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Prevalence, virulence factors and antibiotic susceptibility of *Candida* infection in children

Nora Mahmoud[1], May A. Mohamed[2], Rehab M. Hafez[1], Tarek A. A. Moussa[1*]

[1]*Botany and Microbiology Department, Faculty of Science, Cairo University, Giza 12613, Egypt*

[2]*Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University*

Abstract

Many human infections, including mucosal and invasive candidiasis, can be brought on by Candida species, opportunistic fungal pathogens. An increasing issue in tertiary care institutions around the world is candidemia, the most notable form of invasive candidiasis. One of the most frequent reasons for bloodstream infections is *Candida*. Due to the extensive use of broad-spectrum antibiotics and immunosuppressive treatments, there has been a marked rise in the frequency of candidemia globally in recent years. Critically sick patients are put in danger by invasive candidiasis, a disorder with a high death rate that poses a serious health risk. The risk of death is higher for patients who are newborns, old, or admitted to intensive care units (ICUs). Over the past 20 years, there has been a marked rise in reports of Candida BSIs worldwide. Nosocomial BSIs caused by Candida are the sixth most frequent in Europe and the fourth most frequent in the United States. In this review, we discussed the different Candida infections and their mechanisms and the association of Candida infections with the recent COVID-19 pandemic.

Keywords: Candida albicans; Candida non-albicans; types of infections, mechanism infectious disease; Children; prevalence

1. Introduction

Agostino Bassi, a forerunner of Pasteur and Koch, is credited with establishing the theory of harmful microorganisms. Bassi discovered a mold called *Beauvaria bassiana* in 1835 that caused catastrophic silkworm sickness. It was rapidly followed by the first findings of human illness caused by a fungus, such as candidiasis in 1842 by Gruby, and aspergillosis in 1847 by Sluyter [1].

Mycoses, which are caused by fungi, are significant contributors to human morbidity and mortality. Some fungal illnesses are endemic, and they are typically brought on by fungi that are found in the environment and spread to people by their spores. Other fungal infections are referred to as opportunistic because the fungi that cause them may only produce a little illness in healthy people but may infect and cause a serious illness in immunocompromised people. The possibility of fungus spores reaching lung tissue and causing disease exists because the human airway is constantly exposed to a non-sterile environment.

Additionally, the variety and extent of pathogenic fungi have increased. Overall, the invasive fungal disease is still most usually caused by *Candida* and *Aspergillus* species, but infections caused by previously uncommon hyaline and dematiaceous filamentous fungi are now more regularly documented. This is crucial because infections brought on by opportunistic fungal infections (rare and emergent) continue to be linked to high mortality, high morbidity, and poor patient outcomes despite notable advancements in antifungal therapy [2].

2. Infection of Children

Invasive fungal disease (IFD) is a major source of morbidity and death in children who are undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT). Children may differ from adults in various areas of epidemiology, diagnosis, and therapy of IFD when compared to adults [3].

Invasive fungal infections in children are mostly caused by *Candida* and Aspergillus spp. They're linked to a high risk of death and morbidity, as well as substantial medical costs. During the last two decades, there has been a significant increase in their prevalence. Invasive candidiasis is five times more common in infants and children than invasive aspergillosis. *Candida* sp. is the third most prevalent agent in children's bloodstream infections caused by healthcare. Hematological malignancies and solid

*Corresponding author e-mail: tarekmoussa@cu.edu.eg.(Tarek A. A. Moussa).;

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tumors are more commonly associated with invasive aspergillosis [4].

The importance of *Candida* species in neonatal intensive care units (NICU) is becoming more widely recognized. It is the third most common cause of late-onset sepsis in NICU patients, accounting for 9 to 13% of neonatal bloodstream infections (BSI)[5].

Because healthy children have a great natural response to fungal infections, fungal infections in children are on the rise. Fungi are not all harmful, and their infection is opportunistic. Fungi can take the shape of yeast, mold, or dimorph. In children, fungus can cause superficial infections on the skin, nails, and hair, such as oral thrush, *Candida* diaper rash, tinea infections, and so on. It can also cause subcutaneous fungal infection in tissues beneath the skin, and finally systemic infection in deeper tissues. Most superficial and subcutaneous fungal infections are easily detected and treatable. Opportunistic fungal infections are ones that only cause illness in immunocompromised people [6].

One of the most common reasons for opportunistic infections is the presence of *Candida* species, which can come from either endogenous or external sources. Numerous patients hospitalized to the newborn intensive care unit (NICU) and paediatric intensive care unit (PICU) are infected with *Candida* species that may cause invasive candidiasis, which is a significant independent risk factor [7].

3. *Candida* Infection

However, a few clinicians and mycologists persuaded the public that thrush was caused by an infectious agent. Rosen von Rosenstein defined an invasive form of thrush in 1771. Langenbeck is credited with identifying a fungus in a typhoid fever patient in 1839. "Under the microscope magnified, the pseudo-membranes consisted of an enormous number of fungi." Oropharyngeal and esophageal thrush with pseudo-membranes were discovered at autopsy. Charles Philippe Robin, a distinguished French mycologist, classified the fungus as *Oidium albicans* in 1847, using *albicans* ("to whiten") to name the fungus that causes thrush. In 1923, Berkhout reclassified it under the current genus *Candida*. *Candida* comes from the Latin toga *Candida*, which was a white robe worn by Roman Senators. Berkhout's taxonomy was later hailed as "the beginning of the rational systematics of the non-ascosporogenous yeasts" by prominent French mycologists Maurice Langeron and Paul Guerra [8].

Candida is an asexual, dimorphic fungus that can be found in both the human body and the environment. Due to a surge in the number of immunocompromised, elderly patients getting prolonged antibiotic and harsh cancer chemotherapy or undergoing invasive surgical operations and organ transplantation patients, candidiasis has emerged as an alarming opportunistic disease [9].

Although *Candida* spp. is found in the natural flora of the human oral, gastrointestinal, and genitourinary tracts, it can induce clinical infection if the host is weak or immunocompromised [10].

There are currently over 150 known *Candida* species. However, only 15 of these species have been isolated as infectious agents from patients. *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. guilliermondii*, *C. lusitaniae*, *C. dubliniensis*, *C. pelliculosa*, *C. kefyr*, *C. lipolytica*, *C. famata*, *C. inconspicua*, *C. famata*, and *C. rugosa* [11]. *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, and *C. krusei* account for the vast majority (> 90%) of invasive infections. Furthermore, the number of new *Candida* species isolated from clinical samples increases year after year. The main reason for this could be that clinical microbiology laboratories around the world use various commercially available identification methods to supplement traditional methods of identification [12].

The infection rate of Candida spp. has a tendency to increase with increasing age; however, it is thought that the infection rate of teenagers is relatively low because this age group of teenagers has a strong immune system and participates in few outdoor activities [13].

The number of indwelling medical devices is increasing, and Candida spp. is causing an increasing proportion of device-related infections. Candida spp. produce biofilms on synthetic materials, which aids organism adhesion to devices and makes them resistant to medical therapy. Candida infections caused by medical devices can be difficult to manage. In most cases, removing the infected device is required to cure Candida infections of medical devices. However, because the pathogenesis of Candida bloodstream infection is complicated, more research is needed to determine the role of catheter exchange in patients who have gastrointestinal tract mucositis as well as indwelling catheters. These infections have a massive medical and economic impact [14].

3.1. Candida albicans

C. albicans is the sixth most common cause of nosocomial infections *Candida* species and is thought to be the most dangerous infection. During the last few decades, there has been an increase in the predominance of non-albicans *Candida* species [9]**.** One distinguishing feature of *Candida albicans* is that it can exist in three phases: budding yeast, pseud hyphae, and hyphae. The mycelial form's plasticity is a determinant of drug resistance as well as a crucial form during the infection stage. Furthermore, *C. albicans*' transition from yeast to hypha fungi can use

hypha to evade macrophage phagocytosis. As a result, there is a greater chance of invasion causing more harm to the host tissues [15].

C. albicans colonizes mucosal surfaces asymptomatically; however, any disruption in the host environment or conditions of immune dysfunction allow *C. albicans* to proliferate and invade virtually any site in the host. This highly adaptable fungal species' ability to transition from commensal to pathogen is due to a diverse set of virulence factors. The ability to switch morphology and form biofilms are critical to *C. albicans* pathogenesis. In fact, biofilm formation on host or abiotic surfaces, such as indwelling medical devices, is associated with the majority of *C. albicans* infections, which have a high morbidity and mortality rate. Significantly, *C. albicans* biofilms are naturally resistant to antimicrobial therapy [16].

A vast spectrum of virulent factors and fitness features enable the capacity of *C. albicans* species to infect several host habitats. The capacity to morphologically transition between yeast and hyphae, the development of adhesins and invasions on the cell surface, the creation of biofilms, phenotypic exchange, and the release of hydrolytic enzymes are all virulence factors [17].

The *C. albicans* cell wall proteins, which are essential for virulence and pathogenicity, make them interesting target antigens. Als3p is a glycophosphatidylinositol cell wall protein that is unique to hyphae and is a member of the *C. albicans* agglutinin-like sequence (ALS) family. It is essential for the interaction with host cells. It is a desirable target because of how much Als3p is present on the hyphal surface. For instance, a Phase 2 clinical study for the NDV-3 vaccine, which targets the N-terminus of Als3p, has begun. The monoclonal antibodies (MAbs) 3-A5, MAb 113, and scFv3 are Als3p-specific. Additionally, by recognizing Als3p, MAb C7, MAb 3D9.3, and MAb 2G8, which were intended to detect different targets, have also offered effective protection [18].

3.2. Candida nonalbicans

Several studies have also linked the increased incidence of non-*albicans Candida* (NAC) species to lower resistance to routinely used antifungal medications. *C. parapsilosis* is frequently the second or third most common (NAC) species isolated, depending on the patient population and geographical location. Although regional epidemiological studies are available, we do not have an up-to-date picture of the global incidence of *C. parapsilosis*. It is especially dangerous because it can develop persistent biofilms on central venous catheters (CVCs) and other medically implanted devices, posing a risk to patients who have had invasive medical treatments. *C. parapsilosis* multiplies fast in total parenteral nutrition given to ICU patients, putting undernourished infants and low-birth-weight newborns [19].

C. auris is a newly discovered *Candida*/*Clavispora* clade member that was first isolated in Japan in 2009 from a female patient's ear discharge. Infections caused by *C. auris* have become a global threat in the last decade due to their rapid spread and multidrug resistance. The Centers for Disease Control and Prevention (CDC) issued a clinical alert to healthcare facilities in 2016 warning of the international emergence of *C. auris* infections with high mortality rates, and an update on *C. auris* spread throughout the USA with disinfection information and treatment recommendations in 2017.

C. auris has piqued the interest of researchers in both clinical and basic science fields since its discovery in 2009. *C. auris* has been found in more than Forty countries on six continents. Furthermore, most clinical isolates are resistant to one or more classes of antifungal drugs commonly used to treat *Candida* infections [20].

Only 85.7% and 87.5%, respectively, of the isolate's 26S rDNA D1/D2 domain and ITS region sequences matched those of *C. haemulonii*. The isolate shared phylogenetic relationships with *C. pseudohaemulonii*, *C. heveicola*, and *C. ruelliae*, according to further analysis. Additionally, the isolate's biochemical analysis revealed characteristics that set it apart from other *Candida* species, such as distinct carbon assimilation patterns and the capacity to grow at 42°C, further establishing *C. auris* as a novel *Candida* species [21].

Additionally, due to their weakened immune systems and increased mortality risk from *C. auris* infections, preterm infants and the elderly are probably more susceptible to *C. auris* infections [22]. All these factors make it easy for *C. auris* to spread in hospitals and cause recalcitrant outbreaks. They also contribute to the high mortality rates (30-60% in *C. auris* invasive infections).

The emergence of the SARS-CoV-2 pandemic has resulted in an increase in *C. auris* colonization and candidemia cases. New *C. auris* outbreaks were also reported in critically ill COVID-19 patients, and it was warned that the SARS-CoV-2 pandemic could facilitate the transmission of nosocomial pathogens such as *C. auris*. The genome encoding ATP-binding cassette and major facilitator superfamily transporter families, in addition to drug transporters, may explain *C. auris'* multidrug resistance.

Like *C. albicans*, the *C. auris* isolates have mutations at azole-resistance codons, resulting in azole resistance. Echinocandins are frequently used to treat *C. auris* infections. Although caspofungin is usually effective against biofilms formed by other *Candida* species, it has been shown to be ineffective against *C. auris* biofilms. The exact mechanism of *C.*

auris antifungal resistance remains unknown. A few studies have reported breakthrough fungaemia while on fluconazole, implying an inherent resistance to this drug [23].

C. tropicalis is an emerging pathogen with a high death rate; yet little is known about its pathogenic capability. Biofilm formation (BF) has serious clinical consequences and begins with adhesion to a substrate. The adhesion capability is primarily determined by cell surface hydrophobicity (CSH) and, later, by specific adherence owing to adhesins. The ALS family, which is involved in adhesion and BF in *C. tropicalis*, is represented in multiple CTRG genes [24]. Infections with *C. tropicalis* are frequently connected with cancer, with some studies indicating a greater incidence among individuals with hematologic disorders such as acute myeloid leukaemia. Unfortunately, mortality related with *C. tropicalis* candidemia remains high in these groups, ranging from 30 to 70%, with the elderly having the greatest rate [25].

C. krusei produces cylindrical yeast cells up to 25 m in length. They are typically shaped like long-grain rice, as opposed to the spherical or ovoid shapes of other *Candida* species. *C. krusei*, like *C. albicans*, exhibits thermodimorphism, producing hyphae when grown at 37°C and blastoconidia and pseudo hyphae when grown at lower temperatures. The colony morphology is typical of other *Candida* species, but the components of *C. krusei* are likely to be related to the importance of this structure during host interaction and because it is a target of some antifungal drugs, as discussed in the following sections. Transmission electron microscopy analysis of the *C. krusei* cell wall revealed the presence of three major layers. The outermost layer is an electron-dense layer that surrounds the cell and includes flocculent material, followed by an electron-transparent layer in the middle that appears to be composed of fluffy material and scatter granules, and an innermost electron-dense layer closer to the plasma membrane [26].

The yeast pathogen *C. glabrata* is the second most common cause of *Candida* infections. *C. glabrata* is much more closely related to *Saccharomyces cerevisiae* than *C. albicans*. This yeast appears to have recently changed its lifestyle and become a successful opportunistic pathogen [27].

C. guilliermondii is an *ascomycetous* yeast that is widely distributed in nature and is also a saprophyte in human skin and mucosal microflora. Castellani described *C. guilliermondii* as *Endomyces guilliermondii* at the beginning of the twentieth century. *C. guilliermondii* is a model organism for riboflavin (RF, vitamin B2) overproduction. *C. guilliermondii* has been frequently reported as a *Candida* agent and has been described as an emerging pathogen characterized by its proclivity to develop resistance to antifungal agents even while being treated. *C. guilliermondii* is a rare pathogen that accounts for a small percentage of all candidemia. Recent studies have determined that *C. guilliermondii* accounts for only 1-3% of all candidemia and that the majority of *C. guilliermondii* infections are associated with oncology patients.

C. dubliniensis, which shows several *C. albicans*-like traits Both microbes share key phenotypic characteristics, including the capacity to produce genuine germ tubes, attach to epithelial surfaces, release a variety of aspartic proteinases, and create chlamydospores. *C. dubliniensis* was initially isolated from human immunodeficiency virus (HIV)-positive individuals' oropharyngeal lesions [28].

C. kefyr has also been known as an emerging opportunistic pathogen. Clinical isolates are more likely of *C. kefyr* can exist mostly in the form of haploid cells as does its teleomorphic counterpart *Kluyveromyces marxianus*. Antifungal resistance might be increased by haploidy. Specifically, mutations in the genes encoding the target of anti-fungal [29].

C. lusitaniae is an opportunistic haploid yeast that has been reported as the etiological cause of infection in humans. *C. lusitaniae* is one of the members of the genus that can only form pseudo hyphae and not true hyphae. Dimorphism in fungi, such as *Candida albicans*, is linked to the expression of morphology-specific virulence factors. *Cph1*, a transcriptional regulator that controls filamentous growth; Hgc1, an essential protein for hyphal morphogenesis; and Nrg1/Tup1, transcriptional repressors that contribute to filamentation, are among the main dimorphism regulators found in *C. albicans* [30]

4. Epidemiology and virulence factors of candidiasis

Candida species have been identified as the most common cause of nosocomial infections among fungus and yeast species. Pathogenic fungi are classified as Candida species [31] reported a 207 percent increase in fungal-related sepsis cases in the United States (US) from 1979 to 2000. This trend is accompanied by the fact that fungal infections are common in certain high-risk individuals, such as patients with critical or terminal diseases, neutropenic people, or people who have had organ transplants. When the mucosal microbiota and host immunity are disrupted, *Candida* spp. shift from commensalism to opportunism, which is associated with the induction of key virulence factors [32]**.**

Invasive *Candida* infection (ICI) is a severe disease with an attributable mortality rate in children ranging from 20% to 30%, and a mortality rate in children with ICI ranging from 16% to 31%. *Candida* is either the second, third, or fourth causative agent of sepsis in hospitalized children, following coagulase negative *Staphylococci, enterococci, and S. aureus*, depending on the study. *Candida* spp. colonization occurs in roughly 70% of paediatric patients in the paediatric intensive care unit (PICU). Small children are especially vulnerable to colonization, accordingly the incidence of candidemia in the PICU was 3.5 per 1,000 admissions [4].

4.1. Polymorphism

Dimorphism refers to the transition between yeast and hyphal growth forms, and it has been proposed that both growth forms are important for pathogenicity. It has been demonstrated that the hyphal form is more invasive than the yeast form. The smaller yeast form, on the other hand, is thought to be the form most involved in dissemination *C. albicans* is a polymorphic fungus that can grow as ovoid-shaped budding yeast, elongated ellipsoid cells with septal constrictions (pseudo-hyphae), or true hyphae with parallel walls. White and opaque cells formed during switching are another morphology, as are chlamydospores, which are thick-walled spore-like structures. While yeast and true hyphae are frequently observed during infection and serve distinct functions, the role of pseudo-hyphae and switching *in vivo* remains unknown, and chlamydospores have not been found in patient samples [33].

C. albicans strains with the ability to acquire exclusively hyphal, pseudo-hyphal, or yeast forms can induce differential expression of leukocyte adhesion molecules by endothelial cells. Several lines of evidence also suggest that *C. albicans* morphogenetic status influences the secretory cytokine profiles of dendritic cells and macrophages in response to infection with this organism. *C. albicans* in all three morphogenetic forms is commonly found in the oral mucosa. Because oral epithelial cells are the first line of defense against oral *Candida* infection, we investigated their interactions with the three different morphotypes of this pathogenic organism.

Yeast, pseudo-hyphal, and hyphal organisms' ability to adhere to and lyse oral epithelial cells, as well as their ability to induce a proinflammatory cytokine response were compared. Proinflammatory cytokines produced by oral epithelial cells in response to fungal infection are expected to play a significant role in the initiation of the inflammatory response and possible activation of lysis of the invading microorganism by immune and nonimmune effector cells. The central hypothesis of this study is that true hyphae formation is required for organisms to adhere to oral epithelial cells and trigger a proinflammatory cytokine response. To test this hypothesis, we compared *C. albicans* strains that differ in their ability to naturally undergo hyphal transformation in response to environmental pressure [34].

4.2. Expression of adhesion and invasion of the cell surface

The understanding of the role of *Candida* virulence factors that mediate their pathogen success, such as membrane and cell wall (CW) barriers, dimorphism, biofilm formation, signal transduction pathway, stress tolerance proteins, hydrolytic enzymes (e.g., proteases, lipases, haemolysins), and toxin production. The virulence of clinically important *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. krusei* was extensively studied. *C. albicans* has an advantage over other less related *Candida* species as a human commensal and pathogen due to the white-opaque transition in the mating-type locus MTL-homozygous cells. It discussed how *Candida* ergosterol biosynthesis genes contribute to cellular stress and are required for *Candida* pathogenesis in both invasive and superficial infections. Hydrolases linked to CW play a role in host pathogen interactions. Adhesins play an important role in candidiasis virulence by facilitating colonization and biofilm formation. Calcineurin is involved in membrane stress, CW stress, and virulence. *Candida* lysin, a hyphae specific toxin, invades mucosal cells, allowing fungal invasion into deeper tissues. In candidiasis, expression of this protein promotes resistance to neutrophil killing. The virulence factors stimulate the immune system by activating dendric cells and promoting T cell infiltration and activation. In *Candida* infections, targeting virulence factors can reduce the risk of resistance development [35].

The fungal cell wall is a highly dynamic structure that provides protection, regulates communication with the extracellular environment, maintains cell integrity, and serves as a molecular scaffold for virulence factors to be displayed. This structure contains pathogen-associated molecular patterns (PAMPs), which are recognized by the immune system via PRRs, the majority of which are found on the cell surface of immune cells. Chitin, -1,3- and -1,6-glucans, and N-linked and O-linked mannans are the most common PAMPs found in *Candida* species like *C. guilliermondii*. Human peripheral blood mononuclear cells (PBMCs) are frequently used to assess pathogen-host interactions in various fungal species because they can produce different types of cytokines when PRRs are activated by PAMPs. Although the cell walls of different *Candida* species are similar, some

differences may affect their interactions with innate immunity components [30].

The first event in *Candida* infection is the organism's adherence to host and/or medical-device surfaces, which frequently results in the formation of biofilms. Thus, adhesion is a critical step in the infection process, and its strength is determined by microbial, host, and abiotic surface properties such as cell-surface hydrophobicity and cell-wall composition. The yeast cell wall is the site of microorganism-host physicochemical interactions [36]. *Candida* spp. can develop biofilms on the surfaces of medical equipment, which increases candidemia and antifungal resistance in connection with catheter insertion. The capacity to form biofilms and the level of virulence are positively correlated. The family of glycosylated proteins known as the agglutinin-like sequence (ALS) has three characteristics in common: a conserved 5' domain, a central domain with 108 bps tandem repeats, and a serine- and threonine-rich 3' domain. These proteins are homologous to -agglutinin, which is necessary for Saccharomyces cerevisiae cell-cell recognition during mating. Human buccal epithelial cells (HBEC) and fibronectin are the targets of Als1p and Als5p (Ala1p), which act as adhesins, respectively. Als1p is crucial for the early stage adherence of the organism to the oral mucosa [37].

4.3. Biofilm formation

Candida produces biofilms that are three-dimensional structures made up of a community of core microbial cells (single or mixed species) that are attached to host tissue or abiotic surfaces and immersed in an extracellular polysaccharide material (EPS) that protects the microbes (Figure 1). In recent decades, research in the topic of microbial biofilms has gathered steam, and new scientific information has altered our perceptions of how microbes live. Although microorganisms have typically been studied in free-floating (planktonic) cultures or colonies formed on the surfaces of nutrient agar culture media, it is now widely agreed that biofilms are the preferred and most likely "natural" development condition for most microbes [17].

The mixture of morphological forms found in *C. albicans* biofilms is one of their distinguishing characteristics. Scanning electron microscopy was used to examine biofilm development on catheter discs, which revealed that initial attachment of yeast cells was followed by germ-tube formation after 3-6 hours. After 48 hours of incubation, fully mature biofilms were formed, consisting of a dense network of yeasts, hyphae, and pseudo-hyphae. When the organism was grown in, no hyphal forms were seen [24].

According to speculations, creating a biofilm has ecological benefits such as nutrient availability, metabolic cooperation, and the acquisition of new genetic traits. Biofilms are notoriously difficult to eradicate and are the source of many recalcitrant infections. As a result, the mechanisms by which *Candida* biofilms resist the functions of antifungal agents are poorly understood. Antimicrobial resistance in bacterial biofilms has been attributed to factors such as restricted antimicrobial penetration caused by the exopolymeric material (EP) [38]. These characteristics are influenced by several host and *Candida*-derived variables, including: I physiological conditions, such as pH and oxygen concentration; (ii) fluid flow at the infection site, which influences nutrient exchange and impacts the biofilm's structural integrity; (iii) available nutrients in the growth media, such as sugars, lipids, and serum; and (iv) the material on which the biofilm grows (silicone, latex, and rubber are commonly used in medical devices) [39].

4.4. Penetration and coaggregation

By extracellular neutralization and acid protease of *C. albicans*, the penetration that takes place can disrupt the epithelial surface, giving *C. albicans* a chance to adhere. *C. albicans* sticks to the mucosal surface and competes with other saprophytic commensal microorganisms in the mouth for nutrients. If the microflora in a particular area is disturbed, *C. albicans* will develop into an infectious, unstoppable growth [40].

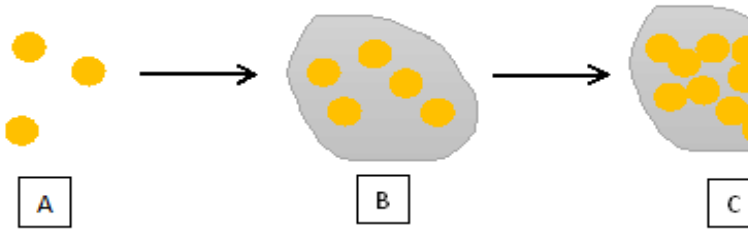

Figure 1: Steps of bacterial biofilm formation. A, attachment to substratum; B, cells adhesion; C, proliferation, growth, and maturation; D, dispersion.

Coaggregation has been observed between some *Candida* species and other oral microorganisms, but the extent of this coaggregation is dependent on growth conditions such as temperature. These interspecies interactions may be important in the microbial colonization that contributes to the progression of oral diseases. It has been proposed that the initial interspecies association is followed by a tight adhesion-receptor interaction mediated by a mannoprotein in *C. albicans* [41].

4.5. Secretion of hydrolytic enzymes

Several hydrolytic enzymes, such as secreted aspartyl proteases (SAPs), lipases (LIPs), and phospholipases, can be produced and secreted by *Candida species*. The pathogenicity of *Candida*, including adhesion, cell damage, and the invasion of host tissues, is closely correlated with the activity of these enzymes. By producing SAPs, *Candida* cells hope to weaken the host's immune system and structural defense proteins, which will make it easier for them to invade and colonize the host tissue [39]. The Sap family is thought to consist of ten members, each of which encodes the Sap1-Sap10 protein. Sap1-8 genes code for secretory proteases, whereas Sap9 and Sap10 code for membrane-anchored proteases. According to research, Sap is an important virulence factor of *Candida albicans* and is required for adhesion, invasion, and pathogenicity. Sap4 and Sap5 expressions are linked to mycelial formation, which can promote hyphal formation. Sap9 and Sap10 enzymes promote biofilm formation and help *Candida* spp. maintain cell surface integrity. Because *C. albicans* frequently exists in the form of biofilms, Saps expression results in the formation of *C. albicans* biofilms and increases their pathogenicity because of the diversity of Saps in host tissues, different nitrogen sources can be used in host development [42]. A-D are the four phospholipases that are secreted (PLA, PLB, PLC and PLD). Because these enzymes hydrolyze one or more ester linkages of glycerophospholipids on the host cell membrane, their activity is extremely high during tissue damage. Additionally, through the production of haemolysin, iron chelators (siderophores), and iron-transport proteins, *C. albicans* is able to obtain elemental iron from host tissues, which is then used by the fungus for metabolism, growth, and the establishment of infection in humans [43]. Phospholipase A catalyzes the lipolytic removal of one of glycerol's two esterified fatty acid moieties. Lysolecithin is a toxic component of many snake and bee venoms. It can destroy erythrocyte membranes, causing hemolysis. Phospholipase A is made up of two isoenzymes, phospholipase A1 and phospholipase A2, which differ in which fatty acid they remove from the glyceride. The outer fatty acid moiety is removed by phospholipase A1, while the inner fatty acid moiety is removed by phospholipase A2. Phospholipase B removes both fatty acids at the same time. In this context, the toxic intermediate product lysolecithin is not formed. Glyceryl phosphorylcholine and two free fatty acids are the reaction products. Phospholipase C breaks the phosphatidylcholine carbon-phosphate bond, releasing phosphorylcholine and diacylglyceride. Furthermore, phospholipase C is involved in signal transduction. Catecholamines (adrenaline, noradrenaline) and other hormones and neurotransmitters, such as vasopressin, angiotensin, serotonin, and acetylcholine, can activate phospholipase C via -1-receptors. Phosphatidylinositol-biphosphate (PIP2) is broken down by activated phospholipase C into the molecules inositol-triphosphate (IP3) and diacylglyceride. Phospholipase D degrades phosphatidylcholine to produce phosphatidic acid [44]. Esterases and lipases are distinguished by their ability to catalyze the hydrolysis of ester bonds in mono-, di-, and triacylglycerols, as well as phospholipids. However, they differ in their ability to act on soluble substrates. Lipases hydrolyze ester bonds at the interface between the insoluble triacylglycerol phase and the aqueous phase in which the enzyme is dissolved, whereas esterases act on soluble substrates. Werner discovered extracellular lipase activity in pathogenic *Candida* species, and Tsuboi classified a secreted esterase as a monoester hydrolase. Sheridan and Ratledge discovered that *C. albicans* can grow in media containing only triolein as a carbon source, implying that other lipolytic enzymes must exist. One of these proteins was identified as the gene product of *LIP1* [45].

5. Systems biology of host-*Candida* interactions

The organs of the immune system, which protects against diseases, are found in the body. It is essential for maintaining health and pathogenesis. It also shields the body from harmful substances, germs, and abnormal cell growth (neoplasm). White blood cells, which can travel throughout the body via blood vessels, are an important component of the immune system. The body exchanges cells and fluids between blood and lymphatic vessels and activates the lymphatic system to monitor for invading microbes. Lymphatic vessels transport lymph. Each lymph node has specialized compartments where antigens can be encountered. Immune cells and foreign particles enter the lymph nodes via the incoming lymphatic vessels. They are transported to tissues throughout the body once they enter the bloodstream. They complete the cycle by patrolling for foreign antigens everywhere and gradually drifting back into the lymphatic system. Immune cells congregate, work, and serve to

confront antigens in lymph nodes and spleen compartments [46].

It is especially significant that the human immune system can distinguish between the commensal colonization phase and the pathogenic invasion phase. To protect the host from *Candida* infection, a strong immune response is required. This immune response is divided into physical barriers and mucosal immune barriers. *Candida* has devised numerous strategies to evade or undermine the host immune system's antimicrobial defense responses. These strategies may allow the fungus to control the host immune response, cross tissue barriers, and spread throughout the human body. *Candida* is stressed by the host and its infected tissue environment, which includes nutrient restriction, temperature, and pH stress. Furthermore, as the first line of defense against systemic fungal infections, the host immune system responds with an innate immune attack. That line of defense is primarily based on humoral complement actions, antimicrobial peptides, and the cellular response mediated by phagocytes, particularly neutrophils and macrophages [47]. Many medically significant fungi invade normally nonphagocytic host cells, such as endothelial and epithelial cells. Host cell invasion is a two-step process that begins with adherence and progresses to invasion. Induced endocytosis and active penetration are the two general mechanisms of host cell invasion. Furthermore, fungi can cross epithelial or endothelial cell barriers via proteolytic degradation of intercellular tight junctions or via a Trojan horse mechanism in which they are transported by leukocytes. Although *Candida* and *Cryptococcus neoformans* have been used to study these host cell invasion mechanisms [48].

After the fungal pathogen is internalized, the phagolysosome is formed inside the phagocytic cells to destroy the overwhelmed microorganism. The organelle contains a damaging and highly toxic internal phagolysosome for pathogen elimination, which includes low pH, hydrolytic enzymes, potent reactive oxygen and nitrogen species (DNA damage), pathogen proteins and lipids. Many antioxidant defense enzymes (catalase, reductase, superoxide dismutase, thioredoxin- and glutathione-dependent peroxidases) have been developed by trapped microorganisms to survive the oxidative burst and escape from the phagolysosome. *C. albicans* and *C.* glabrata only have one catalase gene (*CTA1*). Because both stress and non-fermentable carbon sources can induce *CTA1* expression, it is suggested that its regulation is a combination of two catalase genes found in *S. cerevisiae* that suggests a role in peroxide stress resistance in the host environment [49].

6. Types of Sample Infection

Candida spp. Are prevalent commensal organisms in the skin and gut microbiota, and changes in the cutaneous and gastrointestinal barriers (such as gastrointestinal perforation) promote invasive illness [32].

C. albicans is a kind of yeast. This commensal organism is found in the gastrointestinal, upper respiratory, and genitourinary tracts, and can cause localized infections of the skin and mucous membranes, as well as a life-threatening systemic infection with multisystem organ failure, most commonly in patients with underlying immunosuppressive disorders [50] .

Candiduria may be a marker for disseminated candidemia, which has a crude mortality rate of 30–40%. Candiduria is defined as 10^4-10^5 CFU/ml of yeasts detected in urine, whereas a *Candida* urinary tract infection (UTI) is primarily defined by $< 10^5$ CFU/ml detected, which usually corresponds to the patient's symptoms [51].

6.1. Candidemia

Candidemia was defined as at least one positive blood culture for *Candida* species in the presence of fungal infection symptoms as defined by the Infectious Disease Society of America (IDSA). *Candida* species are the fourth most common cause of nosocomial bloodstream infections (BSI), as well as the third most common cause of BSI in intensive care units (ICU). *Candida* BSI (candidemia) has a high morbidity and mortality rate. *Candida* species can cause a wide range of complications, including mucocutaneous infections, endocarditis, intravascular device infections, bone and joint infections, meningitis, and death. Despite antifungal prophylaxis and definitive therapy, the mortality rate in this life-threatening invasive fungal function is high, particularly in critically ill patients [52].

Persistent candidemia (PC) is defined as the isolation of the same *Candida* species from a positive blood culture for 5 days after the start of antifungal therapy. It is becoming more widely recognized as a complication of candidemia. Previous research found that 8-15% of patients with candidemia developed PC; however, PC was associated with significant mortality, ranging from 20-50%. According to some studies, PC is linked to *Candida* species biofilm production and antifungal resistance. Underlying disease status (e.g., haematological malignancies), low serum drug levels, endovascular infection, deep-tissue abscesses, metastatic infection foci, ineffective empirical treatment, infections associated with prosthetic materials, CVC-related infection, total parenteral nutrition, hemodialysis, and abdominal

surgery were the other major risk factors for PC [53] .

Candidemia is more common in neonates and young infants than in adults, and it is linked to better clinical outcomes but also higher inpatient costs. *Candida* spp. isolation from blood should never be regarded as a contaminant and should prompt an immediate search for its source. *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, and *C. krusei* account for more than 90% of all cases of candidemia in pediatric and adult patients. Since the 1990s, a global shift in the species responsible for candidemia has been observed, with a decrease in infections caused by *C. albicans* and an increase in infections caused by the remaining species, referred to collectively herein as non-albicans *Candida* species (NAC). This shift has been attributed in part to the use of azoles in the prevention and treatment of *Candida* infections [54].

Disseminated candidiasis occurs only when *Candida* evades the immune system, penetrates vascular tissues, and enters the bloodstream. There are two ways for substances to enter the blood: 1.Natural routes (via penetration of epithelial cells at mucosal cell surfaces) 2.Artificial routes (via implantation of medical devices, surgery, and depletion of the natural microbiota by treatment with antibiotics) [55]. Haematogenous *Candida* meningoencephalitis (HCME) is caused by candidemia that spreads via the bloodstream to the brain. central nervous system CNS candidiasis in newborns and children with substantial underlying illness or a cerebrospinal fluid (CSF) shunt has been reported in the pediatric population. In comparison to adults, neonates and immunocompromised children are disproportionately affected by HCME. High rates of mortality and neurodevelopmental problems have been linked to the illness [56].

The epidemiology of candidemia is shifting, with an increase in episodes caused by non-albicans *Candida* species, possibly because of fluconazole prophylaxis in certain individuals. The relevance of infections caused by non-albicans species is underscored by the difficulties associated with treatment options that are exacerbated by innate or acquired antifungal resistance. *C. krusei* and *C. glabrata*, for example, show azole resistance that is both intrinsic and acquired, whereas *C. parapsilosis* and *C. lusitaniae* have decreased sensitivity to echinocandins and amphotericin B, respectively [57].

6.2. Fungal urinary tract infection (Candiduria)

Candida species in the urine (Candiduria) is a rather common clinical finding. *Candida* exists as saprophytes in physiological settings, colonizing mucosal surfaces and external genitalia of both genders, but they are prevalent near the urethral meatus of healthy women of childbearing age. *Candida* species can be discovered in detectable concentrations in voided urine specimens from healthy people in about 1% of instances. In primary care, they represent 5% of all positive urine culture results, and in tertiary care hospitals and specialized centers, they account for 10% or more. *Candida* species in urine (Candiduria) is a common clinical finding, especially in hospitalized patients, with some publications claiming that as many as 90% of patients with *Candida* urinary tract infections (UTIs) were hospitalized and had a urinary catheter [51].

Candida spp. invades the urinary system primarily through two different mechanisms: ascending through the urethra and bladder (retrograde infection) and hematogenous spreading to the kidneys (antegrade infection). The likelihood of an ascending infection in the upper urinary tract rises with blockage, diabetes, or reflux [58].

Although *C. albicans* is the most encountered *Candida* species in urinary tract infections, other species such as *glabrata*, *tropicalis*, *parapsilosis*, *lusitaniae*, and *guilliermondii* have also been identified as pathogens. *C. auris* has recently become very popular. And has been identified as the causative agent in UTIs all over the world [59].

Except in neutropenic patients, very low-birth-weight infants, and patients undergoing urologic procedures, the presence of *Candida* species in urine does not warrant antifungal therapy in asymptomatic patients. Fluconazole is the preferred treatment for symptomatic infections because it achieves high urinary levels. The other azole antifungals and echinocandins do not reach adequate urine concentrations. If fluconazole cannot be used due to resistance, allergy, or failure, amphotericin B deoxycholate is an alternative antifungal agent [58].

6.3. Candida colonization in the respiratory tract

Candida spp. contamination is frequent in mechanically ventilated ICU patients' bronchial samples. It affects roughly 30% of patients who have been on mechanical ventilation (MV) for more than 48 hours and 50% of those who have a clinical suspicion of ventilator-associated pneumonia (VAP). Recovery of *Candida* spp. from the respiratory tract is related to greater MV, ICU, and hospital stay, as well as a worse prognosis. Even after adjusting for immunological function, bronchial colonization with *Candida* spp. was not linked with ventilator-associated pneumonia (VAP) in patients who had been on mechanical ventilation for more than 4 days and had multiple organ failure [60].

Although the fungus *C. albicans* is considered a normal part of the human oral and gastrointestinal microbiome, lower respiratory tract colonization in mechanically ventilated immunocompetent patients has been linked to a longer duration of mechanical ventilation, a higher risk of ventilator-associated pneumonia, and a longer ICU and hospital stay.

Individuals with respiratory tract colonization had a higher death rate in a short prospective investigation of immunocompromised patients. Sputum, bronchoalveolar lavage (BAL) fluid, bronchial brushings, washings, and biopsies, endotracheal aspirates, and pleural fluid, as well as swabs from the mouth, oropharynx, throat, or sinuses, were among the respiratory cultures examined [61].

Primary *C. pneumonia* is an uncommon illness that arises following aspiration of oropharyngeal debris. However, establishing a relationship between *Candida* species and a pneumonic infiltrate is difficult due to their frequent colonization of the respiratory system [56].

Candida esophagitis (CE) is an esophageal fungal infection caused by the *Candida* species. It is one of the most common esophageal infections and is classified as an opportunistic infection associated with HIV infection. CE prevalence ranges from 0.3-10.5%, discovered that patients with end-stage renal disease had a significantly higher prevalence of oral fungal infection (ESRD). Furthermore, lymphocyte numbers and the CD4/CD8 ratio are reduced in ESRD patients. In fact, in the context of chronic renal failure, both the quantity and quality of T-cell activation are impaired. Furthermore, host responses to fungal infections and candidiasis at the gastrointestinal surface rely on cellular mechanisms. T-lymphocyte dysfunction and a decrease in their number are common in patients with mycotic diseases. Reduced T-lymphocyte numbers and ratios of T-helper to T-suppressor cells are critical for explaining decreased IgA production and enhanced adhesion of fungal cells to host cell surfaces [62] .

6.4. Cutaneous Candidiasis

Cutaneous candidiasis is a common skin infection that affects people of all ages, accounting for around 1% of all outpatients 1 and 7% of all inpatient dermatological clinic visits. *Candida* can cause skin illness on its own or because of other skin conditions such as atopic dermatitis, psoriasis, or existing diaper dermatitis. Intertrigo, cheilitis, diaper dermatitis, and interdigital candidiasis are the most common presentations, however they can affect any part of the body. *Candida* species, with *C. albicans* being the most prevalent cause of human infections, might be to blame [63] The burn wound is an ideal environment for opportunistic colonization and infection by bacteria and fungi. The presence of opportunistic fungal species is aided by a large wound surface, impaired local immunity, and broad-spectrum antibiotic therapy. As a result, according to data from burn centers around the world, the incidence of fungal burn wound infections ranges between 6.3 and 44%, with the majority occurring in patients with third-degree burns [64].

Burn patients are at high risk of infection, and it is estimated that infection accounts for 75% of all deaths following burns. As a result, it is critical for a burn institution to identify its unique pattern of burn wound microbial colonization, as well as time-related changes in predominant flora and antimicrobial resistance. Organisms are found in the patient's own endogenous (normal) flora, as well as in the environment and on healthcare personnel. Burn unit overcrowding is a major source of cross infection. Exogenous organisms found in hospitals are more resistant to antimicrobial agents than endogenous organisms. Gram-positive, Gram-negative, and fungal organisms are among the organisms associated with infection in burn patients [65]. Cutaneous candidiasis can cause wound healing to be delayed, particularly in surgical wounds treated with antibacterial ointments and occlusive dressings [66].

Cutaneous congenital candidiasis (CCC) is an uncommon illness characterized by invasive fungal infection of the epidermis and dermis, which primarily affects premature newborns. Maternal vaginal candidiasis is present in half of the cases, however invasive candidiasis during pregnancy or the peripartum period is rare [67].

In newborns weighing more than 1000 g, the most typical CCC presentation was a widespread eruption of erythematous macules, papules, and/or pustules that occasionally progressed to include vesicles and bullae. Premature newborns with extremely low birth weights who weighed less than 1000 g frequently had widespread desquamating and/or erosive dermatitis For newborns with burn like dermatitis caused by *Candida* spp. or positive blood, urine, and/or cerebrospinal fluid cultures, systemic antifungal medication is advised [68].

6.5. Faecal Candida

Many microbes invade the gastrointestinal (GI) tract in a symbiotic relationship, including bacteria, fungus, viruses, and parasites. To maintain homeostasis, these microorganisms interact dynamically with one another and with their host. Dysbiosis, or a change in the gut microbiota's equilibrium, has been linked to a variety of host disorders, such as inflammatory bowel disease, metabolic syndrome, cancer, and infection. Gut microorganisms serve a critical function in preventing colonization and protecting the host against pathogenic germ invasion [69].

Cultivable fungi in feces range from 10^2 and 10^6 CFU/g, constituting a minor component of gut microbiota, and their genes account for less than 0.1% of the entire microbial metagenome. Although several fungal species are found in the normal GIT, their potential role in host health has only been investigated in part [70]. For many years, the role of *Candida* in antibiotic-associated diarrhea (AAD)

has been debated; the presence of small numbers of *Candida* organisms in stool has thus been considered normal, and thus non-pathogenic. Increased *Candida* counts have been linked to diarrhea development in antibiotic-treated patients. *Candida* produces two major virulence factors, namely secreted aspartyl proteinases (Saps) and phospholipases. Saps were produced by all *C. albicans* strains obtained from AAD patients and controls, with no significant difference in the amount produced between the two groups. Furthermore, phospholipase production by faecal *Candida* isolates from AAD patients did not differ from that of controls. These studies indicate that the major fungal virulence factors, Saps and phospholipase, are not responsible for AAD in adult [71].

C. albicans is known to produce aspartyl proteinases, and expression of the secreted aspartyl proteinases (SAP2) gene is primarily responsible for the proteolytic activity seen in most strains developing in the yeast form *in vitro*. Additionally, SAPs have proteolytic activity in the gastrointestinal tract; this has been shown in studies on oral candidiasis and the breakdown of gastrointestinal mucus by SAPs. For a variety of enteropathogens, including *Vibrio cholerae, Shigella* species, *Helicobacter pylori*, and *Yersinia enterocolitica*, the degradation of gastrointestinal mucin by enzymes has been identified as a virulence determinant Mucin degradation by SAP2 may enable *C. albicans*, which colonizes mucosal surfaces, to get closer to epithelial cells and/or modify cellular surfaces. Children with acute and chronic diarrhea have higher levels of secretory *Candida* acid proteinase than healthy controls [72].

7. Antifungal susceptibility testing of *Candida* species

The treatment strategy for invasive Candidiasis is determined by the patient's immune status, the location of the infection, and the severity of the infection. Removal of infected medical devices and antifungal agents, in addition to adequate source control, have been important therapeutic tools for invasive *Candida* infections. Polyenes, azoles, echinocandins, and 5 flucytosine are currently available as antifungal drugs with activity against *Candida* species (5FC) [73].

Multidrug resistant (MDR) was defined as acquired resistance to at least one antimicrobial agent from three or more antimicrobial categories. Extensively drug resistant (XDR) was defined as resistance to at least one antimicrobial agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two antimicrobial categories). Pan drug resistance (PDR) was defined as nonsusceptibility to all antimicrobial agents [74]. These definitions cannot be directly applied to *Candida* resistance. The main reason for this is that only four drug classes are available for systemic treatment of *Candida* infections: azoles (fluconazole, itraconazole, isavuconazole, posaconazole, and voriconazole), polyenes (conventional amphotericin B and its lipid formulations), echinocandins (anidulafungin, caspofungin, and micafungin), and flucytosine.

Only the first three drug classes have been approved for monotherapy against *Candida* infections, and only fluconazole and echinocandins are recommended as first-line agents for invasive candidiasis. In light of this, and in the absence of a standard definition for MDR *Candida*, we defined MDR as an isolate resistant to one agent in two drug classes and XDR as an isolate resistant to one agent in three drug classes [75].

In terms of antimicrobial resistance, organisms in biofilms behave differently than cells in suspension. Antimicrobial agents are highly resistant to bacteria and *Candida* cells in biofilms [14].

In immunocompetent patients, antibody detection is effective for infection diagnosis, especially for dimorphic fungi. There are several procedures for direct and indirect serological testing available, however the interpretation of results can be complicated by a number of circumstances. The interaction between the host, the microorganism, and the laboratory environment may have an impact on test results. A logical initial step is to collect blood biomarkers (galactomannan (GM) and -d-glucan (BDG)) and/or bronchoalveolar lavage (BAL) specimens for fungal staining, culture, and antigen detection. Knowing the fungal pathogen will help guide antifungal treatment, dosage, and duration [76].

7.1. Treatment by different antifungal type and mechanism of action

Several antifungal compounds were discovered from virous origin against *C. albicans* or *Candida* spp. through different mechanisms of action via specific targets (Table 1).

The five main groups of antifungal agents—azoles, echinocandins, polyenes, allylamines, and nucleoside analogues—are often used to treat fungus infections. The most used antifungal medication is the azole fluconazole, which has a low host toxicity, a high water solubility, and a high bioavailability [77].

Polyene antifungals have a macrolide ring of 26-28 carbons with polyunsaturations that is closed by an ester or lactone, with hydroxyl groups conferring the amphipathic character of the molecule. More than 100 different compounds classified as heptaenes or tetraens have been described, but amphotericin B and nystatin are the most commonly used [78]. Amphotericin B (AmB)

is a polyene antifungal agent discovered in 1955 in *Streptomyces nodosus*. AmB is a cyclic molecule with hydrophilic polyhydroxyl and hydrophobic polyene domains. The hydrophobic polyene domain promotes insertion and binding to fungal lipid bilayer membranes. AmB monomers nucleate to form an AmB multimeric pore in the presence of fungal membrane ergosterol, with the lipophilic polyene chains arrayed on the outside of the multimer in contact [79]. Nystatin is a polyene macrolide antibiotic produced by *Streptomyces noursei* ATCC 11455 that is used in human therapy to treat fungal infections on the skin. Nystatin has a similar structure to AmB, the only polyene macrolide currently approved for the treatment of invasive mycoses in humans. In its polyene region, AmB has seven conjugated double bonds, whereas Nystatin has four. This distinction explains AmB's significantly higher antifungal activity, which is presumably due to a more efficient hydrophobic interaction with membrane sterols [80].

The allylamine clinical antifungals naftifine and terbinafine inhibit ergosterol biosynthesis at the point of squalene epoxidation in a variety of pathogenic fungi. Filamentous growth is especially vulnerable to this inhibition, with cell death occurring at drug concentrations that only partially inhibit ergosterol biosynthesis. *Candida* species are more susceptible. The primary target of allylamines is squalene epoxidase, a membrane-bound enzyme. The *C. albicans* epoxidase is highly sensitive to the drugs, and inhibition is unaffected by enzyme solubilization. Squalene epoxidase from mammalian liver is orders of magnitude less sensitive to allylamines. This selectivity appears to be due in part to drug interactions with soluble cytoplasm components, but primarily to intrinsic differences between the respective epoxidase enzymes [81] .

Azoles inhibit 14-sterol demethylase, an enzyme involved in the manufacture of the fungal membrane sterol ergosterol, which is encoded by the ERG11 gene. Because some NAC species are naturally resistant to azoles, their usage is likely a role in the increased frequency of infections caused by these NAC species. Furthermore, several investigations have shown that *Candida* can develop high-level resistance to azole antifungals [25].

Voriconazole, a second-generation antifungal drug with a broad spectrum of activity, is extensively used for the prevention and treatment of invasive fungal infections. It is suggested for the treatment of invasive aspergillosis, candidemia, and disseminated infections caused by *Candida* spp., as well as esophageal candidiasis. Voriconazole inhibits the fungal cytochrome P450 (CYP) enzyme lanosterol 14-demethylase, reducing ergosterol production, which is an essential component of fungal cell membranes. It is metabolized in the liver by CYP2C19, as well as to a lesser extent by CYP3A4 and CYP2C9. It is mostly eliminated in urine (80%) [82].

Echinocandins have good in vitro activity against most *non-C. albicans* spp. and are recommended as first-line agents for candidemia treatment. The echinocandins (caspofungin, micafungin, and anidulafungin) have fungicidal activity against *Candida* spp., including those with intrinsic resistance to fluconazole or dose-dependent susceptibility (*C. krusei* and *C. glabrata*, respectively) or intrinsic resistance to AmB (*C. lusitaniae*). The echinocandins work by non-competitively inhibiting d-glucan synthase, the enzyme responsible for the biosynthesis of 1,3-d-glucan, a major glucan component of the *Candida* cell wall. FKS1p (encoded by the genes FKS1, FKS2, and FKS3) and Rho1p. are two subunits of glucan synthase, FKS1p is a catalytic subunit of the glucan synthase enzyme, and Rho1p is a regulatory protein involved in a variety of cellular processes, including 1,3-d-glucan biosynthesis. Most species die when echinocandins inhibit glucan synthase, resulting in glucan depletion, osmotic instability, cell lyses, and death [83].

Natural compounds with pyrimidine skeletons, such as vitamin B1, and nucleotide bases, are important in life science research. Pyrimidine derivatives have piqued the interest of researchers due to their diverse biological activities. Rashad, for example, synthesized a series of 4-hydrazinopyrimidine derivatives with antimicrobial activity *in vitro*. A novel series of di-aryl pyrimidine and di-hydrobenzyl oxopyrimidine hybrids with potent and broad-spectrum anti-HIV-1 activity in cellular and enzyme assays were described. Different classes of pyrimidine derivatives were synthesized and tested for antitumor activity to provide drug discovery *Candida* Pyrimidine derivatives have also occupied a prominent position in the field of agrochemicals due to their important properties as agricultural fungicides. Commercial pyrimidine fungicides such as azoxystrobin, cyprodinil, pyrimethanil, and diflumetorim have been used in agriculture to date [84].

In terms of antifungal chemoprophylaxis, empirical, preventive, and specific treatment, there are no significant differences between children and adults. Antifungal techniques for children, on the other hand, are limited since a number of antifungal substances are either not permitted for children or have uncertain pediatric dosages [3] .

Table (1) Antifungal compounds from different origins affecting *C. albicans* or *Candida* spp

Origin	Compound	Target	Mode of action
Chemicals	Rezafungin (CD101)	β-d-glucan	β-d-glucan synthase inhibition
	Ibrexafungerp (SCY-078)	β-d-glucan	β-glucan synthase inhibition
	VT-1161	Ergosterol	Specific for fungal Cyp51
	Fosmanogepix (APX001]	Glycosyl phosphatidylinositol	GPI biosynthesis inhibition
	Aureobasidin A	Inositol phosphorylceramide synthase	Sphingolipids biosynthesis inhibition
	Efungumab (or Mycograb)	HSP90	Antibody binds to fungal HSP90
	Geldanamycin-like agents	HSP90	HSP90 inhibition
	AR-12	Probably blocks fungal acetyl-CoA synthetase 1	Downregulation of chaperone proteins
	T – 2307	Mitochondrial membrane potential	Respiratory chain complexes inhibition
	VL-2397 (ASP2397)	Unknown	Unknown, but taken up by Sitl
Medications	Rifampin	RNA polymerase	Enhance the antifungal activity
	Verapamil	Calcium channel	Enhance the antifungal activity
Peptides	Lysozyme	Secreted aspartic protease (SAP)	Reduces SAP activity and secretion
	Lactoferrin (hl.f)	Antimicrobial activity	Production of cationic antimicrobial peptide lactoferricin
	Human b-defensins (HBD)	Cell membrane	Increases membrane permeability
	Histatin-5	Non-lytic ATP efflux	Inhibition of adhesion
	Cathelicidins	Cell membrane	Increases membrane permeability
Plant	*Scutellaria aicalensis* (Flavonoid baicalein)	Unknown	Induces apoptosis in *C. albicans*
	Cymbopogon nardus (Essential oils)	Unknown	Inhibits hyphal growth in *C. albicans*
	Artemisia judaica (Essential oil)	Germination	Inhibits the formation of germination tube and biofilms in *C. albicans*
	Thymol (2-isopropyl-5-methylphenol)	Ergosterol	Binds to ergosterol in the membrane resulting in cell death
	Carvacrol (Phenolic monoterpenoid)	Cell membrane	Alters cellular cytoplasmic membrane and induces apoptosis

7.2. Resistant mechanism of antifungal

Antifungal resistance among *Candida* species, like antibiotic resistance in bacterial infections, poses a serious threat to global public health. According to the US Centers for Disease Control and Prevention (CDC) 2019 report on the threat of antibiotic resistance, drug resistant *Candida* sp. causes more than 34,000 cases and 1700 deaths each year. Furthermore, , 323 cases of multidrug-resistant *Candida* auris infection were reported [73].

Antifungal resistance is a growing concern across the world, complicating the selection of effective antifungal medication. *Candida* spp. strains resistant to first-line antifungals (such as echinocandins and fluconazole) are becoming more common, and their presence is frequently associated with high azole and/or echinocandin background usage in hospitals or specific hospital units10–14. The term multidrug-resistant (MDR) *Candida* sp. refers to *Candida* spp. strains that are resistant to two antifungal medication classes, whereas extensively drug-resistant (XDR) *Candida* spp. strains are resistant to three antifungal drug classes [32]. The modification and overexpression of the drug target, a decrease in the intracellular drug concentration, and the creation of a bypass pathway are all components of this yeast's antifungal resistance mechanisms. Researchers ar e turning to alternative medicines as a result of the threat of antifungal resistance, the dearth of antifungal weapon s, and the difficulties in developing antifungal drugs, whi ch are partially caused by the eukaryotic nature of both f ungus and humans [77].

Azoles are antifungal medications that work by inhibiting the cytochrome P450enzyme 14-sterol-demethylase, a crucial enzyme in the manufacture of ergosterol, a crucial component of the fungal cell membrane. This essential enzyme is inhibited, which causes an accumulation of 14-methylsterols to build up on the fungal surface and stops the development of the fungus. Different azoles have different affinities to their targets, which might explain the variance in their range of action. The structural similarities of azoles, however, may also result in cross resistance across *Candida* spp. The emergence of azole resistance may be caused by several different processes. These processes include up-regulation of genes producing efflux pumps, formation of bypass routes, and changes in the ERG 11 gene, which codes for the drug target enzyme [85]. There are three main ways for *Candida* species to develop azole resistance. The first mechanism involves the inclusion of multidrug pumps in the fungal cell wall, which allow the cell to pump out the drug, reducing enzyme inhibition and altering the fungal cell wall. The pumps are the result of genes encoding efflux pumps being upregulated via point mutations (CDR1/CDR2 and MDR1) and transcription factors (TAC1 and MDR1). The second mechanism that can result in azole resistance is the

alteration or up-regulation of the gene encoding the enzyme under consideration, ERG11. When ERG11 is mutated, the binding site of the enzyme changes, preventing azoles from binding. The final mechanism is that mutations cause the fungal cell to develop bypass pathways. To prevent cell membrane alteration and toxic product accumulation, another non-azole-interrupted pathway is formed, allowing the fungus to maintain functional cell membranes [23].

Polyenes were the first broad-spectrum antifungal medications on the market, and they are still the gold standard for treating a range of fungal diseases after 70 years. Polyenes, such as AmB, have a bad reputation. The mechanism of polyene resistance has been discovered to be a decrease in plasma membrane ergosterol concentration. This results in a reduced affinity of AmB for the plasma membrane. There have been few reports of *Candida* isolates developing AmB resistance. Some species, such as *C. lusitaniae*, *C. lipolytica*, and *C. guilliermondii*, have inherent resistance to AmB. There have been a few instances of *C. albicans* strains being resistant to AmB. *C. rugosa* has been shown to exhibit higher levels of MIC for AmB, particularly in the context of nystatin prophylaxis and breakthrough fungemia in patients already on AmB [86].

They have the largest antifungal medication range, resistance development is still uncommon, and fungicidal capabilities are widespread. However, they have a high host toxicity, which restricts their application. In comparison to other antifungal medication classes, polyenes have an atypical method of action in that they do not target a specific enzyme but rather interact with a key molecule—ergosterol [87].

Echinocandin resistance has also been noticed in C. glabrata since echinocandins were originally used as first line antifungal therapy for most cases of invasive candidiasis. By inhibiting -1,3-D-glucan synthase, echinocandins attack a crucial component of the fungal cell wall, which has a fungicidal impact on *Candida* species. Contrary to *C. albicans*, *C. glabrata* contains the functionally redundant FKS1 and FKS2 genes [88].

Traditional antifungal medications work by inhibiting cell growth or killing fungal cells. In both cases, the drugs exert strong selection pressure and can easily lead to drug resistance. Inorganic antifungal agent research represents a new direction for the development of novel antifungal drugs. Because of their antifungal activity at low concentrations and biocompatibility with mammals, nano-inorganic antifungal agents are regarded as effective and promising antimicrobial agents. Among nano-inorganic antifungal agents, nano-silver (Ag), nano-zinc oxide (ZnO), and nano-titanium dioxide (TiO2) have been extensively studied, but relatively few studies have examined MgO NPs, the potent inhibitory effects of MgO NPs on the major virulence factors of *C. albicans*, such as initial adhesion, two-phase morphological transformation, and biofilm formation [89].

8. Relation between COVID-19 and *Candida* infection

Due to its high prevalence and quick spread, the coronavirus disease 2019 (COVID-19), which began as a pneumonia epidemic in Wuhan, China, in December 2019, has spread throughout the world. Millions of people have died from its worldwide and hundreds of millions of cases have been diagnosed. Along with the virus's negative effects, which include immune system dysregulation and direct injury to the lungs and extra pulmonary tissues, COVID-19 can also be accompanied by infections brought on by other microorganisms [90]. COVID-19 is caused by a new coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), which mostly affects the respiratory system. COVID-19 patients have varying illness symptoms and severity; some can be severe, requiring hospitalization, respiratory failure, or even death [91]. Secondary bacterial and fungal infections, particularly nosocomial pathogens, were associated with a high mortality rate in COVID-19 patients. Enterobacterales, non-fermenting Gram-negative bacilli, Gram-positive bacteria, and fungi are the common pathogens related to co-superinfections (Figure 2) [92].

Candida species was the third most common pathogen of secondary bloodstream infections in COVID-19 patients, after *Klebsiella pneumoniae* and *Acinetobacter baumannii*. Several risk factors, such as lung injury, immunosuppression, oxygen therapy, monoclonal antibodies, and steroid therapy, predispose COVID-19 cases to fungal infections. The prevalence of *C. auris* infections increased to 14% in COVID-19 patients, particularly in those with diabetes, hypertension, and obesity, as well as those with central venous catheter insertion, ICU stay, and broad-spectrum antibiotic use [93].

The risk of infection with any *Candida* species may be significantly increased in severe COVID19 patients (Figure 3). Those patients have more opportunities to be treated with broad-spectrum antibacterial drugs, parenteral nutrition, and invasive examinations, or in patients who have prolonged neutropenia and other immune impairment factors. Invasive Candidiasis (IC) is diagnosed using culture methods such as culture of blood or other samples taken under sterile circumstances, which are typically regarded gold standards for IC, as well as nonculture diagnostic tests such as mannan and anti-mannan IgG testing [94].

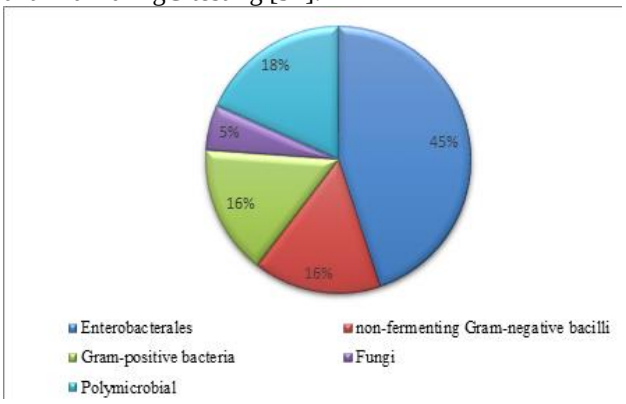

Figure 2: Percentage of pathogens related to co-infections in 109 hospitalized COVID-19 patients.

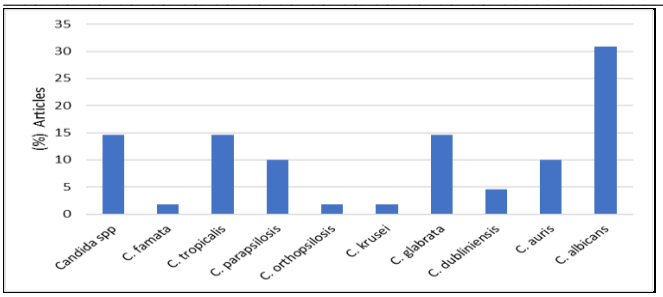

Figure 3: Case studies on different *Candida spp* co-infections in hospitalized COVID-19 patients

Invasive yeast infections (IYIs) are becoming more well-known as a complication of severe COVID-19. A significant proportion of COVID-19 critically ill patients develop acute respiratory distress syndrome (ARDS), necessitating ICU admission and mechanical ventilation, predisposing them to nosocomial infections caused by bacterial and fungal infections. *Aspergillus fumigatus* is becoming more widely recognized as a major source of fungal super infections in critically ill COVID-19 patients [95].

SARS coronavirus 2 (SARS-CoV-2) attacks intestinal cells and may have an impact on the intestinal microbiota. When compared to controls, patients with COVID-19 exhibited substantial changes in their faecal mycobiomes, with *Candia* enrichment *albicans* and a mycobiome that is very diverse at the time of admission to the hospital [91].

During the pandemic, the proportion of COVID-19 patients with central-line-associated bloodstream infections (CLABSI) was five times higher than for non-COVID-19 patients. Furthermore, the average time from COVID-19 diagnosis to developing CLABSI was 18 days, indicating that CLABSI events occurred in COVID-19 patients who were hospitalized for a long period of time [96].

Invasive candidiasis (IC), which includes infections caused by drug-resistant *Candida* species, is the second most common fungal co infection with COVID-19 after COVID-19-Associated Pulmonary *Aspergillosis* (CAPA). *C. glabrata and C. auris* infections had the highest rates [94]. *C. auris* isolation was found to be more common in COVID-19 patients with candidemia, according to studies. The first case of COVID-19 positive *C. auris* fungemia detected in Turkey was presented in this report. A 71-year-old male patient with a history of myocardial infarction, diabetes mellitus, kidney donation, and lobectomy surgery for lung cancer was admitted to the pandemic thoracic surgery service after thoracic computed tomography revealed findings consistent with viral pneumonia [97].

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