Dairy, Beer)
Less common species	Ecology
zqC. Dubliniensis	Birds, digestive tract
C. Africana	Vagina

1.5. DIAGNOSIS OF CANDIDIASI

The absence of distinct clinical signs and symptoms of the illness makes clinical diagnosis more difficult. Additionally, circulating antibodies to Candida species can develop in healthy people due to commensal colonisation of mucosal surfaces, making antibody detection less useful for diagnosing this illness. This makes laboratory diagnosis more difficult. Furthermore, antigen detection tests frequently fall short of the required level of sensitivity because Candida species antigens are frequently quickly removed from circulation. Because blood cultures can be negative in as many as 50% of autopsy-proven cases of deep-seated candidiasis or may only turn positive late in the infection, microbiological evidence is challenging [42]. Although they can happen during a systemic infection, positive cultures from urine or mucosal surfaces do not always signify an invasive disease. Furthermore, species-level identification is crucial for clinical management because different species of Candida differ in their virulence and susceptibility to antifungal medications. Although they have attracted attention, more recent molecular biological tests have not yet been validated in extensive clinical trials or are standardised or easily accessible in the majority of clinical laboratory settings. If sensitive and specific diagnostic tests are available for at-risk patients, laboratory surveillance could lead to

an earlier start of antifungal therapy. These tests are also reasonably priced [43]. Candida albicans continues to be the most prevalent. In both immunocompromised patients and healthy people, abnormal overgrowth in the respiratory, gastrointestinal, and urinary tracts has been documented during the past 20 years. Candidasis is a great example of a multifactorial condition because there are many different factors that can lead to a yeast infection [44]. A candidiasis diagnosis might be very difficult to make. The best "treatment" is prevention, far more so than using antifungal medications to eradicate the yeast. The daily regimen can offer strength protection in several ways that need to be taken into account [45].

2. PREVENTIVE MEASURES FOR CANDIDIASIS

These infections result in unfavourable outcomes like higher patient morbidity and mortality, longer hospital stays, and higher hospital expenses. Candida species that are not albicans have become more common in recent years. Regretfully, some of these species have innate resistance to first-line antifungal medications. Additionally, treatment failure may result from biofilm formation on invasive devices and the central venous catheter. Risk factors for invasive candida infections include the patients' age, co-occurring conditions, the therapeutic units, the antibiotics and antifungals used, and invasive devices [46]. The actions of healthcare professionals can lower some of these risk factors. The primary objective is to prevent invasive candida infections before they happen. To stop the spread of candida in hospitals, infection control measures are crucial. Maintaining proper hand hygiene both before and after interacting with the patient is the most crucial measure to stop the spread of Candida species. Another crucial component of this goal is adhering to the highest barrier precautions when performing invasive catheterisation. To lessen candida colonisation, it's also critical to avoid parenteral nutrition, antibiotics, and needless invasive devices [47]. Globally, the number of patients with compromised immune systems has led to a sharp rise in infections caused by Candida species. Clinical practitioners have implemented a number of strategies to prevent and treat candidiasis. Fluconazole, amphotericin B, nystatin, and flucytosine are among the many antifungal medications frequently used to treat patients with Candida infections. Administering the right medications for antifungal therapy will also depend heavily on the early identification and speciation of the fungal agents. Numerous contemporary technologies, such as real-time PCR, DNA microarray, and MALDI-TOF-MS, are being used to accurately and quickly detect the strains. Antifungal therapy suffers as a result of many fungal pathogens developing resistance to these medications over time. Combining two or more antifungal medications is considered an alternative in this regard to combat the growing drug resistance. In order to treat candidiasis, numerous efflux pump inhibitors have been developed and evaluated in various models [48]. However, biomedicines like antibodies and polysaccharide-peptide conjugates may be safer and more effective ways to prevent and treat diseases than synthetic drugs, which often have negative side effects. Additionally, the genome sequences of Candida albicans and other non-albicans strains are now available, which has made it possible to examine the genes for their functions in disease adherence, penetration, and establishment. Applying various cutting-edge technologies to comprehend the biology of Candida species will aid in the prevention and treatment of illnesses brought on by fungus-related infections [49]. **(Table no:3)**

Aspect	Description
Significance of Invasive Candida	- Major contributor to nosocomial infections in immunocompromised patients and intensive care units. - Results in longer hospital stays, greater expenses, and an increase in morbidity and mortality.
Incidence and Resistance	- Candida species that are not albicans are becoming more common. - Treatment options are made more difficult by certain species' innate resistance to first-line antifungals.
Risk Factors	- Risk factors include invasive devices, treatment units, age, co-morbid conditions, and the use of antibiotics and antifungals. - Some risks can be reduced by the actions of healthcare workers.
Prevention Strategies	- Adhere to hand hygiene guidelines. - Take the most precautions possible when getting a catheter. - Avert needless invasive procedures and equipment.
Treatment Approaches	- Amphotericin B, fluconazole, nystatin, and flucytosine are common antifungals. - Appropriate therapy is made easier by early detection and speciation. - Drug resistance may be combated by combination therapy.
Modern Technologies	- using DNA microarrays, real-time PCR, and MALDI-TOF-MS to quickly identify strains.
Challenges and Alternatives	- Resistance to long-term antifungal treatment is growing.

	- Biomedicines such as antibodies provide safer alternatives to synthetic drugs, which frequently have adverse effects.
Genomic Insights	- Genes involved in disease pathology can be analysed thanks to the genome sequences of Candida species. - Strategies for prevention and treatment can be developed with the help of an understanding of biological mechanisms.

2.1. MANAGEMENT FOR CONTROL OF INFECTION

Infection Typically involves antifungal medications. Antifungal therapy is crucial, with agents such as echinocandins, azoles, or amphotericin B used to depend on the severity and type of infection. **Table no 4:**

Type of candidiasis	Key recommendations	Antifungal agents	Comments
Candidemia and haematogenous candidaemia	Every episode needs to be treated. After the last positive blood culture and the resolution of clinical infection symptoms, therapy should be continued for at least two weeks. Some authors advise treating unstable patients with a combination of medications, primarily flucytosine and amphotericin B.	Amphotericin B 0·6 mg/kg daily, Fluconazole 12 mg/kg daily initially, followed by 6 mg/kg daily* IV–oral switch Lipid formulation of amphotericin B 1–5 mg/kg daily. Caspofungin 70 mg initially followed by 50 mg/daily	Blood cultures ought to be performed both during and after treatment, and species identification and susceptibility testing ought to guide the selection of antifungal agents [50].
Catheter-related candidaemia	It should be methodically considered to remove all vascular access lines. Patients with breakthrough	As above	There is more proof for patients with compromised immune systems. These recommendations

	candidaemia should have all vascular access devices taken out and replaced at a different location.		are also relevant to surgically implanted devices [51].
Catheter exit-site infection	It is advisable to systematically consider the removal of all vascular access lines. In patients with breakthrough candidaemia, all vascular access devices should be taken out and put in at a different location.	As above	[52]
Hepatosplenic candidiasis	usually requires ongoing treatment for a number of months.	Fluconazole 6 mg/kg daily with early IV–oral switch Amphotericin B 0·6 mg/kg daily other antifungals	There has been little experience reported. after marrow recovery from aplastic periods, more prevalent [53].
Candidal pneumonia	Candida species that have been isolated from the respiratory tract, including through bronchoscopic methods, shouldn't be automatically regarded as harmful. Based on histopathological confirmation, a definitive diagnosis is made.	Amphotericin B 0·6 mg/kg daily Lipid formulation of amphotericin B 1-5 mg/kg daily Fluconazole 12 mg/kg daily initially, followed by 6 mg/kg daily IV–oral switch	[54]
Meningitis	Many authors recommend amphotericin B and	Amphotericin B 0·6 mg/kg daily	[55]

	flucytosine as part of a combined therapy.	Lipid formulation of amphotericin B 1–5 mg/kg daily	
Endophthalmitis	In every instance, antifungals and surgical debridement should be taken into consideration. Many authors recommend a combination of flucytosine and amphotericin B.	Amphotericin B 0·6 mg/kg daily Lipid formulation of amphotericin B 1–5 mg/kg daily Other antifungals	Verifies the disseminated candidiasis diagnosis It is important to actively look for the cause of candidaemia [56].
Abdominal candidiasis (peritoneum, pancreas gallbladder)	Although proving that Candida species are pathogenic may be challenging, efforts should be made. Antifungals should be used in conjunction with surgery to treat abscesses and peritonitis. Biliary tree candidiasis should be treated with drainage. Antifungal prophylaxis may be helpful for patients who sustain perforations frequently.	Amphotericin B 0·6 mg/kg daily Lipid formulation of amphotericin B 1–5 mg/kg daily Fluconazole 12 mg/kg daily initially followed by 6 mg/kg daily IV–oral switch Other antifungals	Candida species may not be regarded as harmful if they are isolated in small or moderate quantities or if the initial intestinal damage can be promptly repaired. When pancreatitis occurs, Candida species should be suspected of being harmful [57].
Candiduria	It may be challenging to determine whether Candida species are pathogenic. In most cases,	Amphotericin B 0·6 mg/kg daily Fluconazole 3 mg/kg daily with rapid IV–oral switch Other antifungals	In general, short-term (7–14 days) treatment works well. It might be advantageous to

	asymptomatic catheter-associated candiduria does not require treatment.		install new devices if total removal of foreign material is not feasible. [58]
Non-genital mucocutaneous candidiasis	Treatment with systemic therapy is often necessary for severe oropharyngeal and oesophageal candidiasis.	Amphotericin B 0·6 mg/kg daily Fluconazole 12 mg/kg daily initially followed by 6 mg/kg daily IV–oral switch Itraconazole 5 mg/kg oral Other antifungals	In many situations, topical antifungals have limited effectiveness. Clinically resistant types of oesophagitis can be treated with liquid itraconazole formulations. [59]
Disseminated cutaneous candidiasis in neonate	Befits a disseminated disease classification	See candidemia	[60]

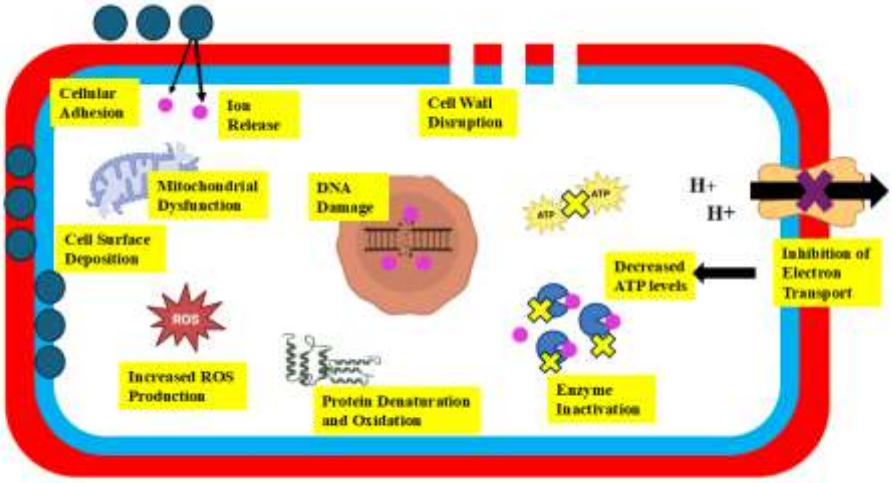
2.2. Limitations

• Toxicology: Traditional antifungal medications may cause detrimental host cell side effects.
• Limited Spectrum: Not all strains of Candida albicans or other fungi may respond well to certain antifungals.
• Relapse of Infections: Despite treatment, patients may continue to get infections, underscoring the difficulties in eradication.
• Administration Route: Intravenous administration of some antifungal drugs may be necessary, which makes treatment regimens more difficult.
• Expensive: Patients may find antifungal treatments prohibitively expensive, which may limit their access.
• Availability: In some areas, certain antifungal medications might not be easily available or authorised for use.
• Emergence of Resistant Strains: Treatment is now more challenging due to the development of resistant C. albicans strains brought on by the overuse and abuse of antifungals.

Innovative treatment approaches for candidiasis, with a focus on nanotechnology. Their inherent antifungal qualities and capacity to improve the delivery and effectiveness of antifungal medications have attracted a lot of interest in nanoparticles. They enhance targeted delivery, drug solubility, stability, and bioavailability [32].

3. Metal nanoparticles

In the field of biomedicine, the creation of nanodrugs and nanocarriers has opened up new avenues for investigation. Because metal nanoparticles may be effective against fungal species of interest in the pharmaceutical, medical, and agricultural industries, they have drawn a lot of attention [61,62,63,64]. Metal oxide nanoparticles, magnetic materials, and noble metals are among the many types of nanoparticles with inorganic cores that have been proposed [65]. Solid particles or particulate dispersions with sizes between 10 and 100 nm are called nanoparticles. Three external nanoscale dimensions are what define them [66]. The physical and chemical characteristics of metal nanoparticles are distinct. Their size, deformability, charge, hydrophobicity, and porosity can all be altered by changing their synthesis process. These changes can have an impact on cellular localisation, internalisation, circulation time, drug charge, particle stability, biocompatibility, and biodistribution [67]. Through mechanisms including ion release, oxidative and nitrosative stress, damage to membranes and cell walls, inhibition of enzymatic activity, regulation of gene expression, lowering of ATP levels, DNA, protein, and mitochondrial dysfunction, metal nanoparticles demonstrate antifungal activity. These characteristics make metal nanoparticles useful for delivering antimicrobial drugs in a variety of ways [64,68,69,70]. The efficacy of metal nanoparticles against Candida albicans may be increased when combined with amphotericin B (AMB), caspofungin (CAS), and fluconazole (FCZ) [71,72,73]. In the fight against C. albicans strains that are resistant to antifungal medications and biofilms that develop on mucosa and medical equipment, metal nanoparticles can be very helpful [70]. Recent research on the application of metal nanoparticles to treat Candida albicans infections is highlighted here, with an emphasis on iron (Fe), gold (Au), and silver (Ag) nanoparticles.



(**Figure2.)** Main mechanisms of action of metallic nanoparticles against C. albicans

Metal nanoparticles against C. albicans [32] Table : 5

Types	Description	References
1.Silver Nanoparticles (AgNPs)	- AgNPs are being investigated for antifungal and anticancer drug delivery, among other biomedical applications. - Compound carrying potential is increased by biocompatibility improvements.	74
1.1AgNPsfor Antifungal Drugs	- Antifungals (such as voriconazole and nystatin) are transported by AgNPs. - Fluconazole has been shown to have synergistic effects on resistant strains of Candida albicans.	75
1.2 Green Synthesis	- Natural compounds are used in environmentally friendly methods to produce AgNP. - Both EG-AgNPs and AV-AgNPs exhibit strong antifungal activity against Candida albicans.	76,77
2.Gold Nanoparticles (AuNPs	- The FDA has approved AuNPs for a number of uses due to their advantageous physicochemical characteristics. - Their application in the delivery of antifungal drugs shows promise for decreased toxicity.	78,79
2.2AuNPsfor Antifungal Drugs	- The antifungal efficacy of AuNPs is enhanced by the formulation of caspofungin. - PEG-FCZ-AuNPs exhibit enhanced delivery efficiency and decreased toxicity.	80
3.Iron Nanoparticles (IONPs)	- It is inexpensive, well-known for its thermal stability, and appropriate for drug delivery.	81,82

	- An FDA-approved IONP that exhibits promise against Candida albicans is ferumoxytol.	
4. Other Metal Nanoparticles	- CuO, ZnO, TiO2, and other elements have antifungal properties against Candida albicans. - Size, charge, and composition are associated with effectiveness.	83,84
5.Bimetallic Nanoparticles	- Research demonstrates that Ag-Fe, Ag-Ni, and other bimetallic nanoparticles efficiently fight Candida albicans via a variety of methods.	85,86
6. Concerns and Future Directions	- Enhancing effectiveness and reducing toxicity in metal nanoparticles requires constant investigation of properties and optimisation.	87

3.1Characteristics and main activities of metal nanoparticles against C. albicans

3.1.1Silver Nanoparticles

Since silver nanoparticles (AgNPs) have a variety of antifungal qualities, they are frequently combined with other substances. For instance, in vitro, AgNPs with a size of 8–12 nm has demonstrated strong growth inhibition and anti-biofilm activity when paired with fluconazole (FCZ). They accomplish this by upregulating the production of reactive oxygen species (ROS) and downregulating the genes involved in ergosterol biosynthesis. This lowers efflux pump activity and shows antifungal efficacy in vivo. Additionally, in vitro growth and germ tube formation are inhibited by 15 nm-sized poly (methacrylic acid)-silver nanoparticles (PMAA-AgNPs) with a zeta potential of -41.83 mV. In vitro, biogenic AgNPs from Anabaena variabilis, which range in size from 11 to 15 nm, have also demonstrated encouraging growth inhibition and anti-biofilm properties. Additionally, the zeta potential of AgNPs made with Erodium glaucophyllum is -10 mV, and their diameter is 50 nm. They have been shown to have antifungal efficacy in vivo and exhibit significant growth inhibition, enzymatic activity reduction, and filamentation limitation. Antifungal activity is also demonstrated by rutin-loaded silver nanoparticles, which have an average size of 59.67 nm and a zeta potential of –11.2 mV. Furthermore, against Candida albicans, AgNPs derived from Vitis vinifera that range in size from 34.43 to 101.63 nm exhibit both growth inhibition and anti-biofilm activity [88].

3.1.2Gold Nanoparticles

The stability and low toxicity of gold nanoparticles (AuNPs) are noteworthy. A 20 nm-sized Caspofungin encapsulated in AuNPs (CAS-AuNPs) with a zeta potential of –38.2 mV efficiently inhibits growth. In a different strategy, 80 nm AuNPs loaded with PEG and FCZ and having a positive zeta potential of +1.6 show improved antifungal activity in vitro. Their ability to inhibit Candida albicans is further supported by chitosan-coated AuNPs (20 to 120 nm, zeta potential −52.39 mV). Tyrosol-functionalized chitosan AuNPs (10 to 15 nm, +45.5 mV) also exhibit strong antifungal activity, preventing the formation of germ tubes and encouraging the generation of ROS. AuNPs derived from olive leaf extract, which have a size of 29.16 nm, also show remarkable antifungal activity in vivo and growth inhibition in vitro [89].

3.1.3Iron Nanoparticles

Iron nanoparticles, such as miconazole complexes (size <50 nm) and chitosan, have demonstrated decreased metabolic activity and growth inhibitory effects. Additionally, there is effective growth inhibition when bovine serum albumin and amphotericin B (AMB) are combined [90].

3.1.4Other Metal Nanoparticles

Copper oxide nanoparticles (10.7 to 36 nm) downregulate morphogenesis and virulence genes while exhibiting noteworthy anti-Candida properties through growth inhibition, anti-biofilm activity, and ROS production. Both metabolic and anti-biofilm activity are decreased by zirconium dioxide nanoparticles (20–40 nm). Nanoparticles of titanium dioxide and PMMA with an average diameter of 26 nm efficiently decrease adhesion [91].

3.1.5Bimetallic Nanoparticles

The combined effects of bimetallic nanoparticles have drawn interest. For example, 13 nm-sized iron and silver nanoparticles show notable growth-inhibitory characteristics. Potential is also shown by those made of chromium and silver (93.14 nm). The capacity of silver and nickel nanoparticles (31.84 to 47.85 nm) to suppress growth and biofilm formation while modifying efflux pump genes is demonstrated. Finally, tin dioxide nanoparticles (1–18 nm) demonstrate antifungal activity against Candida albicans by inhibiting growth and preventing biofilm formation.

These nanoparticles offer novel approaches to treating Candida albicans infections, addressing issues like drug resistance and efficacy. They are distinguished by their distinct sizes, zeta potentials, and antifungal mechanisms [92].

3.1.6Liposomes

Lipid-based nanoparticles known as liposomes have the ability to encapsulate antifungal agents, enhancing their stability, solubility, and targeted delivery. Particularly, liposomes functionalised with targeting moieties have shown improved antifungal activity against species of Candida. Dectin-targeted liposomes have been demonstrated to enhance mouse survival rates in experimental models of candidiasis while dramatically lowering the fungal burden in infected tissues. Particularly noteworthy are formulations like amphotericin B-loaded liposomes, which improve the therapeutic effectiveness of currently available antifungal medications [93]**.**

3.1.7Polymeric Nanocarriers

Antifungal drugs can be encapsulated in polymeric nanocarriers, like those made with chitosan, to improve their tissue penetration and bioavailability. Through prolonged drug release mechanisms, studies have shown how adaptable these materials are for treating vulvovaginal candidiasis and other types of candidiasis. Another promising approach to combating drug resistance is the synergistic effects of antifungal combinations within these polymers [94,95].

3.1.8Dendrimers

Dendrimers are polymeric structures with many branches that possess both active antifungal and carrier characteristics. Their inherent antimicrobial activity and ability to improve drug solubility make them good candidates for treating candidiasis. As an example, peptide dendrimers that are designed to fight fungi have demonstrated efficacy against strains of Candida albicans that are resistant to fluconazole. Furthermore, the creation of dendrimers to transport photosensitiser substances encourages innovative methods of incorporating photodynamic therapy [96,97].

3.1.9Nano emulsions

Nano emulsions are showing promise as efficient delivery systems that can boost the antifungal activity of substances that aren't very soluble. According to recent research, nano emulsions can enhance the solubility and release properties of antifungal medications such as clotrimazole, showing better results against Candida species. These delivery methods are effective substitutes for traditional treatment formulations because they enable targeted action and can optimise drug release profiles [98,99].

Conclusion:

Fungal infections, especially candidiasis caused predominantly by Candida albicans, pose significant global health challenges due to their increasing prevalence, complex diagnosis, and mounting antifungal resistance, particularly affecting immunocompromised patients. Despite progress in antifungal treatments and prophylaxis, managing resistance and biofilm-related

drug tolerance remains difficult, contributing to high morbidity and mortality. The rise of multidrug-resistant strains such as Candida auris further emphasizes the need for enhanced surveillance, innovative therapies, and rigorous infection control. Nanotechnology-based solutions—including metal nanoparticles, liposomes, polymeric carriers, dendrimers, and nano emulsions—show great promise in improving antifungal delivery, efficacy, and safety by overcoming resistance and targeting fungal cells more effectively. Integrating these advanced technologies with genomic insights and personalized medicine will be vital for developing focused prevention and treatment strategies. Ongoing research, clinical validation, and public health efforts, alongside strengthened infection control and improved diagnostics, are essential to optimize management, reduce resistance, and ultimately curb the global impact of candidiasis.

Competing interest – The authors declare no competing interest

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